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Corrigenda and Addenda

Correction: Authors' Response to Peer Reviews of "Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions"

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Related Article:

Correction of: https://xmed.jmir.org/2021/2/e28893/

(JMIRx Med 2021;2(2):e29878) doi:10.2196/29878

In "Authors' Response to Peer Reviews of 'Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions'" (JMIRx Med 2021;2(2):e28893) one error was noted.

The reviewer ID of the anonymous reviewer has been removed from the published article to preserve anonymity.

The correction will appear in the online version of the paper on the JMIR Publications website on April 26, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Author's Responses to Peer Reviews of "Forecasting the COVID-19 Pandemic in Saudi Arabia Using a Modified Singular Spectrum Analysis Approach: Model Development and Data Analysis"

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Related Article:

Correction of: https://xmed.jmir.org/2021/1/e28742

(JMIRx Med 2021;2(2):e29879) doi:10.2196/29879

In "Author's Responses to Peer Reviews of 'Forecasting the COVID-19 Pandemic in Saudi Arabia Using a Modified Singular Spectrum Analysis Approach: Model Development and Data Analysis'" (JMIRx Med 2021;2(1):e28742) one error was noted.

The reviewer IDs of two anonymous reviewers have been removed from the published article to preserve anonymity.

The correction will appear in the online version of the paper on the JMIR Publications website on April 26, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Peer-Review Report

Peer Review of “Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review”

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/27254

Companion article: https://med.jmirx.org/2021/2/e28744/

Companion article: https://med.jmirx.org/2021/2/e27254/

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KEYWORDS

COVID-19; SARS-CoV-2; test and trace; universal testing; mass testing; contact tracing; infection surveillance; prevention and control; review

This is a peer-review report submitted for the paper “Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review.”

Round 1 Review

General Comments

The paper titled, “Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review” [1] is well textured and finely written with sufficient subpoints and clear divisions. The English used is simple but lucid enough and enriched compared to an international journal standard. From the very beginning, the title is so effective and descriptive that it provides a brief outline for the readers. The abstract is finely written, pointing to the outcomes of the paper, which also includes an applaudable inculcation of a nutshell overview of the methods in use. The data analysis, results, and discussion, as well as the detailed structure of the major findings, *P* values, statistical coefficients, and so on, conform to the author's guide. But there are a few minor typographical errors that need to be checked to improve the write-up. Please consider the points in the *Minor Comments* section. The citations mentioned in the paper fit well with the context. Overall, the description of the content is very clear, and every point is academically backed up with either derivations or scientifically validated information, which is commendable. The figures (mainly the flow chart) are very precise but wonderfully narrative. The *Methods* section has been presented in good harmony with the objectives, outcomes, and strategy although my view on the outcomes differs a bit (please look at the *Specific Comments* section). The data analysis section is well structured, maintaining the flow of data management. In total, the paper is a worthy piece but, in my view, it may require a few minor changes. Kindly refer to the following comments.

Specific Comments

1. It is crucial to remove a few points to make the paper easily acceptable for readers and better its viability. I suggest cutting a bit in the *Research in Context* section. It is fine to have a short review of the literature, but the paper overall is full of it so shortening the aforesaid section may increase its impact.

2. I also do not find the validity of having the *Definitions* section. When an author is proposing a new theory bearing some new terminology, this section is needed, but getting acquainted with formal terms is the prime duty of readers.

3. In the *Data Extraction* section, you paced on the author’s details, specifically its singularity, which seems inapplicable to me. Please consider jotting that area down again in a twisted fashion.

It is really commendable the way you have composed this paper. As mentioned earlier, the writing style is very soothing and effective as a worthy academic contribution. Still, a few points need more attention, which have been further segmented into major and minor comments.

Major Comments

1. Reviewers are not asked to look into the grammar and spelling very thoroughly, so I am giving an overview. Please consider reading the paper again as a few words seems to mismatch their application. For instance, in the following sentence in the

Background section, "I concur with the...," the word "concurs" is out of context, so please look into the matter.

2. In the *Research to Context* prior to *Study* section, there is mention of a review; please cite it for a better scholarly approach.

3. The paper bears a good philosophical measure of uncertainty introduced. This section is very nicely formatted in an appreciable way.

4. Outcomes occur within the *Methods* section, which is not advised. Adding the outcomes here creates a sense of biasedness since outcomes can never be assumed beforehand, which is why you may consider removing these points from here.

5. The section *How the Intervention Should Work* ought to be included under *Methods*. I would suggest replacing its name with *Active Runs of Intervention* as a subsection. The objectives and outcomes further include some basic information about COVID-19 and the strain itself. This is really unimportant, so please remove that portion to reduce the word count of the paper.

6. In the *Outcomes* section, the third point: there is a point on safety; however, the tone of safety in mass testing methods seems to be understated so I would like to propose emphasizing the safe nature of MTT. Again, the paper is really a worthy piece for me, so consider these points as a proposal for improvement.

Minor Comments

1. Many paragraphs lack the use of full stops at the end line. Please have it checked with a little care.

2. There are some issues with grammatical usages; please consider fixing them. You may opt for artificial intelligence–based screening to get better results (eg, Grammarly).

3. The importance of the separate column for vote count in the relative study of TT and MTT is not clear to me so please try to express its viability in a line or so for clarity.

Conflicts of Interest

None declared.

Reference

1. Mbwogge M. Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review. JMIRx Med 2021 Apr 12;2(2):e27254 [FREE Full text] [doi: 10.2196/27254]

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Peer-Review Report

Peer Review of “Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review”

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/27254

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KEYWORDS

COVID-19; SARS-CoV-2; test and trace; universal testing; mass testing; contact tracing; infection surveillance; prevention and control; review

This is a peer-review report submitted for the paper “Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review.”

Round 1 Review

General Comments

This review paper [1] assessed the importance of mass testing in controlling the spread of COVID-19 in the United Kingdom.

Specific Comments

This is a great, comprehensive work; congratulations to the author. However, I have some suggestions:

1. The information provided in the *Methods* section is extra and should not be mentioned there. The *Methods* section covers the methodology of the study, not the background.

2. The references to the studies mentioned in the *Results* section do not follow the journal’s requirements. Please kindly fix those.

3. For Table 1, my suggestion is to add more columns explaining the summary of the study in a structured format. For example, you can distribute the information you have in the description as number of participants, the country under study, etc.

4. Do not repeat the methodology in the *Results* section.

5. Headers in the *Results* section do not follow the journal’s requirements.

6. Put abbreviations used in the paper at the end of the paper as well (follow journal style).

Conflicts of Interest

None declared.

Reference

1. Mbwogge M. Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review. JMIRx Med 2021 Apr 12;2(2):e27254 [FREE Full text] [doi: 10.2196/27254]

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Peer-Review Report

Peer Review of “A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation”

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/20461

Companion article: https://med.jmirx.org/2021/2/e28334/

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KEYWORDS

cancer; mobile app; gamification; bone marrow transplant; alpha testing; physical activity

This is a peer-review report submitted for the paper "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation."

Round 1

Comments for Authors/Editors

General Comments

1. This was a novel and interesting manuscript [1] on the development and user evaluation of a walking app for hematopoietic stem cell transplant (HSCT) patients. The main comment is that clarity on who comprised the usability samples (survey respondents, initial usability testers, additional usability evaluators), and who specifically the target sample for the game is (HSCT patients can be fairly diverse), would enhance the paper.
2. In general, the conducted and planned usability testing seemed heavy on the expert testing and light in terms of planned testing with patients. In addition, the focus appeared to be very much on usability testing, without much acknowledgment that there would be a need in the future to test the impact on walking behavior.
3. While there is no doubt that expert usability testing is important, and it is nice to see clear descriptions of the early development processes, it does not seem sufficient to then do a short usability test with patients and release the app to the public.
4. It would be good to acknowledge that rigorous evaluation (including feasibility, acceptability, and measured impact on walking) would be required prior to release. I am sure that this is planned and has been considered, but perhaps a flowchart or figure/table outlining each of the development steps, the samples involved in these steps, and details on a trial exploring the impact on walking within the target sample might bring clarity.

Specific Comments

These are mostly for clarity rather than any issue with the study.

Abstract

1. Minor, but rather than “the aim of this paper,” replace with “the aim of this study” or “the aim of this paper was to describe….”
2. Make it clear that the paper describes only the evaluation, rather than a behavioral evaluation (ie, impact on physical activity), and that the evaluation took place with game development experts and clinicians rather than patients. This was not clear until quite far into the methodology. Some of the results (eg, “moving tiles”) lack context in the abstract.

Introduction

1. In general, this section is well written but could have included more details on interventions that have tried to promote physical activity in HSCT patients in other contexts to give a full lay of the land.
2. While the hypotheses around the reasons why the app might encourage walking are logical, it would have been good to include some references to support these, and some of the justification for app content might have been better placed in the *Methods* section.
3. It might have been good to give an indication of the likely target sample(s) (eg, in terms of age) and information on smartphone ownership in these groups because the population (particularly age range) can be very diverse. It

would be interesting to get a sense of whether there was a particular target demographic in mind for this game.

Methods

1. Tied to the comment above, it was nice to see some formative survey work. Again, it would be interesting to get an idea of the age range and other demographics of the response sample and whether these are exactly in line with the target sample for this new game (eg, Candy Crush tends to be more popular among specific demographics).
2. Per the comment above, it was not immediately clear that this paper would describe testing with game experts and a nurse, rather than patients. This could be outlined early in the methodology.
3. Table 1 looks like it discloses emails; this should be removed if they are genuine.
4. Aside from replicating the model of Candy Crush, was there any consideration for, or attempt to, include some of the key behavior change techniques that are important for physical activity change (eg, goal setting, self-monitoring, feedback)? I can imagine they are probably in there by default, but it would be nice to see which behavior change techniques map to which game features and if there was any consideration of a theoretical basis in the app development process.
5. The qualitative analysis is not mentioned until the *Data Analysis* section—what was the purpose and how was it carried out? It is worth acknowledging in the *Methods* to provide context. In addition, I found the sentence describing the qualitative analysis difficult to follow. Could this be simplified?
6. The sentence on step counters, "To improve the accuracy of our step counters of our designed WW, we recruited 5 additional usability evaluators who were nursing informatics graduate students," could have been described in the *Methods* section, as it came out of the blue in the *Results*. In general, clarity on who comprised the usability samples (survey respondents, testers, additional usability evaluators, and the actual target sample for the game) would enhance the paper.

Discussion

1. Discussion and conclusion are very short—it would have been good to describe more current findings in relation to other relevant studies. Another sample of 30 individuals (students and programmers) was described here, which seems like it might be planned work, but this was not entirely clear. Perhaps a flowchart or table with all of the planned steps and samples involved would be useful.
2. Per the general comment at the start, the focus seems very expert heavy, with only a brief evaluation with patients and a strong focus on usability rather than the impact on walking behavior. It would be important to trial the app in patients to determine whether it has an impact on walking behavior. To what extent does it matter whether people find it usable and like it if it does not actually change the target behavior?

Conflicts of Interest

None declared.

Reference

1. Cerbas S, Kelemen A, Liang Y, Sik-Lanyi C, Van de Castle B. A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation. JMIRx Med 2021 Apr 13;2(2):e20461 [FREE Full text] [doi: 10.2196/20461]

Abbreviations

HSCT: hematopoietic stem cell transplant

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Peer-Review Report

Peer Review of “A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation”

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/20461

Companion article: https://med.jmirx.org/2021/2/e28334/

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KEYWORDS

cancer; mobile app; gamification; bone marrow transplant; alpha testing; physical activity

This is a peer-review report submitted for the paper "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation."

Round 1 Review

General Comments

I appreciate the chance to review this study [1], and I applaud the authors for their pursuit of an important topic. This paper details the development and usability testing of Walking Warrior, a mobile app designed to help increase physical activity (PA) levels in individuals who have undergone hematopoietic stem cell transplant (HSCT). The study presents some important and valuable insights into the development process of an mHealth (mobile health) app. I appreciate that there may exist some tension between more formative app development and the level of strict adherence to scientific principles that one would expect in late-stage efficacy testing, but nonetheless, I believe the manuscript as written is not yet sufficiently grounded in scientific frameworks, theory, models, or methods to be suitable for publication. I offer some suggestions below.

Specific Comments

Major Comments

Introduction

1. I would recommend further developing the link between how increasing PA can positively impact HSCT patients; at present, this is not sufficiently developed.
2. The reference for the statement “Unfortunately, adherence to recommended levels of PA is low in cancer patients” is not appropriate.
3. The rationale and argument for the use of gamification and game design elements to increase physical activity in cancer survivors are not sufficiently developed. I recommend incorporating some of the relevant theory and literature detailing why this approach may be useful for physical activity promotion in this population.
4. Develop the gap in the literature—why is the lack of PA mobile apps specifically for HSCT patients important? What unique challenges faced by this population may make existing PA app options less than ideal?
5. The stated hypothesis, that the game will “motivate HSCT patients to walk,” does not appear to align with the study aims centered on expert heuristic usability evaluation.
6. Why would you hypothesize that the “game will motivate HSCT patients to walk due to…continued game play requires walking: if they want to play more, they will need to walk”? This is not readily apparent.

Methods

1. There does not appear to be a scientific model, framework, or theory undergirding the development process. I suggest taking care to align the development process with an existing scientific approach. You state that “The entire development process was based on user-centered design,” but there is no accompanying citation, and it is not clear what this entails.
2. It was stated that “A 40-item expert heuristic questionnaire was designed and validated,” but this does not seem to be the case. How was the instrument validated?
3. The qualitative data analysis methods do not seem to have been grounded in a scientific framework. A description of the hierarchical factor analysis methods is not present in the *Methods* section.

Results

1. I would recommend providing more information about the characteristics of the study sample.
2. Interpretation of the descriptive statistics seems arbitrary. Are there normative values that can be referenced?
3. Key methods are presented in the *Results* section (eg, "To improve the accuracy of our step counters of our designed WW, we recruited 5 additional usability evaluators who were nursing informatics graduate students").

Discussion

1. The discussion should present study findings in the context of the existing literature. How do your results compare to other studies centered on usability testing of physical activity apps?

Round 2 Review:

I thank the authors for their responsiveness to reviewer comments. I do have remaining concerns that need to be addressed before this manuscript is suitable for publication.

1. At the end of the *Introduction* section, you state:
   "We hypothesize that our game will motivate HSCT patients to walk due to: (1) large portion of HSCT patients earlier reported to enjoy playing match-3 puzzle game such as Candy Crush which is similar to our game; (2) continued game play requires walking: if they want to play more, they will need to walk; (3) patients are educated that walking is part of their therapy, playing the game reinforces this behavior; 4) walking will allow players to unlock additional levels and allows them to earn higher scores; (5) game playing and walking performance data are automatically collected and displayed on a website that allows patient self-tracking and provider review; (6) the game is mentally challenging, this provides entertainment, logical thinking opportunity, the element of chance, and high replayability; (7) tiles to move in the puzzle are displayed as cell types and medications which are relevant to the HSTC patients' condition and provide education to players enhancing their knowledge of the underlying biology and treatment they receive; (8) in addition to their automatically collected data, patients will participate in a survey which will serve as a tool for software evaluation and additional development showing the individual patient's true experience and opinions are valued and integrated into the next phase of software development.
   However, the purpose of this project is not to test these or any hypotheses. Please revise accordingly, removing all references to hypotheses (which imply that they will be tested).
2. You state that "A 40-item expert heuristic questionnaire was designed and validated." I appreciate that you provided more details in response to previous comments. However, based on what you have shared, I believe that claiming to have "validated" the questionnaire would be misleading. Please revise. For example, you may remove the word "validated" and say something like, "Two experts assessed the face validity of the 40-item expert heuristic questionnaire." This is a subtle but important distinction.
3. Additionally, building on comment #2, the fact that this was not a measure with established psychometric properties is a limitation of the study that needs to be explicitly addressed as a limitation in the *Discussion* section.
4. I am skeptical of the finding articulated in the abstract as "Findings from the expert usability evaluation suggest the game's assets of clarity, ease of use, appropriateness, quality, walking motivation, and mental effort were all favorable." In the *Results* section, you state, "although 2 categories' means were close to neutral (3.1), which is considered favorable due to the wording of those items," but taking a look at the actual items, this is not clear to me. Please provide more evidence or commentary to substantiate this claim, or otherwise revise accordingly. I think it could be useful to talk about some of the potential opportunities for improvement of this very interesting intervention.
5. Please provide evidence to support the claim that "HSCT patients…carry a smartphone."
6. Consider revising the sentence, "There is no personally identifiable information in the database, only user's names and performance data" to state "usernames," not "user's name," if appropriate.
7. Please address the fact that there was only 1 bone marrow transplant nurse to complete the expert heuristic usability evaluation of WW as a limitation of this study in the *Discussion* section. This seems to be a major limitation, and that person's scores seemed to be markedly different from the programmers' scores in some domains. Please provide some commentary on this.
8. Related to this, this statement is quite unclear to me given that there was only 1 bone marrow transplant nurse: "Hierarchical cluster analysis confirmed that the bone marrow transplant nurse and the computer programmer neither least nor most represented their domain group." Please clarify.
9. Please move this statement, "The process of using "game design elements in non-game contexts" is known as gamification [24]" to the *Introduction* section.

Conflicts of Interest

None declared.

Reference

1. Cerbas S, Kelemen A, Liang Y, Sik-Lanyi C, Van de Castle B. A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation. JMIRx Med 2021 Apr 13;2(1):e20461 [FREE Full text] [doi: 10.2196/20461]

Abbreviations

HSCT: hematopoietic stem cell transplant
mHealth: mobile health
PA: physical activity

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Peer-Review Report

Peer Review of “Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions”

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Related Articles:

Companion article: https://preprints.jmir.org/preprint/21269

Companion article: https://med.jmirx.org/2021/2/e28893/

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KEYWORDS

COVID-19; testing strategy; skew-normal distributions; lockdown; forecast; modeling; outbreak; infectious disease; prediction

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Round 1 Review

General Comments

This paper [1] is very interesting and approaches the problem at hand with an innovative perspective. The statistical analysis is quite enlightening, showing how the available data should be interpreted and used to improve health systems’ response to the crisis and explaining why the working strategies of countries like Germany and South Korea are so effective. I fully support the publication of this paper. I suggest only a more careful review to correct a few typos in the main text. Other than that, I endorse this paper’s publication.

Conflicts of Interest

None declared.

Reference

1. De Leo S. Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions. JMIRx Med 2021 Apr;2(2):e21269 [FREE Full text] [doi: 10.2196/21269]

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Peer-Review Report

Peer Review of “Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21269

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KEYWORDS

COVID-19; testing strategy; skew-normal distributions; lockdown; forecast; modeling; outbreak; infectious disease; prediction

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Round 1 Review

General Comments

The title, abstract, and text of this manuscript [1] all aim to answer multiple questions pertaining to the dynamics and control of the COVID-19 pandemic in multiple regions/countries, using mathematical methods. However, neither of the questions nor the answers are clear, and the author has not completed any “translation” work, that is, translating mathematical calculation into descriptions, predictions, and control strategies of the pandemic.

My suggestion is that the author should focus on *one* specific issue about the COVID-19 pandemic; for example: when will adequate herd immunity be established in Sweden, the United Kingdom, and other European countries per the curves? Or how many people will die in the coming months in some European countries? Or which control strategy is the best or better for European countries? Then, the author should give a *clear* answer to the question through mathematical calculations.

Round 2 Review

After reading the responses of the author to my comments, I read again with patience the manuscript, which actually has not been revised. I understand it is tough for a mathematical researcher to conduct this work as they need to acquire a lot of knowledge in virology, immunology, and infectious diseases. However, this manuscript really needs to be revised greatly for the following reasons:

1. In general, this manuscript is written in the style of lecture notes rather than a scientific report. For example, multiple tables were used without titles and legends, and none of the tables were in the standard format of a scientific report. Multiple tables could be deleted.
2. Per the author’s response, the main purpose of this paper was to prove that massive testing strategies are probably the best choice for managing the COVID-19 pandemic. Has this conclusion been given in the findings or interpretation discussed in the abstract (the answer is no)? Has this question been mentioned in the *Introduction* section (the answer is no)? What strategies are inferior to massive testing strategies; which are probably the best? Why and how should this conclusion be made through mathematical calculations?
3. The author should focus on the key question mentioned in the responses. The wordy explanation and calculation in the first three sections should be shortened. Otherwise, readers will not know what the author wants to convey using mathematical language.

The author could consider the following structure: the COVID-19 situation; the question this paper will answer; the effects of the control measures (eg, distancing) that will be involved in the mathematical model; the roles of the parameters (eg, TCCpM) that will be involved in the mathematical model; the principle of the mathematical model; the mathematical model; the answer to the target question through calculation using the model and the epidemiological data.

Reference

1. De Leo S. Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions. JMIRx Med 2021 Apr;2(2):e21269 [FREE Full text] [doi: 10.2196/21269]

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Peer-Review Report

Peer Review of “Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/25204/

Companion article: https://med.jmirx.org/2021/2/e29608/

Companion article: https://med.jmirx.org/2021/2/e25204/

(JMIRx Med 2021;2(2):e29604) doi:10.2196/29604

KEYWORDS

pediatrics; appendectomy; spinal anesthesia; general anesthesia; laparoscopy; vomiting; keyhole; surgery; anesthesia; appendix

This is a peer-review report submitted for the paper "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series"

Round 1 Review

General Comments

This paper [1] is a retrospective case-control comparative study between spinal and general anesthesia for laparoscopic appendectomy in children. The manuscript is very well written with a good study design and robust statistical analysis and display to defend the conclusion.

Specific Comments

Minor Comments

1. Objective: “The objective of this study is to demonstrate that laparoscopic appendectomies are successful under spinal anesthesia and elicit clear advantages over general anesthesia.” The authors state the objectives with the conclusion in mind. Normally, the objective should be: “Comparing spinal and general anesthesia for the following variables…” This was done again in the last paragraph of the *Introduction* section where the final conclusion is stated.
2. Methods: Should include only what was done and how it was done; results (Table 1) should be moved to the *Results* section.
3. Results: In Table 2, it is not enough to have only a summary of the results (significantly higher or lower); the actual numbers should be presented.
4. Results: Should include only data and numbers with no discussion or comments (make sense, encouraging, etc).
5. Discussion: Please explain what is meant by extremity surgery here: “Laparoscopic surgery is now the method of choice for lower abdominal and (extremity) procedures.”

Round 2 Review

General Comments

The authors have adequately answered the reviewer’s comments.

Conflicts of Interest

None declared.

Reference

1. Hannan MJ, Parveen MK, Nandy A, Hasan MS. Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series. JMIRx Med 2021 Apr;2(2):e25204 [FREE Full text] [doi: 10.2196/25204]

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Peer-Review Report

Peer Review of “Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series”

Anonymous

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(JMIRx Med 2021;2(2):e29605) doi:10.2196/29605

KEYWORDS

pediatrics; appendectomy; spinal anesthesia; general anesthesia; laparoscopy; vomiting; keyhole; surgery; anesthesia; appendix

This is a peer-review report submitted for the paper “Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series.”

Round 1 Review

General Comments

The authors of this paper [1] should be commended for their hard work in advocating for the interesting and potentially beneficial yet underused practice of neuraxial spinal anesthesia in the pediatric population for laparoscopic surgery. While this is certainly a topic worthy of additional research and publication, this report in its current form presents several significant challenges that will need to be addressed prior to acceptance for publication. While it is certainly understandable for the authors to attempt to demonstrate the potential benefit of this technique compared with the standard-of-care general anesthetic, I am concerned that the data as presented (or lack thereof) render this less appropriate as a case-control study and more appropriately a case-series report (describing the experience and outcomes of patients undergoing the spinal technique, not comparing them against patients undergoing a general anesthetic). In the absence of randomized control, and without describing a protocol for how the anesthetic technique was decided, the possibility of confounding factors becomes unacceptably large when attempting to draw conclusions from a sample size of this magnitude.

Additional information that can be provided to strengthen case-control studies, which this manuscript could benefit from (see Moola et al [2]) include:

1. Were the groups comparable apart from the choice of anesthetic (and age)—were underlying medical conditions, weight, family history of postoperative nausea and vomiting, developmental history similar?
2. Was the presence of postoperative nausea or vomiting a binary measure?

Specific Comments

Major Comments

The focus on the incidence of postoperative nausea or vomiting between the spinal and general anesthetic groups is particularly problematic given what is described regarding the protocol (and the authors’ own admission in the *Discussion* section, which states “confounding factors from different adjuncts delivered intraoperatively make these results somewhat more difficult to interpret—in fact, the entire subject of postoperative nausea and vomiting can be quite complex”). Even without a significant description of the protocols (both experimental and anesthetic) provided, questions can be raised about the construction of the study. Patients undergoing spinal anesthesia received sedation with diazepam and ketamine (both drugs with a long duration of effects and antiemetic properties), while patients undergoing general anesthesia had nitrous oxide (and possibly a volatile agent?) throughout the duration of the case—a fact that alone is likely to put that patient population at significant risk for postoperative nausea or vomiting. The fact that a number of additional analgesics, antiemetics (which antiemetics were administered to all patients—ondansetron or another agent?), and adjuncts may be given by a number of different providers raises the potential for significant confounding of these measures.

Minor Comments

1. There are minor grammatical and sentence construction choices that would benefit from additional copyediting.
2. What currency is used in describing the cost of the procedure?

Conflicts of Interest

None declared.

References

1. Hannan MJ, Parveen MK, Nandy A, Hasan MS. Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series. JMIRx Med 2021 Apr;2(2):e25204 [FREE Full text] [doi: 10.2196/25204]
2. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. Adelaide, Australia: Joanna Briggs Institute; 2017.

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Peer-Review Report

Peer Review of “Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series”

Theodoros Aslanidis[1], MD, PhD

Intensive Care Unit, St Paul General Hospital, Thessaloniki, Greece

Related Articles:

Companion article: https://preprints.jmir.org/preprint/25204

Companion article: https://med.jmirx.org/2021/2/e29608/

Companion article: https://med.jmirx.org/2021/2/e25204/

(JMIRx Med 2021;2(2):e29607) doi:10.2196/29607

KEYWORDS

pediatrics; appendectomy; spinal anesthesia; general anesthesia; laparoscopy; vomiting; keyhole; surgery; anesthesia; appendix

This is a peer-review report submitted for the paper “Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series”.

Round 1 Review

General Comments

A good written presentation of the study [1] was conducted by the authors.

Conflicts of Interest

None declared.

Reference

1. Hannan MJ, Parveen MK, Nandy A, Hasan MS. Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series. JMIRx Med 2021 Apr;2(2):e25204 [FREE Full text] [doi: 10.2196/25204]

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Peer-Review Report

Peer Review of “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”

Rebecca Krukowski[1], PhD

Department of Preventive Medicine, The University of Tennessee Health Science Center, Memphis, TN, United States

Related Articles:

Companion article: https://preprints.jmir.org/preprint/20617

Companion article: https://med.jmirx.org/2021/2/e29421/

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(JMIRx Med 2021;2(2):e28720) doi:10.2196/28720

KEYWORDS

COVID-19; learning health systems

This is a peer-review report submitted for the paper “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”.

Round 1 Review

General Comments

This paper [1] is interesting in its examination of the challenges with data use during the COVID-19 pandemic and the recommendations for a system of data collection and management. The authors appropriately address the potential privacy concerns. It is a well-written piece.

Specific Comments

Major Comments

1. The authors should ensure that their points are supported by citations, appropriate to a scientific manuscript.

2. The authors should address several main barriers to the recommendations made—*who* would regulate the sharing of the data across systems and international borders (with potential language differences), *who* would coordinate the analyses conducted with shared data to make sure that there is efficiency (to ensure multiple teams are not conducting the same analyses) and that appropriate analyses are conducted, and *where* would the funding coming from (when most health systems are losing money due to cancellation of nonessential procedures).

3. Not all authors use preprints, and peer review has not been effective in addressing some rushed science, particularly in the last few months. How should these concerns be addressed?

Round 2 Review

General Comments

The authors have been responsive to the reviewers’ comments and have improved the piece. I have a few remaining concerns, as noted below.

Specific Comments

1. The paper could still benefit from references to support the authors’ points. For example, the first paragraph does not include a single reference. As another example, point 7—what evidence do the authors have that, “the more relevant the data of the registry and the larger the potential research community, the bigger the bottleneck is likely to be”?

2. Epidemiological data are, in fact, telling us who is more likely to be infected—by race, ethnicity, age, etc. The authors should clarify the unique contribution of clinical data.

3. It is not clear what the authors mean by “In large health systems that cover most of the population cases can be captured rather quickly if the learning system is implemented and coordinated across sites (hence the need for regulating and standardising the methods).”

4. The authors do not clearly define the health learning system in contrast to current practices.

Conflicts of Interest

None declared.

Reference

1. Prieto-Merino D, Bebiano Da Providencia E Costa R, Bacallao Gallestey J, Sofat R, Chung SC, Potts H. Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation. JMIRx Med 2021 May 5;2(2):e20617 [FREE Full text] [doi: 10.2196/20617]

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Peer-Review Report

Peer Review of “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”

Laura Lafon-Hughes[1,2], PhD

[1]Departamento de Genética, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo, Uruguay

[2]Grupo de Biofisicoquímica, Departamento de Ciencias Biológicas, Centro Universitario Regional Litoral Norte, Universidad de la República, Salto, Uruguay

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(JMIRx Med 2021;2(2):e28722) doi:10.2196/28722

KEYWORDS

COVID-19; learning health systems

This is a peer-review report submitted for the paper “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”.

Round 1 Review

General Comments

This paper [1] addresses a pressing issue: pandemic data collection and processing.

The paper provides a clear diagnosis of why we are losing the war against COVID-19 on the data front (first part of the title), including all types of variables like technical aspects, medical staff overload and lack of time to fill in forms, ethical issues management, and bottlenecks for project presentations and analysis. However, the “how to reverse the situation” section (the second part of the title) is not in-depth and could be readdressed from a more practical, useful point of view. Below are some suggestions.

Specific Comments

1. It is true that health staff are overloaded. Discuss alternative solutions regarding who could fill in the forms. For example, could the patient or patient’s family complete a form on a cellphone, using an identifier to track the patient but not the person themselves and send the data to the system? In so doing, the patient would be providing consent to use the data for research purposes. Alternatively, should researchers be recruited to work alongside doctors and nurses and complete the forms, which they can analyze at the same time?

2. Please suggest a structure for the data set. What important information should be recruited? What would a universal data sheet look like? Here are some variables I can rapidly think of. Discuss whether these should be included or not and why, and add other ones. The data set could take into account the long-term effects that may occur.

Patient-specific code: _____

To be filled in by the patient or family

- Country, region, or city; urban/rural
- Age
- Biological sex
- Population ancestry (Africa, Asia, Europe, the Americas)
- Preexistent conditions: allergy, immunodepression, AIDS, frequent respiratory illness, diabetes, hypertension, heart attack, heart surgery, renal problems, liver problems, gastrointestinal problems, psychiatric problems (depression, anxiety, other)
- Care availability, running water supply and soap to wash hands, exposure to extreme temperatures, mask wearing, general living conditions, unemployment, hunger
- Symptoms: a cold, a sore throat, fever, diarrhea, cardiac, neural (loss of taste or smell, dizziness, disorientation)
- Vaccine received? Specify which one and when. Important: People should be instructed to retain their vaccine data, lab, lot, etc, even in clinical trials

To be completed by medical staff

- COVID-19–positive personal contacts
- Days before symptom onset
- Open or closed space
- Mask wearing: yes or no
- Diagnosis confirmed by polymerase chain reaction (day after first symptoms)
- Antibody test (day after symptoms)

- Clinic and paraclinic pneumonia
- ACV
- Blood clots
- Renal failure
- Liver failure
- Treatments attempted (to be completed by doctors)
- Respirator (which one, how many days)
- Anti-inflammatory therapy (which one, how much, when)
- Nonspecific antiviral therapy, for example, remdesivir (which one, how much, when)
- Specific anticoronavirus therapy
- Days in hospital
- Survival?
- Relapse (when, how)
- Long-term changes that may or may not be related to COVID-19
- Neurodegeneration
- Liver failure
- Heart failure
- Lack of strength
- No preexistent depression
- No preexistent diabetes

3. Can you suggest existent public database platforms that could be immediately used for data collection?

4. Do you or does somebody you know have software ready or one that can be easily developed to perform the automatic data processing? Maybe Johns Hopkins University could help? (It is just an idea because they have been automatically collecting COVID-19 diagnosis and deaths by country.)

Conflicts of Interest

None declared.

Reference

1. Prieto-Merino D, Bebiano Da Providencia E Costa R, Bacallao Gallestey J, Sofat R, Chung SC, Potts H. Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation. JMIRx Med 2021 May 5;2(2):e20617 [FREE Full text] [doi: 10.2196/20617]

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Peer-Review Report

Peer Review of “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”

Anonymous

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KEYWORDS

COVID-19; learning health systems

This is a peer-review report submitted for the paper “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”.

Round 1 Review

Dear authors and editor, I thank you for the opportunity to review this manuscript [1]. The paper addresses a topic of extreme relevance to public health and economy. This paper is well established, and the subject is interesting, but some major revisions should be considered.

1. It is hard to follow how future patterns can be predicted as enterprises navigate new corporate social responsibility strategies through the epochal challenges presented by COVID-19.

2. The abstract should briefly state the purpose of the research, the principal results, and the major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone.

3. The necessity and innovation of the paper should be presented in the *Introduction* section.

4. The structure of the paper should be presented at the end of the *Introduction* section.

5. Here are some new, related references, which should be added to the reference list: Khorram-Manesh et al [2] and Purngagen et al [3].

6. Please ensure your conclusions underscore the scientific value added by your paper, and/or the applicability of your findings/results, as indicated previously. Please revise the conclusion section to include more details. Basically, you should enhance your contributions and limitations, underscore the scientific value of your paper, and/or discuss the applicability of your findings/results and future study in this section.

Conflicts of Interest

None declared.

References

1. Prieto-Merino D, Bebiano Da Providencia E Costa R, Bacallao Gallestey J, Sofat R, Chung SC, Potts H. Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation. JMIRx Med 2021 May 5;2(2):e20617 [FREE Full text] [doi: 10.2196/20617]
2. Khorram-Manesh A, Carlström E, Hertelendy AJ, Goniewicz K, Casady CB, Burkle FM. Does the Prosperity of a Country Play a Role in COVID-19 Outcomes? Disaster Med Public Health Prep 2020 Aug 12:1-10 [FREE Full text] [doi: 10.1017/dmp.2020.304] [Medline: 32782059]
3. Purnhagen KP, De Ruijter A, Flear M, Hervey TK, Herwig A. More Competences than You Knew? The Web of Health Competence for European Union Action in Response to the COVID-19 Outbreak. Eur J Risk Regul 2020 Apr 16;11(2):1-10. [doi: 10.1017/err.2020.35]

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Peer Review of “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”

Anonymous

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(JMIRx Med 2021;2(2):e29418) doi:10.2196/29418

KEYWORDS

COVID-19; learning health systems

This is a peer-review report submitted for the paper “Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation”.

General Comments

This paper [1] is an important call to action for the health data community. We have a lot to learn about our failings in addressing this pandemic, and the authors highlight important and pragmatic holes. The authors would benefit from providing more concrete solutions. For example, rather than saying “we need standard data,” why not propose a data standard that can be universally adopted and modularly modified as needed? Rather, provide a list of key variables that everyone should include.

Specific Comments

Major Comments

1. In the *What Can Be Done?* section, I suggest including a proposition for a data structure. We have time and time again called upon folks to collect data, just to be stuck with a bunch of disparate data that takes a heavy lift to integrate. If you do not have a specific structure, consider referring to an existing standard or calling upon the Centers for Disease Control and Prevention or Health Level Seven International to define a standard.

2. This paper lacks mention of existing companies, health systems, and government organizations that are already working on this. Highlighting existing initiatives will go a long way toward avoiding further data silos.

3. This paper is missing a key player in this work—electronic medical record vendors. They have the data, they know the data structures, and they have fewer checks and balances to data use than health systems do.

Conflicts of Interest

None declared.

Reference

1. Prieto-Merino D, Bebiano Da Providencia E Costa R, Bacallao Gallestey J, Sofat R, Chung SC, Potts H. Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation. JMIRx Med 2021 May 5;2(2):e20617 [FREE Full text] [doi: 10.2196/20617]

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Peer-Review Report

Peer Review of “COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?”

Anonymous

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Companion article: https://med.jmirx.org/2021/2/e29517/

(JMIRx Med 2021;2(2):e29068) doi:10.2196/29068

KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

This is a peer review submitted for the paper "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

Round 1 Review:

General Comments

The contribution “COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?” [1] is written with good language quality and is easy to understand. It is a Viewpoint on cybersecurity in COVID-19 times. Based on this topic, it is of interest for the journal.

Unfortunately, the contribution is not in the general JMIR style, which needs to be checked by the editor.

To summarize, there is nothing new in this article that has not been reflected in the general news media. Even for a Viewpoint, the technical references are completely missing. In the end, I do not see any value in this well-written but technically weak viewpoint.

Specific Comments

Major Comments

1. The authors present their viewpoint, but all points are more or less mainstream. What is the “new message,” what is different from all the others?
2. Several points have technical backgrounds, which do not need to be described in a viewpoint article; however, the authors need to show that they are familiar with the literature in the mobile health cybersecurity domain. I do not see this point, and it needs strengthening.
3. When it comes to contact tracing apps, the presentation is rather weak, and several questions or facts are not resolved (eg, the distance estimation of tracing apps needs to be as correct as possible; otherwise, a lot of false positives or false negatives will plague this type of app). There are a lot of concepts in different countries for tracing apps; the authors do not describe these. In some countries, the reaction to a warning is left to the user, but what happens if larger groups disobey the warnings of tracing apps?
4. One argument has not been presented, namely that the increased use of electronic equipment in social distancing times increases the cybersecurity attack surface.
5. In the section on data sharing, the potential of false positives needs to be discussed, eg, technical limitations of distance estimations between different smartphone types should be critically reflected and a reference to this discussion should be given.
6. The authors do not reflect on the general cybersecurity risks of implemented mobile health apps (eg, transport security).
7. There are some reflections on difficulties for tracing apps, but they are not backed by references.
8. The title is very general, and the content does not fit the title; it needs to be less general and has to reflect that this is not a technical paper but a Viewpoint.

Round 2 Review:

General Comments

This paper is improved, but I am not convinced about the content, which is noncomprehensive and not novel (which has been well explained by the authors). There is no typical research method behind it, such as a scoping review or similar, which may be the reason that I do not like it. In my opinion, the world does not need such a viewpoint paper, but the editors have to decide.

Reference

1. Ferreira A, Cruz-Correia R. COVID-19 and cybersecurity: finally, an opportunity to disrupt? JMIRx Med 2021 May 5;2(2):e21069 [FREE Full text] [doi: 10.2196/21069]

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Companion article: https://med.jmirx.org/2021/2/e29517/

Companion article: https://med.jmirx.org/2021/2/e21069/

(JMIRx Med 2021;2(2):e29070) doi:10.2196/29070

KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

Round 1 Review:

This paper [1] presents a viewpoint on the cyber threat issues in the context of COVID-19. It is well written and comprehensive. The scope matches the journal and is of interest to the challenging topic of privacy in contact tracing. However, there is a lack of new evidence or new conclusions. The reported alerts and the discussions are normative and minimal; most of them have already been widely discussed in newspapers and mainstream media.

However, the topic of cybersecurity and privacy will never be outdated since the evolution of COVID-19. The authors must work a lot more to identify the knowledge gap in the existing literature first and then propose novel viewpoints to bridge the gaps. Before drawing a conclusion, the authors must add a discussion on how their findings compare to other studies (references) that were published very recently.

Appropriate references to related work are not covered sufficiently in the list, especially for the contact tracing section. A systematic review of the global deployment status of contact tracing apps is recommended, as in [2].

In addition to the majority of qualitative descriptions, quantitative statistics are suggested to complement and support the statements in the manuscript.

Round 2 Review:

After the first round of review, the reviewer appreciates the revision effort the authors have made in improving the manuscript.

However, the authors may need to redefine the contribution and the title in a more specific and unique manner.

The current title looks quite broad and not new, as a number of similar articles have been disseminated on the web (eg, [3,4]).

The authors might consider reducing the overlap with published work as illustrated above.

References

1. Ferreira A, Cruz-Correia R. COVID-19 and cybersecurity: finally, an opportunity to disrupt? JMIRx Med 2021 May 5;2(2):e21069 [FREE Full text] [doi: 10.2196/21069]
2. LI J, Guo X. Global Deployment Mappings and Challenges of Contact-tracing Apps for COVID-19. SSRN Journal. Preprint posted online on May 26, 2020. [doi: 10.2139/ssrn.3609516]
3. Theme 3: Covid-19, privacy rights and cyber security risks. Principles for Responsible Investment. 2020 Sep 07. URL: https://www.unpri.org/covid-19-resources/theme-3-covid-19-privacy-rights-and-cyber-security-risks/6343.article [accessed 2021-03-30]
4. COVID-19’s impact on data privacy, protection and security. Episerver. URL: https://www.episerver.com/guides/covid-19-privacy-considerations [accessed 2021-03-30]

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Please cite as:
Anonymous
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Peer-Review Report

Peer Review of “COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21069

Companion article: https://med.jmirx.org/2021/2/e29517/

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(JMIRx Med 2021;2(2):e29096) doi:10.2196/29096

KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

This is a peer-review report submitted for the paper "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

Round 1 Review:

Dear Authors,

Thank you for the opportunity to read and review this paper [1]. I found it very interesting, useful, and well-written. I have made some comments on how the paper, in my view, can be further enhanced. Please consider them as suggestions:

Introduction

For reader-friendliness: provide a short explanation of abbreviations (eg, COVID-19) the first time they appear in the text.

I miss some references in a few sentences, such as “Within the literature, recommendations are that data analyses are initiated and concluded openly, in accordance with the law and with respect for privacy.”

I also think that this section can be expanded.

At the end, when you outline the focus of the study and possible implications, it would be interesting to learn more about in the way in which documentation can serve as a learning tool. I recommend adding examples of practical and theoretical implications.

COVID-19, Cybersecurity, Privacy, Security, and Safety

I would like to see information on how we are dealing with misinformation and false news and groups resisting the response to the pandemic under the topic of Education/Media, as this is an important issue the European Union and other countries are facing. Is this an EU or country-by-country initiative?

Conclusion

The introduction to the conclusion is very similar to the beginning of the paper. The conclusion, to me, has the feel of being more of a summary than an actual conclusion. I would recommend narrowing down this section.

Language

The language is overall very good. Some editing is recommended to ensure consistency in terminology and structure.

Limitations

The paper is very positive without discussing limitations, challenges, and problems sufficiently. I suggest either incorporating this discussion throughout or providing a section at the end that also discusses the effectiveness of the measures as understood to date as well as current and future anticipated challenges.

References

References should be expanded to include current literature. You should also add more references. Please include the following references: [2-6].

References

1. Ferreira A, Cruz-Correia R. COVID-19 and cybersecurity: finally, an opportunity to disrupt? JMIRx Med 2021 May 5;2(2):e21069 [FREE Full text] [doi: 10.2196/21069]

2. Ahmad T. Corona virus (COVID-19) pandemic and work from Home: challenges of cybercrimes and cybersecurity. SSRN Journal. Preprint posted online on April 5, 2020. [doi: 10.2139/ssrn.3568830]
3. Ali Khan N, Brohi SN, Zaman N. Ten deadly cyber security threats amid COVID-19 pandemic. TechRxiv. Preprint posted online on May 11, 2020. [doi: 10.36227/techrxiv.12278792.v1]
4. Goniewicz K, Khorram-Manesh A, Hertelendy AJ, Goniewicz M, Naylor K, Burkle FM. Current Response and Management Decisions of the European Union to the COVID-19 Outbreak: A Review. Sustainability 2020;12(9):1-12.
5. Johnson H, Gossner CM, Colzani E, Kinsman J, Alexakis L, Beauté J, et al. Potential scenarios for the progression of a COVID-19 epidemic in the European Union and the European Economic Area, March 2020. Euro Surveill 2020 Mar;25(9) [FREE Full text] [doi: 10.2807/1560-7917.ES.2020.25.9.2000202] [Medline: 32156332]
6. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020 Apr;76:71-76 [FREE Full text] [doi: 10.1016/j.ijsu.2020.02.034] [Medline: 32112977]

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Peer-Review Report

Peer Review of “COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?”

Anonymous

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21069

Companion article: https://med.jmirx.org/2021/2/e29517/

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(JMIRx Med 2021;2(2):e29414) doi:10.2196/29414

KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

This is a peer-review report submitted for the paper "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

Round 1 Review:

Minor Comments

Dear Authors, the article [1] is well written; however, in my opinion, there is a need to rephrase the *Conclusion* section in order to make it more clearly informative.

Reference

1. Ferreira A, Cruz-Correia R. COVID-19 and cybersecurity: finally, an opportunity to disrupt? JMIRx Med 2021 May 5;2(2):e21069 [FREE Full text] [doi: 10.2196/21069]

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Peer-Review Report

Peer Review of “COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?”

David W Chadwick[1]

University of Kent, Kent, United Kingdom

Related Articles:

Companion article: https://preprints.jmir.org/preprint/21069

Companion article: https://med.jmirx.org/2021/2/e29517/

Companion article: https://med.jmirx.org/2021/2/e21069/

(JMIRx Med 2021;2(2):e29417) doi:10.2196/29417

KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

This is a peer-review report submitted for the paper "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

Round 1 Review:

General Comments

This paper [1] provides an overview of cybersecurity and privacy risks arising from COVID-19. Overall, the paper is quite generic, and I did not think that it identified any new issues or presented any new results.

Specific Comments

Major Comments

1. When discussing data sharing privacy versus public health for the contact tracing apps, why didn't the author compare what dictatorial regimes such as China are doing at one extreme (eg, recording every railway carriage that someone travels in) with the more privacy-protecting method championed by Google and Apple?
2. When discussing fraud and theft, why didn’t the author mention the fact that Google still accepts “paid” advertisements from fraudulent financial services and publishes these at the top of search results, even though Google has known about this problem for years?

Minor Comments

There are a few grammatical errors, as follows:

1. “time is of essence” should be “time is of the essence”
2. “elder people” should be “elderly people” (twice)

Reference

1. Ferreira A, Cruz-Correia R. COVID-19 and cybersecurity: finally, an opportunity to disrupt? JMIRx Med 2021 May 5;2(2):e21069 [FREE Full text] [doi: 10.2196/21069]

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Peer-Review Report

Peer Review of "Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study"

Ojelanki Ngwenyama[1], MS, MBA, PhD

Institute for Innovation and Technology Management, Ted Rogers School of Management, Ryerson University, Toronto, ON, Canada

Related Articles:

Companion article: http://preprints.jmir.org/preprint/25703

Companion article: https://med.jmirx.org/2021/2/e29626/

Companion article: https://med.jmirx.org/2021/2/e25703/

(JMIRx Med 2021;2(2):e29632) doi:10.2196/29632

KEYWORDS

AYUSH Sanjivani app; COVID-19; traditional medicine; Ayurveda; Siddha; Unani; homeopathy

This is a peer-review report submitted for the paper "Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study"

Round 1:

I would like to thank the authors for doing an investigation of how health apps might help individuals manage their personal health. However, this paper makes some claims that cannot be defended based on the research design [1]. For example, the authors state, "79.1% of the users responded that the practice of AYUSH measures gave an overall feeling of good health and improved immunity." I have no problem with claims of "overall feelings of good health", but claims of improved immunity to COVID-19 are misleading. There is no possibility for the subjects to claim "improved immunity." This would have required clinical testing for antibodies to the SARS-CoV-2 virus.

I believe that the fundamental problem is with the study design, especially the questions the researchers asked concerning reasons for using the AYUSH Sanjivani app: "Helped in prevention from COVID-19" and "Reduced the symptoms while having COVID-19." There is no scientific basis to ask such questions in the context of their study.

Conflicts of Interest

None declared.

Reference

1. Srikanth N, Rana R, Singhal R, Jameela S, Singh R, Khanduri S, et al. Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study. JMIRxMed 2021 May;2(2):e25703 [FREE Full text] [doi: 10.2196/25703]

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Please cite as:
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Peer-Review Report

Peer Review of “Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study”

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[2]Department of Computer Science, Government Champhai College, Champhai, India

Related Articles:

Companion article: http://preprints.jmir.org/preprint/25703

Companion article: https://med.jmirx.org/2021/2/e29626/

Companion article: https://med.jmirx.org/2021/2/e25703/

(JMIRx Med 2021;2(2):e29634) doi:10.2196/29634

KEYWORDS

AYUSH Sanjivani app; COVID-19; traditional medicine; Ayurveda; Siddha; Unani; homeopathy

This is a peer-review report submitted for the paper "Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study"

Round 1:

General Comments

The research was timely and interesting, the claimed results seem acceptable and up to the mark, the work shows originality but slightly weak technical support. However, the authors are advised to consider the following few comments in the current version.

Specific Comments

Major Comments

1. It is believed that the paper reflects on the current COVID-19 (SARS-CoV-2) pandemic; therefore, it is suggested to modify SARS-CoV to SARS-CoV-2 as and when required. However, if the author targeted the 2003 pandemic caused by SARS-CoV, it looks fine, but various web sources posted that the AYUSH Sanjivani app launched recently, in May 2020. Please provide a clear definition for the same.
2. Readers will benefit if the structure of the questionnaire is added in tabular form, indicating the details of the survey including the self-reporting questionnaire. Please add a screenshot of the mobile app if possible.
3. In the current version, the *Data Sources and Data Collection Methods* subsection seems to have redundant information. Please review the second and third paragraphs.
4. It will be beneficial if the structure of the three-layer module used for collecting data mentioned in the *Study Design* section is depicted in detailed tabular form.
5. The current version of the manuscript seems weak, especially in the *Methodology* section. Please review and restructure the structure and content of the same. Considerable information should be added.
6. Please add the tools used for the statistical analysis.
7. The *Results and Discussion* section contain mixed-up information. It is advised to review/restructure the same in the revised version.
8. Throughout the paper, it is unclear where the authors classified/identified a person infected with COVID-19. Please mention clearly how the authors dealt with the same.
9. Technical support seems a little weak. It is advised to provide more support for your findings.
10. The novelty of the manuscript needs improvement.
11. Grammatical errors throughout the manuscript require major proofreading.
12. The references need major revision.

Round 2:

General Comments

It is been observed that the revised version of the manuscript addresses every review comment made in Round 1. Therefore, after reviewing, the whole change shows its originality.

However, I am still concerned about the structure of the Questionnaire (which was just added for Round 2)! It does not contain any provable information about patients/subjects with COVID-19. The questionnaire is distributed in a public network,

but the self-report does not filter whether the subject is an expert in the medical area. Therefore, the report could be inaccurate. If the questionnaire were selectively collected from medical students or a cohort of patients with COVID-19 taking Ayurvedic medication, there could be some relation with the claimed contributions.

Therefore, I kindly request that the authors change the title and claims to match their results. In the meantime, I do value and enjoy reading your work.

Conflicts of Interest

None declared.

Reference

1. Srikanth N, Rana R, Singhal R, Jameela S, Singh R, Khanduri S, et al. Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study. JMIRxMed 2021 May;2(2):e25703 [FREE Full text] [doi: 10.2196/25703]

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Peer-Review Report

Peer Review of “Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study”

W Benjamin Nowell[1], MSW, PhD

Global Healthy Living Foundation, Nyack, NY, United States

Related Articles:

Companion article: https://preprints.jmir.org/preprint/25560

Companion article: https://med.jmirx.org/2021/2/e28917/

Companion article: https://med.jmirx.org/2021/2/e25560/

(JMIRx Med 2021;2(2):e28919) doi:10.2196/28919

KEYWORDS

data collection; herpes simplex; registry; machine learning; risk assessment; artificial intelligence; predictor; risk

This is a peer-review report submitted for the paper “Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study.”

Round 1 Review

General Comments

This paper [1] describes the process of designing and implementing an algorithm to lay the groundwork for developing a patient registry for people at risk of becoming infected with, or already living with, the herpes simplex virus (HSV). Specifically, the authors used a machine learning method (random forest modeling) to design an HSV patient registry that uses a limited number of lifestyle predictors for HSV infection and flare-up to choose the questions that are most relevant for registry participants. The authors were able to optimize the number of questions needed to achieve high accuracy in predicting HSV infection using this method. The authors situate their innovative method within the broader context of both the challenges associated with building a patient registry for a stigmatized condition, as well as the opportunities to create new registries by using publicly available data sets (eg, US National Health and Nutrition Examination Survey [NHANES]) and machine learning tools.

Specific Comments

Major comments

1. The sections of the paper describing the method and results are strong, but sections such as the *Background*, *Challenges of Developing Patient Registries*, and *Discussion* need to be strengthened to set the context with a clearer focus. There are at least 3 examples of how this could be improved in my comments that follow.

2. First, a number of challenges associated with developing “a usable and effective patient registry” are highlighted, and the authors claim that their project “aimed to address these challenges by developing an innovative machine learning method for patient data collection and predictive analytics to improve data availability and quality in medical registries.” However, the approach and the 8-step process described by the authors would not actually address all of the four challenges equally well. The paper would be strengthened by being more specific and focused on which of the challenges are truly addressed by the process described here and which would likely require additional strategies. For example, it was not clear to me how this process would address patients’ or users’ concerns about privacy and control over their own data (the last of the 4 bullets) or necessarily meet the needs of patients. It is fine not to be able to address all of the challenges with the process you described, but I suggest you specify which of the challenges or concerns would be most directly solved by your process.

3. Second, you mention ArthritisPower, a research registry collaboration that brings together a patient advocacy organization and an academic medical center, in an effort to respond to the needs of patients with a smartphone app that facilitates symptom tracking, but the genesis of that registry/database is quite different than what you describe for the HSV registry. ArthritisPower participants already knew that they had a diagnosis of rheumatoid arthritis or another condition when they enrolled. Perhaps that is the point of citing the ArthritisPower example, since your process offers a contrast or alternative approach to assembling a patient registry, but this needs to be stated plainly if that is the case.

4. Third, you present an 8-step process that concludes with improvement of the precision of your model with real-world data. Later, in the *Discussion*, you note that future research and development of the system will go beyond that step to "examine important anonymity, consent, interoperability, and data security concerns, and develop and evaluate a holistic patient registry system (with a front-end user interface and a back-end data architecture)." These are important steps, but since these are outside the scope of this paper, I would take the opportunity earlier in the paper, like in the *Background* and registry challenges sections, to help narrow the focus to how your specific aims to build this model for HSV (and the 8-step process you outline) would be able to advance a registry's efforts to the point where the steps beyond it might proceed with fewer barriers and more benefits to the end-users (patients and researchers).

5. The study appears to have been what one would consider secondary data analysis, but there was no mention of any human subjects or ethical research review in the United States or the United Kingdom. Typically, for this type of study in the United States, one might expect that the study was reviewed by an institutional review board (IRB) and received an exempt determination. As all of the authors are located in the United Kingdom, but the NHANES database is US-based, I am not sure what the established procedure should have been. Please describe any interaction with IRBs or institutional research ethics committees related to this research.

Minor Comments

6. Pg 3, lines 3-4: "...the value of these registries can be severely limited by a lack of high-quality..." Is the word "data" missing here? Either add a noun or perhaps edit to "lack of quality" followed by a full stop.

7. Pg 3, line 7: "...would provide significant benefits for research and clinical care." Provide a few brief examples here (or later in the *Discussion* section) about the specific value for research and care since the sentence that follows is fairly general and applies to all registries, not specifically to one for HSV. What pressing questions about HSV could we answer with such a registry? How might this improve clinical care for HSV? This helps the reader understand why an HSV registry should be prioritized (ie, over other diseases) in the first place. This could be introduced in the *Background* and more fully explained in the *Discussion*.

8. Pg 6: Some explanation of the rationale for each of these criteria would be helpful; also, some of the criteria seem to overlap. For example, an extensive list of variables would naturally lend itself to the existence of a large number of rows, so I wondered why this needed to be stated in the second bullet. Perhaps the second requirement could be shortened to "clinically verified HSV diagnostic data."

9. Pg 6, line 20: "…building a lifestyle-focussed questionnaire" only needs one "s" in "focused" for US readers. In fact, there are a handful of places throughout the paper where British vs American English conventions are inconsistent. For example, both spellings, "analysing" and "analyzing" were present. I am not sure what the exact editorial guidelines are for JMIR but would make sure this is consistent either way.

10. Pg 7, lines 16-17: "…confirmed negative or positive cases reported in NHANES were divided into two sub-datasets for training and validation of the model with a ratio of 0.8 to 0.2. The training dataset was used to train the model and the validation dataset was used for accuracy scoring." Can you provide a rationale for dividing by the 0.8 to 0.2 ratio or at least give a citation for why this particular ratio was used? Is it due to statistical convention or because it maximizes the amount of data in the training data set with enough remaining data to conduct the validation or is there another reason?

11. Pg 8: "The model was designed to process the data in the following way..." The list of 8 steps in the process should perhaps be followed by a final sentence in that section to specify that the process or results described in this manuscript include steps 1 to 7 and that the next step (outside the scope of this paper) will be to conduct step 8 (ie, improve its precision with real-world data). This is implicit here, and then later mentioned more explicitly in the *Discussion*, but there it is accompanied by a longer list of next steps.

12. Pg 9, lines 24-26: "The model selected a set of 62 questions that form shorter sequences for each user based on their age and gender. On average, a user would be asked 40 questions, with a minimum of 21." Does this mean the max set of questions a person might answer is 62? If so, state that explicitly. If not, please clarify. Currently, it reads as though you have provided an average number of questions that participants must answer, and a minimum number, but no maximum. If known, it might also be informative to readers to state the average amount of time it took participants to answer the original ~150 NHANES questions versus the 40 questions. This gives the reader a more concrete sense of how much you were able to reduce participant burden with your optimized questionnaire for HSV compared to the original. Even an estimate of the time, if the exact time is not known, would be instructive.

13. Pg 10, line 1: The header would be clearer if it read, *NHANES Questions With Added Questions* or *NHANES Questions With Supplementary Questions*. The word "added" seems to be dangling.

14. Pg 11, lines 13-14: "The ultimate aim of this project is to increase the quality and quantity of data collected and improve the probability of users disclosing sensitive information and volunteering for clinical trials." It is intuitive to assume so, but is there evidence you can cite that supports the fact that fewer questions are better for more sensitive information, above and beyond the usual benefit of minimizing participant burden for any questionnaire, and is there evidence that this ultimately leads to patients providing more data? I would suppose it can if the optimized original survey frees you up to then ask other questions.

15. Pg 11, line 21: Consider replacing "on" with "regarding" (ie, "to generate more insights regarding what questions…" instead of "to generate more insights on what questions…").

16. Pg 12, lines 5-6: "…and members of the public." Please specify what is meant by the eligible "public" users of the

platform. There are presumably some differences in the data that would be available to users in different places or different nomenclature based on different health care systems or linguistics and terms in different places. Is this for US users, UK users, or both?

17. Pg 12, line 22: What is meant by "pseudo-anonymised data"? Please be specific or provide an example.

Round 2 Review

General Comments

The authors have addressed the suggestions and comments from the first review, and I believe this paper is ready for publication, pending minor revisions.

Specific Comments

Major Comments

Insufficient edits were made to address the concerns I had about clarity and consistency of syntax in the first review. Please address syntax and copyediting issues throughout. I have specified several suggested edits in the *Minor Comments*, but this paper needs a thorough copyediting review by the authors or a paid service. Moreover, I saw that there are still many places where British English is used rather than American English. This should be a relatively easy change to make via MS Word. For example, "analyz-" should be used in lieu of "analys-" (except in the case of the word "analysis"), "maximise" should be "maximize," "optimize" should be "optimize," and in the US context, we use "-er" in lieu of "-re" (eg, patient-centered).

Minor Comments

1. This sentence is confusing; it needs to be made more concise or broken into two sentences instead of one:

Actual: For example, the lack of data on people who are living with HSV but not developed symptoms calls to specific need to collect data outside of clinical settings from populations who have not developed symptoms and are not motivated to complete extensive data collection forms, therefore requiring non-intrusive and time-efficient methods to reliably identify high-risk groups.

Suggested: For example, the lack of data on people who are living with HSV but have not developed symptoms requires collecting data outside of clinical settings from populations who may not be motivated to complete extensive questionnaires or, worse, take offense at being asked to do so. Therefore, nonintrusive and time-efficient methods are necessary to reliably identify high-risk groups.

2. *Actual*: One type of decision support model, decision trees, can be applied to analyse the flows of user-generated content and to determine the strategy that is the most efficient and the most likely to be successful means of achieving a certain goal.

Suggested: One type of decision support model, decision trees, can be applied to analyze the flows of user-generated content, and to determine the strategy that is most efficient and most likely to successfully achieve a certain goal.

3. *Actual*: The ArthritisPower registry platform also proved a more effective means of engaging patients with research and enabling patient-generated data capture, however is limited to users who had been already diagnosed and are actively motivated to participate. In addition to increased patient engagement with research, the growing focus on patient-centred care has resulted in an increased place for patient reported outcomes in clinical care and research, and are a key component of patient registries.

Suggested: The ArthritisPower registry platform has proved to be an effective means of engaging patients to participate in research and enabling patient-generated data capture; however, the registry is limited to users who have already received a physician diagnosis and are actively motivated to participate. In addition to increased patient engagement with research, the growing focus on patient-centered care has led to a new emphasis on the use of patient-reported outcome measures in clinical care and research, and PROs now constitute a key component of patient registries.

4. Each of the four challenges listed in the *Introduction* should begin with a shorthand label of the challenge to make it easier to read. For example:

1. Efficient use of data. Collecting sufficient and high-quality data...
2. Patient-centric design. To be usable and effective...
3. Selection bias...
4. Privacy concerns...

5. *Actual*: Similarly, the patient-centric design (the second challenge) requires the consideration of user expectations such as ease of completion, avoiding, where possible, a significant effort, both mental and physical, which also can contribute to improve the selection bias (challenge three), by, for example increasing completion rates by those less motivated or having less capacity.

Suggested: Similarly, a patient-centric design (challenge 2) requires consideration of the user experience, which includes minimizing participant burden. This may also ultimately reduce selection bias (challenge 3) by increasing completion rates.

6. *Actual*: Therefore, this project is aimed primarily at addressing the challenges of long, time-consuming questionnaires with many sensitive questions for creating a prediction model that would reliably assess whether a particular person has an increased risk of HSV. We have explored the applications of innovative machine learning methods for optimizing the question list while maintaining high quality and relevance of the collected data.

Suggested: Therefore, this project is aimed primarily at addressing the challenges associated with time-consuming questionnaires containing sensitive questions by creating a prediction model to reliably assess whether a particular person has an increased risk of HSV. We explored the applications of innovative machine learning methods in order to optimize the questions asked of participants, while maintaining the high quality and relevance of collected data.

7. *Actual*: For the future studies, it is suggested to integrate this approach with privacy-preserving and trust-enabling solutions to strengthen all four of the areas.

Suggested: For future studies, we suggest integrating this approach with privacy-preserving and trust-enabling solutions to more comprehensively address the four challenges described above.

8. *Actual*: In the current study we design and test an algorithm that follows steps 1-7. The step 8, the improvement of precision as the result of integration within the live data collection system, is intended as a direction for the future work.

Suggested: In this study, we designed and tested an algorithm that follows steps 1 to 7. Step 8, improvement of precision via integration with a live data collection system, is intended as a direction for future work.

9. *Actual*: Researchers will be able to use the registry to complement clinical research and facilitate patient recruitment for clinical trials. Researchers will need to register, be verified by the system administrator, and login to their account before accessing pseudo-anonymized data, that is the data that underwent procedures to remove personally identifiable information and is anonymized, where however the links to the original personal data are preserved.

Suggested: Researchers will be able to use the registry to complement clinical research and facilitate patient recruitment for clinical trials. Researchers will need to register, be verified by the system administrator, and login to their account before accessing pseudo-anonymized data (ie, data where personally identifiable information have been removed, but links to the original personal data are preserved).

Conflicts of Interest

None declared.

Reference

1. Surodina S, Lam C, Grbich S, Milne-Ives M, van Velthoven M, Meinert E. Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study. JMIRx Med 2021 Jun 10;2(2):e25560 [FREE Full text] [doi: 10.2196/25560]

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Peer-Review Report

Peer Review of “Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study”

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Companion article: https://med.jmirx.org/2021/2/e25560/

(JMIRx Med 2021;2(2):e28922) doi:10.2196/28922

KEYWORDS

data collection; herpes simplex; registry; machine learning; risk assessment; artificial intelligence; predictor; risk

This is a peer-review report submitted for the paper “Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study.”

Round 1 Review

General Comments

The authors of this research [1] discuss a platform containing a random forest classifier applied to the medical reports of patients suffering from the herpes virus. The manuscript describes an introduction to the proposed topic, the problem the authors intend to solve, the solution, and a discussion. Although the research seems interesting, the manuscript has some weaknesses that the authors must resolve.

Specific Comments

Major Comments

1. Authors should read the authors’ guidelines at https://www.jmir.org/content/author-instructions. I suggest that they adapt their manuscript to the templates offered by JMIR; the title does not match the format proposed by the journal, the appendices do not have a caption, the tables can go in the manuscript, etc.
2. In relation to the content of the manuscript, there is no exhaustive bibliographic review in which existing studies applied to a classification problem such as the one the authors present are mentioned. Because of this, the justification for the development they propose is quite weak and can be improved upon.
3. Authors indicate that they separated the data sets by *train_test_split*; however, there is no clear description of the content of these two data sets. It is not known whether the classes are balanced or not, and no data preprocessing was done to ensure that the generated model is optimal for any type of data. Authors should indicate if they have done a cross-validation when training their model or not. If not, I recommend that they do it.
4. It would be enlightening to show the matrix of confusion as well as to indicate in a table a comparison of the measures of precision and accuracy on random forest with different hyperparameters.
5. To search for the best hyperparameters, I suggest using GridSearchCV or similar.
6. Finally, it is necessary to make a comparison between the proposed model and others that already exist.
7. Authors are requested to upload their code and the models to a repository to guarantee their reproducibility.

Round 2 Review

I thank the authors for their work in improving this manuscript. They have responded correctly to all my suggestions, and I consider that the manuscript has improved in quality and can be considered for publication in this journal.

Conflicts of Interest

None declared.

Reference

1. Surodina S, Lam C, Grbich S, Milne-Ives M, van Velthoven M, Meinert E. Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study. JMIRx 2021 Jun 10;2(2):e25560 [FREE Full text] [doi: 10.2196/25560]

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Authors' Response to Peer Reviews

Author's Response to Peer Reviews of "Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review"

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Companion article: https://med.jmirx.org/2021/2/e27254/

(JMIRx Med 2021;2(2):e28744) doi:10.2196/28744

KEYWORDS

COVID-19; SARS-CoV-2; test and trace; universal testing; mass testing; contact tracing; infection surveillance; prevention and control; review

This is the author's response to peer-review reports for "Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review."

Round 1 Review

Editor: We are very grateful for your valuable comments in improving this manuscript [1] so that it meets the required standard. We read every comment with much interest and addressed them accordingly. Given that our manuscript was a transfer version from a preprint server, we did not have the chance to comply with the editorial guidelines. We note that your comments, most of which were already addressed in the initially revised manuscript, have permitted us to further improve on our work. We thank you for the immense input and expertise.

1. All in-text references have now been corrected in addition to previous corrections.

2. Footnote changes were already made in the initially revised manuscript.

3. All URLs were already updated and cited in the revised manuscript.

4. We have modified the design in the title, from "rapid review" to "systematic review."

5. The corresponding author has now been listed as recommended.

6. All major headings were already updated.

7. Subheadings were already updated as recommended.

8. We already verified that each section had at least two subsections in the initial version.

9. We have slightly modified the *Methods* subsections to mirror those in the *Results*. Each *Results* subsection, notably *Search Results*, *Methodological and Risk of Bias Assessment*, *Synthesis of Results*, and *Interstudy Variability*, has been explained in the *Methods* section under *Database Search*, *Data Quality Assessment*, *Standardized and Synthesis Metrics*, and *Heterogeneity Assessment*, respectively.

10. The reporting of *P* values has been updated with the correction of a few errors.

11. Multimedia appendices were already inserted as recommended in the previous version.

12. We have now included a statement on the study aim to wrap up the introduction.

13. A summary of findings under *Discussion* was already included.

14. Lengthy tables were already moved to the multimedia appendices section according to the guidelines.

15. The abstract was already structured according to the guidelines.

16. The results in the abstract were already fleshed up in the initially revised manuscript.

17. The references were already cleaned up in the previous version of this manuscript.

18. Percentages have been restricted to 1 decimal place and expressed in absolute values.

19. The issue of numbered headings was already corrected in the initially updated version.

20. Tables were already placed where they needed to appear in the body of the text.

21. We have cited a few more scholarly articles (some from JMIR Publications) as recommended.

22. All field codes were already removed in the previously updated manuscript.

23. Invented abbreviations were already taken care of in the previous version.

24. Not applicable to this study.

25. Not applicable to this study.

26. Tables were already modified, following the guidelines, in the previous version.

27. All figures and tables have been edited and uploaded to reflect these changes.

Response to Reviewer H

General Comments:

Reviewer H [2]: We are amazed by your outstanding comments and attention to detail. We cannot thank you enough for your expert knowledge and encouraging words. Your efforts in bringing this manuscript up to standard for better readership are highly applauded. We are happy to say that we agreed with all the comments and are pleased to submit a revised version.

Specific Comments:

1. The *Research in Context* section has been sized down.

2. The section on definitions has been removed.

3. The *Data Extraction* section has been modified accordingly.

Major Comments

1. We thank you for highlighting this. We have truly improved on the work further.

2. The review in question was cited in the *Discussion* section. However, this has now been updated.

3. Thank you very much for the valuable compliments.

4. Your comments on outcomes are very pertinent. Outcomes were defined as part of the PICO (population, intervention, comparison, and outcome of interest) statement. As a result, we have moved this to the section on eligibility criteria.

5. The section *How the Intervention Should Work* has been moved and modified as suggested. The objectives and outcomes subsection has been modified as recommended.

6. The safe nature of the mass testing and tracing program has been emphasized.

Minor Comments

1. We have verified that a full stop has been applied to each paragraph.

2. The grammar has now been reviewed; thanks for the suggestion.

3. We have included a statement for the column regarding vote counts.

References

1. Mbwogge M. Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review. JMIRx Med 2021 Apr 12;2(2):e27254 [FREE Full text] [doi: 10.2196/27254]
2. Roy A. Peer Review of "Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review". JMIRx Med 2021 Apr 12;2(2):e28719 [FREE Full text] [doi: 10.2196/28719]

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Authors' Response to Peer Reviews

Author Response to Peer Reviews of "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation"

Shannon Cerbas[1,2], MSc; Arpad Kelemen[2], PhD; Yulan Liang[2], PhD; Cecilia Sik-Lanyi[3], PhD; Barbara Van de Castle[2], DNP

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Companion article: https://med.jmirx.org/2021/2/e20461/

(JMIRx Med 2021;2(2):e28334) doi:10.2196/28334

KEYWORDS

cancer; mobile app; gamification; bone marrow transplant; alpha testing; physical activity

This is the authors' response to peer-review reports for "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation".

Response to Round 1 Reviews

The authors of the manuscript [1] are grateful to the editor and reviewers [2,3] for their invaluable input and feedback.

Response to Reviewer P [2]

Specific Comments

Major Comments

Introduction

1. Agreed, this was changed.
2. Agreed, this was changed.
3. This was added.
4. This population varies between inpatients and outpatients so an app for this type of varied use is appropriate. A discussion was added.
5. We agree. New discussion points were added.
6. Yes, continued game play requires walking a clinically set number of steps. We further explained this in the updated manuscript.

Methods

1. We changed the text from "user-centered design" to "we focused on the intended users." We achieved this by (1) collecting data from the intended users about games they already enjoy, and we chose Candy Crush as a template for our game design; (2) a survey of clinical nurses who worked with the target patient population to tailor the game to the intended users; (3) evaluation of the game and step counter by nurses, some of whom worked with the target population; and (4) the project is scheduled to be played by the intended users to collect data from them for future changes.

2. We added discussion points on this.
3. Hierarchical cluster analysis and exploratory factor analysis are quantitative analysis methods. We added more details about this in the *Methods* section. The results and interpretations are included in the *Results* section.

Results

1. We added more information about the characteristics of the study sample.
2. There are no known normative values.
3. We moved this to the *Methods* section.

Discussion

1. While this would be an additional important topic to cover, the review we received from the journal states that this paper is already too long and we need to reduce the word count, which we agree with. It would be a lot of new content to add, with only marginal relevance and little benefit for this paper. Therefore, we prefer not to add other studies to the *Discussion* section at this time. We discussed some other related studies in the *Introduction* section.

Response to Reviewer V [3]

General Comments

1. We added more details about this.
2. We added more about the planned patient testing. Impact on walking behavior is a long-term goal. The past work that we report on in this paper is heavy on expert testing.
3. Thank you for pointing this out. The decision to release the game to the public is not a current consideration of this project. We are far from that decision. We need to administer it to our patients first, then analyze that data. We replaced the release part with the walking behavior test part since that should happen first.
4. We added text on the issues raised. Since the paper is already too long, maybe adding another figure is not needed.

Specific Comments

Abstract

1. We have made the changes accordingly.
2. We changed the paper to make this clear.

Introduction

1. Added.
2. We made the changes accordingly.
3. Age and Android smartphone ownership were added. We are targeting all of these patients in the clinical setting.

Methods

1. Added.
2. We made the changes accordingly.
3. Emails were removed.
4. Thanks for asking this. Yes, goal setting on walking is done by clinicians. We coded that into the frequency and number of steps needed to play the game. Self-monitoring and feedback are done through the online database we discussed. We have now added these aspects to the paper to clarify.
5. The purpose and the software used to conduct analyses were added in the *Methods* section. We made some changes and additions to the paper.
6. Thank you for pointing this out. We made these changes.

Discussion

1 and 2. Yes, these are all good points. We responded to each of these comments in the responses above and in the paper.

Response to Round 2 Reviews

Reviewer P [2]

1. All references to hypotheses were removed. However, note that testing those hypotheses are long-term objectives of this project that reach well beyond the scope of this paper and beyond our current programming and evaluation objectives.
2. Changes were made as suggested.
3. Discussion of this limitation was added as requested.
4. It was revised to remove ambiguity. The potential opportunities for improvement are already discussed in the paper. These include improvements to each of the 40 items surveyed in the expert usability evaluation; improvement on the step counter's accuracy, robustness, cheat proofing, the game's speed, movement of tiles, graphical appearance, "pause" and "back" buttons; the addition of a tutorial and other features; ease of use; optimizing for phone battery drain; developing our own open-source step counter; developing a separate step counter for iPhones and making the game compatible with iPhones; coding to exploit different hardware technologies; designing and developing artificial intelligence and machine learning algorithms to improve the step counter; training and fitting the step counter to individual users; usability improvements; bug fixes; user-driven modifications; changing the frequency and amount of steps for individual users; optional release of scores for public view, competitions among users, social community building; adjusting the game per HSCT patients' feedback and recommendations; extending the project to a rigorous evaluation that includes feasibility, acceptability, patient walking behavior, and comparison of physical activity between Walking Warrior users and nonusers; and measuring impact on walking. These are all the major improvements our team can think of at this time.
5. Evidence was added.
6. Done.
7. Please see the newly added explanation and commentary in the *Results* section regarding the score differences. We also discussed this limitation in the *Discussion* section.
8. We made some changes and added more explanations.
9. Done.

References

1. Cerbas S, Kelemen A, Liang Y, Sik-Lanyi C, Van de Castle B. A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation. JMIRx Med 2021 Apr 13;2(2):e20461 [FREE Full text] [doi: 10.2196/20461]
2. Robertson MC. Peer Review of "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation". JMIRx Med 2021 Apr 13;2(2):e28649 [FREE Full text] [doi: 10.2196/28649]
3. Fisher A. Peer Review of "A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation". JMIRx Med 2021 Apr 13;2(2):e28339 [FREE Full text] [doi: 10.2196/28339]

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions"

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Companion article: https://med.jmirx.org/2021/2/e21269/

This is a corrected version. See correction statement: https://xmed.jmir.org/2021/2/e29878

(JMIRx Med 2021;2(2):e28893) doi:10.2196/28893

KEYWORDS

COVID-19; testing strategy; skew-normal distributions; lockdown; forecast; modeling; outbreak; infectious disease; prediction

This is the author's response to peer-review reports for "COVID-19 Testing Strategies and Lockdowns: The European Closed Curves, Analyzed by Skew-Normal Distributions, Forecasts for the United Kingdom, Sweden, and the United States, and the Ongoing Outbreak in Brazil."

Round 1 Review

The author of the manuscript [1] is grateful to the editor and reviewers [2,3] for their invaluable input and feedback.

Response to Reviewer D

We thank the reviewer [2] very much for their positive report. As suggested, we have corrected the typos in the main text.

Response to Anonymous

We thank the reviewer [3] for their comments. The main purpose of this paper was to prove that massive testing strategies are probably the best choice for managing the COVID-19 pandemic. This was clearly demonstrated in section II where the pandemic in Germany and Italy was analyzed. As observed by reviewer D, "the statistical analysis is quite enlightening, showing how the available data should be interpreted and used to improve health systems' response to the crisis and explaining why the working strategies of countries like Germany and South Korea are so effective." The mathematical points of this paper enabled us to predict the peak by a dynamical analysis, as shown in Figure 9, and the end of the outbreak by using skew-normal distributions. In our conclusions, we have added a discussion on these aspects to satisfy your suggestions.

Round 2 Review

We thank the reviewer [3] for their suggestions and observations. Below we list responses and changes done in the revised version.

1. In the revised version, the table in section II, where we introduce the effectiveness factor (EF), is now labeled A and has a legend. The three tables in section III were reduced to two tables (B and C), and now appear with their corresponding legends. These tables are important to justify our discussion on the different testing strategies adopted by Italy, Germany, the United States, and Brazil, and show how the effective testing strategy of the German authorities made a great difference compared to Italy.
2. In the revised version of the manuscript, we, following the suggestions of the reviewer, added in some sentences on interpretation in the *Abstract* section: "The massive testing strategy adopted, in the early stage of the disease, by German authorities made a great difference with respect to other countries, in particular with respect to Italy, where an effective testing strategy was adopted too late. This explains why, despite a strictly indiscriminate lockdown, the mortality rate was one of the highest in the world."
The *Introduction* section of the revised version now begins with: "In this paper, by analyzing in detail the testing strategies of the German and Italian authorities, in the early stage of the COVID-19 disease, and fitting the pandemic curves by skew-normal distributions (this allows us to compare the outbreak spread in different European and American countries by mathematical parameters), we show how massive testing strategies are more effective than strictly containment measures (full lockdowns) adopted by some countries."
3. Following the suggestions of the reviewer, in section III, we shortened our mathematical discussion.

Conflicts of Interest

None declared.

References

1. De Leo S. Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions. JMIRx Med 2021 Apr;2(2):e21269 [FREE Full text] [doi: 10.2196/21269]
2. Maia G. Peer Review of "Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions". JMIRx Med 2021 Apr;2(2):e28681 [FREE Full text] [doi: 10.2196/28681]
3. Anonymous Reviewer. Peer Review of "Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions". JMIRx Med 2021 Apr;2(2):e28743 [FREE Full text] [doi: 10.2196/28743]

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series"

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Companion article: https://med.jmirx.org/2021/2/e25204/

(JMIRx Med 2021;2(2):e29608) doi:10.2196/29608

KEYWORDS

pediatrics; appendectomy; spinal anesthesia; general anesthesia; laparoscopy; vomiting; keyhole; surgery; anesthesia; appendix

This is the authors' response to peer-review reports for "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series."

Round 1

The authors of the manuscript [1] thank the editor and the reviewers [2-4] for their valuable comments and suggestions to improve the paper. We have substantially modified the manuscript to address the issues raised. We will address them individually.

Anonymous [2]

Specific Comments

Minor Comments

1. We have changed the wording in the *Abstract* and *Introduction* sections.

2. We have addressed this and moved the descriptive statistics table to the *Results* section.

3 and 4. We have significantly modified the results and their presentation. The mosaic plots in the figures have been replaced with tables with *P* values from the Fisher exact tests for all comparisons. We have also now included odds ratios for these with upper and lower confidence levels (95%). We believe this adds to the robustness of the statistical analysis while enabling the written description of the results to follow with more brevity. We believe it is easier to read.

5. We have deleted this part as we agree it is a bit ambiguous.

Anonymous [4]

General Comments

1. The groups were similar in age and gender.

2. Yes, the presence of postoperative nausea or vomiting was a binary response.

Specific Comments

Major Comments

We agree that the attempts to correlate pain scores with anesthesia were going to be confounded by the analgesics, which is why we had those figures as supplemental material. However, this was described in the manuscript proper, which we have since removed (and the supplemental figures as well).

We have left the incidence of vomiting as a measure of patient comfort in the paper. It was our goal to compare the two procedures (spinal vs general anesthesia), and by procedure, this includes the usual standard-of-care protocols for each anesthetic. Naturally, it would have been better if the exact same protocols could have been used during the administration of both anesthetics, but that is not possible. Even if the vomiting is largely a result of nitrous oxide use in the general anesthetic, that could be a good enough reason to use spinal anesthesia all by itself. Our results verify this. Additionally, there is evidence that this nitrous oxide effect is mostly predominant in longer procedures. According to Peyton and Wu [5], a "duration of exposure to nitrous oxide less than 1h has little effect on the rate of postoperative nausea and vomiting." The maximum operation times in our study were ~45 minutes.

Minor Comments

1. A native English speaker has reviewed and made further copyediting changes.

2. The currency (Bangladesh taka) has now been listed in the text and along the figure axis title.

Round 2

Further Editorial/Peer-Reviewer Comments

The study has been labeled a "case-series report" as advised.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation"

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KEYWORDS

COVID-19; learning health systems

This is the authors' response to peer-review reports for the paper "Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation".

Round 1 Review

The authors of the manuscript [1] thank the reviewers [2-5] for their comments. In addition to making changes in response, we have also updated the paper in various places given the changing nature of the pandemic and the response to it.

Reviewer A

General Comments

The *What Can Be Done?* section has been rewritten with much more detail.

Specific Comments

1. Thank you for your suggestion. Details on procedures for data collection and processing will be very dependent on the characteristics of each health system and the data routinely collected for clinical care, so it will be difficult for us to suggest here a particular system. However, in point 2 of the *What Can Be Done?* section, we have added some points that any health

system should consider when planning the data collection strategy.

2. Thank you for the suggestion; we actually asked some expert colleagues informally for their opinion on a possible data structure, and we received different answers (more or less overlapping in some variables). We realized that defining the data set is a task that should be done by an expert panel considering not only the disease but also the characteristics of the health system that will collect the data and the cost/benefit of collecting each piece of data. We have now elaborated on this idea in point 1 in the *What Can Be Done?* section.

3. "Immediately used for data collection" is a relative term as any platform would have to be adapted to the decided data structure. There are many tools out there with different degrees of adaptability, but the point here is to use as much as possible the existing health information systems in place to extract the data and create feedback loops to the health care system, rather than setting up separate platforms.

4. Automatic data processing is not a problem of software. Any modern statistical software can be programmed to repeat data processing of analytical routines. The key issue is to decide what to analyze and with what statistical models. The statistical experts will define the models needed to answer the questions asked by the medical/epidemiological experts.

Reviewer L

Specific Comments

Major Comments

1. Thank you for the suggestion; we have tried to improve this, including adding some more citations.

2. Thank you for highlighting these interesting points. We have internally discussed the idea of *who* should be coordinating the international effort to combine data and analysis and we largely agree with it. However, we feel that exceeds the scope of our original aim for this paper—to highlight the missing opportunity of implementing learning health system within health care systems and taking it to the next level of international coordination of health learning systems.

About the funding, that will depend very much on the kind of health systems and even the society where the health system is embedded, and we cannot comment on each case separately. For example, in the countries where the authors work and live, the health systems are mainly publicly funded, and we would expect the competent public authorities to make that funding effort just as they did with the extra effort for medical care during the pandemic. Other systems might have to find other resources. In any case, one needs to consider this as an investment because the earlier we learn to effectively manage the pandemic, the more we can reduce costs in the long run.

3. We do not really know the answer to this certainly very important question, but we believe it is complex enough to require a separate piece of research. For the problem that we are trying to address here, about implementing health learning systems, we must assume that each system will try to find the most up-to-date and "reliable" scientific information available at the time. We understand that the most recent information could be incomplete and possibly unreplicated so far. So, the learning health system should be constantly revised and updated as new solid information is made available. We have added a new point 8 in the *What Can Be Done?* section discussing this issue.

Anonymous [4]

1. Thank you for the comment; we certainly do not try to predict how information on the pandemic will evolve in the future. We rather try to denounce how the opportunity has been missed to implement a useful, responsive health information system embedded in the health care system.

2. Thank you for the comment. Because the paper is not a typical research paper with an introduction, methods, results, discussion, etc, we found it difficult to follow a similar structure in the abstract. However, we have revised the abstract to clarify the purpose of the research in its final paragraph.

3. Thank you for the comment. We do not have an *Introduction* section as such, but we have split this into 2 sections, *The Problem* and *What Do We Need to Solve the Problem?*, which we believe address the purpose of this paper.

4. Because the paper is not a typical research paper, we do not have an *Introduction* section as such.

5. Thank you for the references. They look very relevant for a discussion on public policies to tackle the pandemic. We are not sure how to fit them in our paper, which focuses on learning health systems, but we will consider them in future works.

6. Thank you for the comment. Because the paper is not a typical research paper, we found it difficult to follow a typical structure in the *Conclusion* section. However, we have added some sentences at the beginning and a final sentence to address your points.

Anonymous [5]

Specific Comments

Major Comments

1. Thank you for the suggestion. We actually asked some expert colleagues informally for their opinion on a possible data structure, and we received different answers (more or less overlapping in some variables). We realized that defining the data set is a task that should be done by an expert panel considering not only the disease but also the characteristics of the health system that will collect the data and the cost/benefit of collecting each piece of data. We have now elaborated on this idea in point 1 of the *What Can Be Done?* section.

2. Thanks for the comment. In the section *What Is Being Done?*, we did include references to some initiatives that were taken to collect and analyze COVID-19 clinical data. There are, of course, many more, but it is not the aim of this paper to review them. We included some points discussing the shortcomings of many of these systems, mostly independent from actual health care systems. We have now included references to some initiatives at the national level (most notoriously one in the

United Kingdom) but note that we still fall short of the concept of the learning health system that we propose.

3. Yes, we can see your point, although we regard electronic medical record (EMR) vendors as service providers who do not actually own the data or the right to exploit it. We believe this to be the situation at least in Europe where the data mostly "belong" to the institutions providing the health services (in the sense that they are the "data controllers" under GDPR [General Data Protection Regulation] regulations). We are assuming that is up to these institutions to decide what data they collect, process, analyze, and share, and we view EMR vendors just as companies providing software support. Maybe in other countries the situation is different. To discuss all these different situations will make the paper too long and probably deviate from the main message of implementing learning health systems integrated with health care systems. Maybe one can consider EMR vendors as an element of the "health care system" in general with a role to play in implementing the learning health systems.

Round 2

Reviewer L

Specific Comments

1. Thank you for your comment. We acknowledge that more references could have been provided. On the other hand, we would not want to overload the reader with references for points that are quite well known to the public, such as the situation of the pandemic and the actions of many countries to tackle it, that we mention in the first paragraph. Regarding point 7, this proposition is of a speculative nature rather than affirmative. We have not verified it with data; we have just derived it from the logic that the more appealing a given resource is, the more demanded it will be by the potential beneficiaries of its use and the more likely that a bottleneck will be created if the access points to that resource are kept at a constant capacity of delivery. Certainly, these bottlenecks would be ameliorated if the capacity to deliver that resource is improved to keep up with the demand, and we have included this idea by adding the following sentence "(unless more resources are put into place to deal with the requests)."

2. In the third paragraph of *The Problem*, we mention some limitations of the epidemiological data. Epidemiological data are very valuable for monitoring the epidemic and deciding on public health measures but are more limited for understanding the risk factors for getting infected and for predicting the prognosis of patients or their response to treatment. Epidemiological data might provide the distribution of cases by age groups, gender, ethnicity, etc, but they provide limited information on the combinations of these risk factors. If we want to combine the distribution of several risk factors (eg, sex, age, ethnicity, socioeconomic status, previous comorbidities, etc), it is unlikely that the epidemiological reports will provide this. Another limitation is that continuous variables such as age, BMI, blood pressure, and respiratory rate are categorized to produce report tables, and the usefulness of the variable is reduced. Also, epidemiological reports normally do not include parameters collected in hospitals during the progression of the disease that could be critical for creating prognostic models to predict which patients would benefit more from what treatments. We have included some sentences clarifying these limitations in that third paragraph.

3. A critical point to solve a research question with a learning health system is to find suitable cases. The learning health system would check every new patient in the system to see if they match the research question criteria to be included. A health system implemented only at one center will answer the question with enough certainty when enough patients have been recruited at that center. Noncoordinated health systems implemented separately at different centers will take as much time to get to an answer, but if they were coordinated and share data pertaining to new, valid patients, then they will be closer to answering the question.

4. Our point is precisely that at the moment current practices do not implement what we call a health system as defined in our references 3 and 4. We have tried to illustrate in the section *The Problem* the failure to answer the most pressing clinical questions even after having millions of cases, hundreds of thousands of deaths, and vast amounts of epidemiological data. This failure is in itself a manifestation of the lack of a health learning system (we are not learning fast enough). In section *What Can Be Done?*, we provide some examples of the innovative initiatives taken to tackle this problem, but we also argue why they fall short of being a health learning system. In this section, we propose the characteristics of what we would consider a learning health system, which can be summarized as:

1. An organizational architecture that facilitates the formation of communities of patients, families, front-line clinicians, researchers, and health system leaders who collaborate to produce and use big data;
2. Large electronic health and health care data sets (big data);
3. Quality improvement for each patient at the point of care brought about by the integration of relevant new knowledge generated through research;
4. Observational research and clinical trials done in routine clinical care settings.

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Abbreviations

EMR: electronic medical record
GDPR: General Data Protection Regulation

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

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KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

This is the authors' response to peer-review reports for "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?"

Round 1 Review:

Reviewer B:

General Comments

Thank you very much for your comment [1]. In this case, the paper [2] is a viewpoint and not an original research article. Its main objective is to raise important cybersecurity issues for further discussion and improvement that had not yet been raised in the research literature (as of May 2020). Therefore, there are no new identified issues or results to provide at this stage, but we provide more awareness and the ability to reach different stakeholders and the population in general. Indeed, no new or novel cybersecurity issues were found, but we discuss the exacerbation of already existing issues due to the pandemic, which do not yet have proper solutions. Finally, as mentioned in the submission, this was a summarized version of another research paper (at the time still under review) which has since been accepted for publication in conference proceedings [3]. This full research paper, which obtained the Best Paper Award, was also added to the References section of the viewpoint for more details and completeness. Also, a new sentence ("More details on the background research that was performed as a basis to this viewpoint can be found here [3].") was added at the end of the introduction to make readers aware early in their reading that more details can be found in that reference.

Specific Comments

Major Comments

1. Thank you very much for your comment. Due to the aim of this viewpoint, it was not possible to further extend the discussion to all the presented subjects. However, the authors opted to focus on the message they wanted to give in all of them. In the case of contact tracing apps, the main point the authors wanted to make is that there are still many security and privacy issues that are not yet well defined and understood. These need to be addressed first in order to ensure that these apps can be used in the most private, secure, and useful manner. Comparing and discussing how various countries and cultures worldwide are adopting this technology and adapting it to their reality was not a goal of this viewpoint, although the authors see how interesting and relevant this topic is. Nevertheless, this could also enter the realm of ethical, political, social, cultural, and humanitarian-related subjects, which could not be well addressed in this very short and general document.
2. Thank you very much for your comment. As mentioned in the previous answer, the authors could not discuss every single cybersecurity issue in this viewpoint. Furthermore, the subject you refer to does not seem to be directly related to the aim of the document or to COVID-19.

Minor Comments

Thank you very much for your comment. Corrections have been made accordingly.

Anonymous [4]

General Comments

1. Thank you very much for this comment [4]. The editor's comments and requirements will certainly be taken into account.
2. Thank you very much for this comment. In fact, with the aim to provide the most recent references, and to focus on a broad topic such as cybersecurity in a viewpoint, it was not possible to refer to many technical aspects because this would not be feasible in such a short document. However, in the revised version of this viewpoint, there are at least 8 references (24%) that focus on the most common issue on the literature at the time (May 2020)—contact tracing apps—which are certainly related more to technical security and privacy content. Moreover, as mentioned in the submission, this viewpoint is a summarized version of another research paper (at the time still under review), which was then accepted for publication in conference proceedings [3]. In this full research paper, a literature review returned only 18 scientific documents, of which only 10 were full articles that aimed to discuss challenges and concerns related to cybersecurity and COVID-19 at the time (May 2020). The paper, which received the Best Paper Award, was also added to the reference list of this viewpoint to provide more details and completeness. A new sentence ("More details on the background research that was performed as a basis to this viewpoint can be found here [3].") was also added at the end of the Introduction section to quickly refer interested readers to more details. In conclusion, this viewpoint was written with the goal to simply and quickly reach a variety of stakeholders (in multidisciplinary fields) as well as the general population, so its content could not be too specific or too technical. Finally, no new or novel cybersecurity issues were found, but we discussed the exacerbation of already existing issues due to the pandemic, which do not yet have proper solutions.

Specific Comments

Major Comments

1. Thank you very much for this comment. At the moment when this viewpoint was written (May 2020), there were still few studies available in the literature that focused on the cybersecurity issues closely associated with or exacerbated by the pandemic, and those that existed focused on specific issues such as contact tracing apps and the issues involved in sharing data to further research and understand the evolution of the pandemic; however, very few studies addressed other issues that were more consequential or indirect challenges that were more hidden, such as physical security, remote cybersecurity, or the increase of social engineering attacks. Although these topics were at times mentioned in the news/media, there was no comprehensive list of the many issues involved or any attempt to categorize them. With a keen interest in cybersecurity, the authors realized that such a viewpoint, submitted to a well-reputed and well-known scientific journal, could be a useful means to reach a wider audience, not only in cybersecurity and health care but also in other areas. The goal was not to send a "new message" but to bring to light more hidden issues that were not yet thought of but that still need to be stressed, with the aim of developing new, quick, and innovative solutions (eg, theft and fraud, physical security and cybersecurity, and privacy vulnerabilities and threats from working from home/homeschooling). Indeed, no new or novel cybersecurity issues were found, but we discussed the exacerbation of existing issues due to the pandemic, which do not yet have proper solutions.
2. Thank you very much for this comment. In the impossibility to provide an extended discussion on this relevant issue, a new phrase was added in the "Data Sharing" section, together with two references to support this subject: "Further, the lack of IT and cybersecurity literacy may make it harder for most individuals to adequately install and use those apps, which may, just by themselves, integrate several security vulnerabilities and risks [5][6]."
3. Thank you very much for your comment. Due to the aim of this viewpoint, it was not possible to further extend discussion on the presented subjects. However, the authors opted to focus on the message they wanted to give in all of them. In the case of contact tracing apps, the main point the authors wanted to make was that there are still many security and privacy issues that are not yet well defined and understood. These issues need to be addressed first in order to ensure those apps can be used in the most private, secure, and useful manner. Comparing and discussing how various countries and cultures worldwide are adopting this technology and adapting it to their reality was not a goal

of this viewpoint, although the authors see how interesting and relevant this topic is. Nevertheless, this can enter into the realm of ethical, political, social, cultural, and humanitarian-related subjects, which could not be well addressed in this very short and broad document. In addition, as the main cybersecurity literature at the time (May 2020) focused mostly on contact tracing apps, the authors wanted to bring the attention of the research community and the general public to other important cybersecurity and COVID-19–related subjects that were being neglected; therefore, the authors chose to aggregate more relevant issues, but unfortunately without leaving much space for detailing them in a viewpoint.

4. Thank you very much for this comment. Indeed, not all issues were introduced and discussed because this was not an original research paper but was based on another conference paper [3], so not all issues were covered/discussed equally. The authors needed to choose which issues to highlight in this viewpoint. However, the authors have included within the manuscript the following sentence, which highlights a similar issue: "Increased risky behaviours with individuals constantly online in all sorts of activities, using home/personal digital infrastructures and devices (not security-prepared), for different contexts, requirements and goals." at the end of the paragraph of the section *COVID-19, CYBERSECURITY, PRIVACY, SECURITY AND SAFETY*, which may also raise the issue identified by the reviewer.
5. Thank you very much for this comment. In fact, the authors referred to this very relevant issue in the viewpoint (in the section *COVID-19 AND CYBERSECURITY: DIRECT CONSEQUENCES*: "It is also very difficult to control de boundaries of the protocol itself, since many 'false positive contacts' can be obtained when Bluetooth and/or GPS signals can traverse walls, cars, etc, where individuals were not really in contact with someone infected, but may have walked past on the other side of those boundaries"), although not much detailed discussion was provided. As such, the authors felt it was relevant to complement this mention with additional text and references [7-9]:
"i) Bluetooth and/or GPS signals can traverse walls, cars, where individuals were not really in contact with someone infected, but may have walked past on the other side of those boundaries. In this case, the distance estimation may also change depending on the type or smartphone brand/protocols that are used as well as the environmental characteristics and context where they may be communicating with each other. There may be the need to adjust the way this is done according to the pandemic evolution. For instance, it may be safer to have higher false positives than high false negatives, especially if the virus is very contagious [7];
ii) real people misreport their symptoms;
iii) spoofing attacks of GPS coordinates to an app are very easily performed in apps with no authentication mechanisms [8]."
6. Thank you very much for this comment. Because it is impossible to provide an extended discussion on this relevant issue, a new phrase was added in the *Data Sharing* section, together with two references to support this subject: "Further, the lack of IT and cybersecurity literacy may make it harder for most individuals to adequately install and use those apps, which may, just by themselves, integrate several security vulnerabilities and risks [5][6]."
7. Thank you very much for this comment. When the authors wrote and submitted this viewpoint, very few references on this issue were available (May 2020). Due also to other reviewers' comments, several references were added and some replaced (references already used in the viewpoint were repeated in places where they were needed—the first paragraph of the *Data Sharing* section). References [10,11] were replaced, and references [7-9] were added.
8. Thank you very much for this comment. Due to the very insightful reviews of this viewpoint, it is obvious that it needs to be clear that this research document is a viewpoint, with viewpoint characteristics. As such, the authors altered the title of this viewpoint to reflect just that: "COVID-19, Cybersecurity and the Human Right to Privacy: A Viewpoint."

Anonymous [12]

Minor Comments

1. Thank you very much for this comment [12]. Indeed, the authors agree that the conclusion was too broad, and they have summarized the main points that need awareness and addressing so that at the end of the document, the readers will remain interested and will want to know more about those subjects. The added sentence is the following:

"This viewpoint is a crucial alert for the many cybersecurity issues that need proper and adequate measures, which have not yet had a voice in the existing literature, e.g.: i) research integrity and the need for a balance between anonymity and data quality; ii) hidden privacy and technical and non-technical issues related to contact tracing apps; iii) the pressure or stress in existing vulnerable and underbudgeted or obsolete healthcare infrastructures; iv) the exponential increase of social engineering messages (phishing and ransomware) during the pandemic time and the incapacity or inexistence for proper prevention, detection and recovery solutions; v) the pressure to manage the exacerbation of other health conditions with unsecure home-based virtual infrastructures with unaware patients; and vi) the same issues to deal with, when performing every other daily activities online, with the high exposure of both digital and physical entities with many impacts on privacy, cyber and physical security of the entire world population."

Anonymous [13]

1. Thank you very much for this comment [13]. All abbreviations were explained accordingly.
2. Thank you very much for this comment. This was corrected accordingly; because the references in the following sentence were also related to this one, the authors merged the two sentences and thus the references are clearly stated now.
3. Thank you very much for this comment. The authors agree with the reviewer on this subject; however, due to space

constraints and the paper being a viewpoint, it is not possible to make detailed discussions on this issue. However, the authors have introduced a last paragraph before the Limitations and the Conclusion section, in which they raise awareness of the fact that cybersecurity technology and solutions may exist but that they do not mean much if the human element (more or less knowledgeable) is not prepared. Training, research, and documentation are examples of ways to improve this knowledge; therefore, the following text and reference were added to the viewpoint:

"And finally, none of these recommendations will be enough if they are not complemented with objective, useful and accurate procedural data and documentation for the general public to adequately protect themselves. Since the majority of cyber incidents are human enabled there needs to be a shift to research underexplored areas of social and behavioral aspects of cybersecurity, to improve the current situation [14]. Cybersecurity literacy is essential, and even more, during pandemic times. One way to do this is by generating scientific research, such as this viewpoint, to raise awareness, provide recommendations and try new or improved solutions. Furthermore, training and awareness material needs to be personalized because users can have different understandings, experiences, backgrounds, motivations, and so on. The unpredictable nature of human behavior and actions make Human an important element and the main enabler of the level of cybersecurity each system can and will have [14]."

4. Thank you very much for this comment. The authors agree that this subject is very important in pandemic times, when people rely almost exclusively on the digital tools available to communicate. Therefore, the authors performed a query in several research engines but did not obtain much scientific data on how the European Union is addressing this issue; available work focuses more on specific studies from specific countries. Commonly, machine learning methods are being used and tested to improve misinformation detection. However, due to the relevance of this subject, the authors have added a sentence in which this subject is discussed, in the last paragraph on page 6, together with two references:

"Our representatives and the ones that are responsible to communicate and educate the public through news, media, social networks or similar means (which can quickly exponentiate these type of actions), need to be able to pass the correct message as misinformation and fake news can generate confusion and insecurity among the population [15]. Digital tools associated with the virus should not be used to perform political attacks, donation solicitations, business promotion, stock market advice, animal rights campaigning, bioweapons conspiracy theories, unverifiable claims by politicians or to sell face masks or other materials which may not necessarily protect the wearer [16]. The most important, in the end, is to enforce the message that, although with the appropriate care, security and safety measures, people need to be assisted and treated humanely and correctly, because the loss of one is always the loss of all, either now or in the future."

5. Thank you very much for this comment. Indeed, the authors agree that the conclusion was too broad; however, as this paper is a viewpoint and not an original article with new results or outcomes, the authors felt it was necessary to restress the main points they want the reader to remember and therefore have summarized them at the end of the document, so as not to be just a repetition of the abstract but also to take into account another reviewer's suggestion. The added sentence is the following:

"This viewpoint is a crucial alert for the many cybersecurity issues that need proper and adequate measures, which have not yet had a voice in the existing literature, e.g.: i) research integrity and the need for a balance between anonymity and data quality; ii) hidden privacy and technical and non-technical issues related to contact tracing apps; iii) the pressure or stress in existing vulnerable and underbudgeted or obsolete healthcare infrastructures; iv) the exponential increase of social engineering messages (phishing and ransomware) during the pandemic time and the incapacity or inexistence for proper prevention, detection and recovery solutions; v) the pressure to manage the exacerbation of other health conditions with unsecure home-based virtual infrastructures with unaware patients; and vi) the same issues to deal with, when performing every other daily activities online, with the high exposure of both digital and physical entities with many impacts on privacy, cyber and physical security of the entire world population."

6. Thank you very much for this comment. The paper has been edited accordingly.

7. Thank you very much for this comment. Although the goal of this viewpoint was not to detail any specific cybersecurity subject, and at the time of performing a review for the article [3] on which this viewpoint is based (May 2020), there were not enough studies in the literature to be able to understand the provided solutions, developments, and so on, the authors have included a limitation sentence to highlight this issue, and they have altered the title of the viewpoint to make sure readers understand that this document is just a summary to raise awareness of the subject and have stressed this in the *Conclusion* section. In fact, that article [3] was also included as a reference in the viewpoint for the possibility of providing more detail on this research to the interested parties.

"This viewpoint has some limitations. The fact that it is a viewpoint, with space constraints, and based on an original paper published in conference proceedings makes it harder to include more technical and detailed discussion about the introduced subjects and related recommendations. However, the main goal of this viewpoint is to summarize, raise awareness and reflect the opinions of its authors to contribute to a wider acknowledgement of the importance of cybersecurity, how it suddenly affects every human activity and the impact it can have on people's security, privacy and safety."

8. Thank you very much for this comment. The authors are very pleased to accept these suggestions and have added the mentioned references as relevant to the viewpoint references section, accordingly, with the numbers written at the end of each suggested reference, when applicable.

1. Added as [17]
2. Added as [18]
3. Added as [19]
4. No major focus on cybersecurity
5. No major focus on cybersecurity
6. Repeated above; added as [18]

Anonymous [20]

1. Thank you very much for your comment [20]. In this case, this paper is a viewpoint and not an original research article. Its main objective is to raise important cybersecurity issues for further discussion and improvement that had not yet been raised in the research literature (as of May 2020). Therefore, there are no new identified issues or results to provide at this stage, but more awareness and the ability to reach different stakeholders and the population in general. Indeed, no new or novel cybersecurity issues were found, but we discuss the exacerbation of already existing issues due to the pandemic, which do not yet have proper solutions. In addition, material has been scattered in the media and so on, but there was no single document to alert and provide a wider overview and awareness of the many cybersecurity issues directly and indirectly linked to COVID-19. Moreover, as mentioned in the submission, this was a summarized version of another research paper (at the time still under review) which was then accepted for publication [3]. This full research paper, which obtained the Best Paper Award, was also added to the *References* section of the viewpoint to provide more details and completeness. Also, a new sentence, "More details on the background research that was performed as a basis to this viewpoint can be found here [3]." was added at the end of the introduction to make readers aware early in their reading that more details could be found in that reference.
2. Thank you very much for your comment. Please refer to the previous comment and the response, which explains that the knowledge gap with the identification of the current state of the art at that time (May 2020) was identified within a published award-winning article on this subject, on which this viewpoint is based.
3. Thank you very much for this comment. At the moment of writing this viewpoint (May 2020), the scientific work to be found in this area was more limited. As such, it is possible that this work was not yet available or was still in press. However, in order to enrich and complete the referred work, the suggested reference was added as [9].
4. Thank you very much for your comment. In this case, this is a viewpoint and not an original research article, with space and content constraints for the wide subjects that the authors wanted to highlight. Its main objective is to raise important cybersecurity issues for further discussion and improvement that had not yet been raised in the research literature (as of May 2020); therefore, it is more generic and provides more qualitative descriptions. For more quantitative analyses, please refer to the research paper this work is based upon [3], a reference to which is also included in the viewpoint.

Round 2 Review:

Dear Editor(s), thank you for your comments and suggestions. I have responded below to the reviewers who still have some problems with the manuscript. Please let me know your decision as soon as possible. Kind regards, and thank you for the opportunity.

External Peer-Review Reports

Anonymous [4]

General Comments

Thank you very much for your comment. First of all, we want to remind the reviewer that this viewpoint was submitted in early June 2020, when not much related work was available and when this manuscript could have made a greater impact on society and the journal itself. Moreover, this work is based on a full paper that was already accepted for publication; therefore, as previously mentioned, it comprises a "typical" research method, such as that of a literature review, which at the time did not comprise many articles on the subject, but included an extraction, analysis, structure, and synthesis of the content of the revised articles. This is not described in the viewpoint because it would be a repetition of work (as previously mentioned). The main aim of this viewpoint was to extract the main issues found at the time on the subject, to make the scientific community and the general public think and be aware of these crucial aspects. However, this work is still very relevant 8 months later, and readers can be referred to the full accepted paper. Please see below extracts from the mentioned work [3], with more details on the undertaken methodology, which constitutes the basis of this viewpoint. I apologize for the formatting, but it is not possible to upload tables or figures in this space, so I also attached these at the end of the new uploaded manuscript as well:

"A literature review of the research performed in this area (Jan-May, 2020) was performed. Search queries were applied to research database engines, and works were reviewed by their titles and abstracts and repeated works were excluded. From the included works, a summary includes: Type of work (article, letter, comment, etc); Database engine; Direct/Indirect consequence from COVID-19; Main subject; Goal(s); Problem raised; and Proposed solution."

Queries used to search in the various databases and works included in the review (illustration of the methods performed in this work):

Database Query N found N included

*Scopus TITLE-ABS-KEY((security OR privacy OR confidentiality) AND (covid OR pandemic)) 82 10 + 1**

*Pubmed ((security OR privacy OR confidentiality) AND (covid OR pandemic)) 131 5 + 1**

Xplorer (security OR privacy OR confidentiality) AND (covid OR pandemic) 21 1

ISI TS=((security OR privacy OR confidentiality) AND (covid OR pandemic)) 33 0

ACM [[All: security] OR [All: privacy] OR [All: confidentiality]] AND [[All: covid] OR [All: pandemic]] AND [Publication Date: Last 6 Months] 9 0

*TOTAL 276 1 6 + 2**

Anonymous [20]

Thank you very much for your comment. First of all, we want to remind the reviewer that this viewpoint was submitted in early June 2020, when not much related work was available and when this manuscript could have made a greater impact on society and the journal itself. It is therefore normal that by now (almost 8 months later), there are many more studies about similar subjects, as this is still a very critical and essential topic (this work has been available as a preprint since June 2020 [21]). Moreover, the examples given by the reviewer are not from scientific publications but from websites. Nevertheless, the authors have altered the title to a more clean, unique one by removing the word "cybersecurity," namely, "COVID-19 and the Human Right to Privacy: A Viewpoint". Unless the work is altered in its essence and objective, making a more specific contribution was not the main goal of this viewpoint but, again, to "expose, as well as increase awareness and discussion of COVID-19 consequences to cybersecurity and healthcare."

Round 3 Review:

Further Editorial/Peer Reviewer Comments:

Dear Editor, thank you for your suggestion. Although a long time has already elapsed (7 months) since we first submitted the first manuscript of this viewpoint, we still think that the subjects discussed are as important now as they were then. However, the authors also agree that this viewpoint has the potential to propose some novel advances and perspectives that have not yet been considered and that were suggested by you. These can have more impact on the ways to address existing cybersecurity issues to foster a change in the current paradigm. Hence, this is what the authors have reviewed, within the manuscript, to consider your suggestion:

- The title has been changed to "COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?" in order to reflect the new changes proposed by the editors.
- The Abstract was edited to include objective arguments on what needs to be done to address current problems and raise the issue of how cybersecurity needs a change in paradigm, with or without a pandemic, according to the authors' perspectives and expertise in the area.
- At the end of the Introduction, there is a clear mention of the change of structure within the viewpoint.

Section 2, which enumerates the various cybersecurity challenges both directly and indirectly linked to the current pandemic, was left almost the same; however, for section 2.2.2, we provided a clearer description of the cybersecurity challenges ("Impact on privacy and physical integrity"). These challenges are raised in this part, and recommendations to address them are presented in a new section, "What needs changing in cybersecurity."

Section 3 was added to enrich the viewpoint with novel ideas and perspectives to contribute to advancing the discussion of cybersecurity as a whole discipline. This section introduces the idea that humanity can go back to "normal," but the authors stress the need for change in the way technology is thought of and how humans interact with it. Technology evolved much faster than humans could adapt in terms of how relationships and trust are established. The main perspectives provided by the authors are:

- The need for better and more adapted means to provide education and information technology literacy; moreover, now with constant mixed contexts and 24/7 web-based activities, there is not much time to process information. This needs to be more objective, intuitive and easy to grasp.
- As privacy and security are great challenges in human-computer interaction, technology design and development must focus on the pervasive line concept of all relations: trust. The authors discuss that trust needs to be properly studied and incorporated within technology development, as to date, there have been attempts to solve various pieces of the puzzle but not the real picture that needs to happen in the end. Therefore, existing solutions are clearly not enough. The authors also substantiate this perspective with recent literature supporting this subject.
- When trust is addressed, other related issues can be advanced. These include (1) better understanding of human behavior, personality traits, and victimization features, which are helpful to advance in social engineering studies; (2) extraction of trust/relation patterns, which can be useful to promote more personalized interactions as well as the identification of specific needs of users to foster more successful and trustable interactions; and (3) confident use of novel technologies such as high-fidelity digital humans as well as augmented reality to simulate the currently greatly needed contexts via videoconference (work, school, shopping, leisure, exercise, etc), with more control and integrated privacy features.

The previously provided perspectives require time and resources and may not be so quick to implement or provide adequate outcomes; therefore, the authors also suggest the development of alternative tools to easily test required cybersecurity features within technology. This can be done using anonymous simulated contexts ("digital twins") in order to integrate usability and interaction methods to mock up interactions without the required coding (which would certainly take much longer). These digital twins can be used by anyone in the world who uses the internet, which currently is a lot of people, anonymously (to comply with legislation requirements and protect users' privacy) but while still simulating real interactions so to easily understand the main factors that improve trust in relations and how to more quickly integrate these into technology development.

The last two paragraphs of Section 3 were maintained from the previous version.

The *Conclusion* section was also altered to reflect the changes described above.

The authors hope that with these alterations, the viewpoint is a document that can generate interest as well as have a disruptive impact.

Round 4 Review:

Dear Editor, thank you for your reviews. Here is what the authors have changed according to your suggestions:

- Regarding suggestion 1, this was done mostly with the summarization of Section 2, as proposed in the third point below. Other important sections were changed to be more objective and to the point, such as Section 3, the Abstract, and the Conclusion. The viewpoint now has 3004 words. The authors hope that this is now in accordance with the Editor's size requirements.
- Regarding suggestion 2, as mentioned, the first part is a summary of the already published and referenced work, but the second part is novel and has not been published anywhere. It was drafted specifically for this viewpoint according to the previous reviews by the Editor. Hence, the last paragraph of the introduction was changed to reflect just that; there is a reference to each mentioned part (eg, Section 2 for the first part of the paragraph and Section 3 for the second part). Further, to better clarify where the second part comes from, a last sentence was added: "These comprise authors' original recommendations specific to this viewpoint."
- Regarding suggestion 3, the authors have made Section 2 more concise and more objective, also by taking out repeated text. We hope that this section reads better and highlights the required key points.

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study"

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(JMIRx Med 2021;2(2):e29626) doi:10.2196/29626

KEYWORDS

AYUSH Sanjivani app; COVID-19; traditional medicine; Ayurveda; Siddha; Unani; homeopathy

Round 1:

Thank you for giving us the opportunity to submit a revised draft of our manuscript [1] titled "Utilization of AYUSH Advocacies and Measures in the Indian Population for the Prevention of COVID 19: Insights from a Mobile Application" to JMIR. We appreciate and are grateful for the time and effort that you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We have been able to incorporate the proposed substantial changes to address all the suggestions provided by the reviewers. We are also submitting the previous draft with the amendments made in Track Changes mode for your perusal along with the final "clean" manuscript.

Reviewer CS:

1. Thank you for pointing this out [2]. We agree with this comment. Therefore, we have deleted the same from the manuscript.
2. You have raised an important point here. Here, the questions in the app were intended to capture whether the use or practice of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) measures either helped in the prevention of disease or aided in reducing the symptoms of the disease. The purpose of the app was to capture the extent of utilization and acceptance and any benefit that the respondents obtained while using these preventive measures, and we performed a cross-sectional analysis to document and synthesize the same.

In the initial draft, this aspect was not very clear, and in the revised draft, the methodology and the purpose of the app have been elaborated to address this to avoid any misunderstanding.

Reviewer DL:

1. Agree [3]. It was an inadvertent error. We have modified SARS-CoV to SARS-CoV-2 in the current manuscript.
2. We agree with this, and we have considered this suggestion and have added the screenshot of the welcome page of the mobile app in Multimedia Appendix 1 and the questionnaire in Multimedia Appendix 3.
3. We are thankful to you for pointing this out, and in consideration of your comment, the data sources and data collection methods have been revised to address this issue.
4. We agree with this, and the details of the three modules and layers have been incorporated as Multimedia Appendix 2 for easy understanding.
5. Thank you for this suggestion. We have revised the section and tried to strengthen it with more technical and such other information relevant to the cross-sectional analysis performed on the data documented from the AYUSH Sanjivani app.
6. The tools and methods used for statistical analysis have been incorporated in accordance with your suggestion.
7. We agree that the *Results* and *Discussion* sections were a bit jumbled in the initial version. We have tried our level best to restructure the entire *Discussion* section to avoid redundancies while highlighting and evaluating the results of the cross-sectional analysis.
8. In the app, specific questions were included for the respondents to report whether they have undergone laboratory testing (under medical guidance or by themselves, owing to suspected exposure or due to manifestation of clinical symptoms) and to self-report their disease and symptomatic status.
9. Necessary technical additions and revisions were made to enhance the technical merit of the manuscript.
10. The novelty of this study is that despite being a country with pluralistic health care services and a long history of practice of traditional systems of medicine (Ayurveda, yoga, Unani, Siddha, and homeopathy), the extent of their utilization and acceptability from the perspective of the public has not been explored to date. This is even more relevant because India accounts for more than 17.1% of the total population of the world. However, there are limitations in this study to attain the intended objective, which have been suitably addressed.
11. Proofreading has been done, and identified spelling mistakes and grammatical errors have been rectified.
12. The referencing pattern and style have been changed to comply with the journal standards, and we have incorporated references from recent years.

We look forward to hearing from you in due time regarding our submission and to respond to any further queries and comments you may have.

Round 2:

We acknowledge the suggestions given by the reviewer and have made the necessary changes in the manuscript.

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Abbreviations

AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, and homeopathy

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Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study"

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KEYWORDS

data collection; herpes simplex virus; registries; machine learning; risk assessment; artificial intelligence; medical information system; user-centered design; predictor; risk

This is the authors' response to peer-review reports for "Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study."

Round 1

Thank you for your consideration of our manuscript [1] for publication in *JMIR Medical Informatics*. We have made amendments to the manuscript reflecting the valuable review comments [2,3] forwarded to us and feel the paper is now acceptable for publication. Please let us know if there is anything we can do further to improve our paper.

Reviewer Z

General Comments

We thank the reviewer [2] for their time and consideration in the review of our manuscript.

1. Thank you for your feedback; the issues raised have been addressed as advised by reworking the *Introduction*, *Challenges*, and *Discussion* sections in order to improve the focus and clarity of the paper.

2. We agree that there was a lack of precision in specifying the challenges and overlap in the problems described. We have edited the list and the objectives to focus on data collection and user experience in the *Aims and Objectives* section.

The privacy and security considerations, while remaining a critical element of the registry development, are not directly addressed in our study and have been set aside for future work.

Control over one's own data is linked to the amount of disclosed data (perceived and objective), so it is related to the objectives addressed by the algorithm.

3. Thank you for the comment. As this paragraph lacked clarity on the fact that the goal of using the ArthritisPower example was to illustrate the variety of approaches and the specificity of registry contexts, design approaches, and purpose, we have highlighted the differences and limitations of design studies for registries such as ArthritisPower.

4. In the *Introduction*, we have added the section *Review of Past Studies*, which narrows down the focus of our study and better places it in the context of past research.

5. In using the US National Health and Nutrition Examination Survey (NHANES) data set, we were guided by the NHANES data disclosure terms, which indicate that all data sets comply with the anonymization requirements and have been approved by the National Center for Health Statistics Research Ethics Review Board (previously the NHANES Institutional Review Board [IRB]; protocol #2018-01). Hence, since we only analyzed anonymized data without identification, no direct communication with the IRB was made. The guidance terms and conditions used can be found online [4].

We have added a corresponding comment to the *Database Used* subsection. The sentence was expanded.

Minor Comments

6. Pg 3, lines 3,4: The word "data" has been added.

7. Pg 3, line 7: We have updated the *Introduction* section with a few examples and a reference to our previous study, which focused on the unique challenges that a herpes simplex virus (HSV) registry design poses [5]. Paragraphs in the *Introduction* and *Discussion* sections have been expanded

8. Pg 6: Thank you for the comment; the criteria in the list have been edited to clearly differentiate between each point. Clarifications were also added. Bullet points were edited and expanded upon.

9. Pg 6, line 20: As JMIR uses the American Medical Association style guide, we edited the spelling to be consistent with American spelling. Spelling was changed in 17 instances.

10. Pg 7, lines 16,17: This ratio was chosen in order to keep the variance low and to leave enough data for training, and it is used as a standard split. A smaller training set was tested; however, it resulted in poorer performance. The text was clarified to add the rationale.

11. Pg 8: A sentence has been added to clarify the process and the scope of the paper.

12. Pg 9, lines 24-26: We have edited the paragraph to include the indication of the maximum possible number of questions (n=62) and predicted time to complete the full questionnaire. Moreover, we additionally reviewed the literature to estimate the expected improvement in drop-off rates and added this to the text. The maximum number of questions (n=62) has been added to the text, as well as an estimate of an average reduction in time that is needed to answer the questionnaire to generate a high-reliability risk group prediction.

13. Pg 10, line 1: The edit was made accordingly.

14. Pg 11, lines 13,14: We primarily relied on the result of our previous study [5], where semistructured reviews indicated these challenges and such links. In terms of quantitative evidence from the literature, it was hard to estimate the degree of possible improvements; the existing research highlights such complexity due to the multifactorial nature of "response burden," but multiple research papers showed evidence of an improvement when using shorter questionnaires, with some cases of better retention among particular groups [6,7]. One future direction would be to test the actual change in real data once the model is trialed. Moreover, some of the sensitive questions (that are usually the best indications for HSV type 2) were removed at the data preprocessing stage, still obtaining a high accuracy for the model. The *Data Set Preparation* section has been expanded.

15. Pg 11, line 21: This has been changed to reflect the suggestion.

16. Pg 12, lines 5,6: Although the users are based in the United Kingdom and the study focused on the UK context, for the purposes of this study, we used a US data set due to the free access, sufficient size, and presence of extensive variables. Our research aims to lay the groundwork that would be applicable for patient data collection systems both among UK and US users. The *Intended User Journey* subsection has been edited.

17. Pg 12, line 22: A more detailed description has been added.

Reviewer BK

General Comments

We thank the reviewer [3] for their time and consideration in the review of our manuscript. The issues raised have been addressed in view of the peer-review feedback provided.

Specific Comments

Major Comments

1. We have reviewed the guidelines and applied the following changes:

- Structure
- Changed *Background* to *Introduction*
- Heading format (removed numbering)
- Added titles for the multimedia appendices
- Shorten the paper by moving a figure into the *Multimedia Appendices* section
- Removed author-made abbreviations
- Edited title
- Edited the order of sections

2. In the *Introduction*, we have added the section *Review of Past Studies*, which narrows down the focus of our study and reviews studies applied to the classification problem in the context under consideration.

3. We have added the clarification that the split into the train and test subsets was done at random to ensure the data in both data sets were evenly distributed. We thank you for highlighting the missing details on preprocessing; this was separated into a subsection and clarified. Cross-validation: thank you, this indeed wasn't described in the text. We have now added a section describing these steps.

4. A matrix of confusion has been added.

5. Thank you for the suggestion; we have used GridSearchCV but did not mention it in the previous version of the paper. We have added a section describing these steps.

6. In the *Review of Past Studies* section, we have compared existing models with the proposed approach.

7. The code has been added to an open repository on GitHub and is now available online [8].

Round 2

Reviewer Z

Specific Comments

Major Comments

Thank you for your valuable review comments [2]. We have now worked on a copyediting review, addressing the UK English spelling instances among other issues.

Minor Comments

1-3. The text has been edited as suggested.

4. The labels have been added.

5-9. The text has been edited as suggested.

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Original Paper

Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series

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Abstract

Background: Owing to the widespread use of general anesthesia, administration of spinal anesthesia in pediatric patients is not widely practiced. Yet there is ample positive evidence demonstrating its safety, effectiveness, and success.

Objective: The objective of this study is to compare postoperative patient comfort, length of hospital stay, and cost-effectiveness of pediatric laparoscopic appendectomies performed under spinal and general anesthesia with the usual standard-of-care procedures employed in the hospital.

Methods: This is a case series of 77 consecutive pediatric laparoscopic appendectomies (involving 5-8–year-old children) that took place in a hospital in Chittagong, Bangladesh, in 2019. A total of 40 patients underwent spinal anesthesia and 37 patients underwent general anesthesia. Variables such as surgery and operation theater times, pain score, incidence of postsurgery vomiting, analgesic usage, discharge times, and hospital costs were recorded. Statistical analysis was used to analyze the data as a function of anesthesia type.

Results: The probability of vomiting when using spinal compared to general anesthesia was lower within the first 5 hours (P<.001) and 6 hours (P=.008) postoperation. A significant difference (P<.001) was observed between the total costs of the two procedures, with spinal anesthesia being less expensive. Patients were more likely to be discharged the same day of the procedure when spinal anesthesia was used (P=.008).

Conclusions: Spinal anesthesia has many advantages compared to general anesthesia for pediatric laparoscopic appendectomies. Patient comfort is improved due to a significant decrease in vomiting. This allows for more rapid hospital discharges and substantial cost savings, without compromising the outcome of the procedure.

(JMIRx Med 2021;2(2):e25204) doi:10.2196/25204

KEYWORDS

pediatrics; appendectomy; spinal anesthesia; general anesthesia; laparoscopy; vomiting; keyhole; surgery; anesthesia; appendix

Introduction

The history and success of pediatric spinal anesthesia procedures, beginning with the 1898 report by Bier and several studies by Gray and Cantab a few years later, has recently been documented [1]. Due to improvements in general anesthesia, there was little interest in pediatric spinal anesthesia until the 1950s, when more studies advocated for its use in children [2]. Since then, the spinal anesthetic approach has increased dramatically in children, and the potential problems and risks of general anesthesia in pediatrics have been documented [3]. However, even by 1984, Abajian et al [4] noted that despite reports of spinal anesthesia use in children and confirmation that it is a safe alternative to general anesthesia even for patients under 1 year of age, it remained underutilized. In 2006, Williams et al [5] found complication rates to be very low among 1554 procedures and recommended spinal anesthesia for lower abdominal or extremity surgery in infants. An Italian and Finnish collaborative published a study of 1132 children, aged 6 months to 14 years, with similar conclusions (specifically with hyperbaric bupivacaine) [6]. Imbelloni et al [7] reported an excellent rate of success in 307 consecutive cases of patients under the age of 13 years in a Brazilian setting, although they cautioned that spinal anesthesia in children should be administered only by anesthesiologists already trained in spinal anesthesia in adults. They further noted that the cost to the facility was 54% less than the cost of general anesthesia, which is an important consideration in countries with limited financial resources. In Nigeria, even as recently as 2010, only general anesthesia was used. The first study in Nigeria indicated that spinal anesthesia in children caused minimal hemodynamic disruption and was classified as a safe technique for lower-extremity surgeries [8]. In 2010, Polaner and Drescher [9], and a year later Ecoffey [10], reviewed the safety record and concluded that although usage of regional anesthesia, whether as adjuncts, primary anesthesia, or postoperative analgesia, was becoming increasingly common in pediatric practice, data on their safety remained limited because of the scarcity of large-scale prospective studies required to detect low-incidence events. Despite this, their study concluded that regional blockades in infants and children appeared to have a very high degree of safety. They noted the importance of attention to technique, detail, and prudent patient selection to avoid possible complications.

Despite these positive outcomes, even as recently as 2018, there have been some debate regarding pediatric spinal anesthesia. The European Society of Regional Anesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine published their recommendations on local anesthesia and adjuvant dosage in pediatric regional anesthesia, conspicuously noting that up to that point there was a large variability of dosages used in clinical practices. Their recommendations were intended to curb that variability [11]. The technique is still gaining traction, and even as recently as 2019, its benefits have been again summarized [12]. A recent report out of Pakistan [13] noted the successful use of spinal anesthesia in surgeries for the past 20 years, with the only real danger being when it was applied by poorly or untrained personnel.

Another recent area of debate is the applicability of spinal anesthesia to laparoscopic approaches to surgery. One of the first reports of laparoscopy under spinal anesthesia was reported by Islam et al [14] in 2014, where laparoscopic pyloromyotomy procedures in infants were investigated. Of the 12 cases studied, 9 were successful, while the other 3 cases required conversion to general anesthesia. The 3 failures were related to the inability to access the intrathecal space and an inadequate block level so that the infant did not tolerate insufflations of the abdomen. More recently, Chiao and Boretsky [15] presented 3 case reports employing laparoscopic surgery for inguinal hernia repair. All procedures were successful, with 1 patient experiencing hypertension and tachycardia during insufflations with brief supplemental use of sevoflurane. The authors concluded that the use of spinal anesthesia for laparoscopic surgery was successful, with the advantage of decreased exposure to opioids and general anesthesia agents, some of which are potential neurotoxins that may negatively affect brain development. This can provide an additional anesthesia option for providers and families. The authors claimed that laparoscopy could, perhaps, no longer be viewed as being incompatible with the use of spinal anesthesia in infants.

Despite the increased prevalence and positive outlooks of spinal anesthesia in children, it is still not practiced everywhere owing to the widespread use of conventional general anesthesia. In this paper, we present a case series of 77 consecutive pediatric laparoscopic appendectomy patients, comparing their postoperative comfort (measured by the incidence of vomiting in the postoperative period), length of hospital stay, and cost-effectiveness of the procedure performed under spinal and general anesthesia.

Methods

Overview

This case series of 77 consecutive pediatric (5-8–year-old children) laparoscopic appendectomies took place at South Point Hospital, Chittagong, Bangladesh, between January 1 and December 31, 2019. Anesthesia choices were not predetermined

but decided during the operation. Those receiving spinal anesthesia (n=40) also received sedation with diazepam or ketamine hydrochloride injection as an adjunct to alleviate their anxiety and help them remain calm. Patients who received general anesthesia (n=37) also received nitrous oxide gas throughout the intraoperative period as analgesics and were kept relaxed by rocuronium. These represent the current standard of care for these procedures at the hospital.

Spinal anesthesia consisted of 0.5% bupivacaine in 8.5% dextrose at a dose of 0.4 mg/kg of body weight. CO_2 insufflations pressures were kept under 8 mmHg, and the flow was maintained between 2.0-2.5 L/min. For all procedures, irrespective of the type of anesthesia, antiemetics were administered at the start of the procedure, while dosages of NSAIDs (nonsteroidal anti-inflammatory drugs) were administered toward the end of the operation, per the usual practice in hospitals. Feeding was recommenced 4-5 hours postoperation for the general anesthesia group and 2-3 hours postoperation in the spinal anesthesia group.

The ethical clearance for this study was provided by South Point Hospital (Admn/SPH/191/2020).

Hypotheses

We hypothesized that spinal anesthesia is better than general anesthesia for pediatric patients in terms of postoperative comfort and cost-effectiveness. Our null hypotheses were as follows: probability of vomiting <5 hrs postoperation is greater for spinal than general anesthesia; probability of vomiting >6 hrs postoperation is greater for spinal than general anesthesia; and probability of same-day discharge is greater for general than spinal anesthesia.

Statistical Analyses

Statistical analysis of the data was performed using JMP statistical software (SAS Institute). Significance was held at the 95% level unless otherwise noted (minimum 90% level). Chi-square and Fisher exact tests were used for contingency analysis of categorical data. Parametric (Student *t* tests) or nonparametric tests (Wilcoxon) were used for comparison of continuous numerical data depending on the normality of the data, determined using the Shapiro-Wilk test. The effects of anesthesia on vomiting during the first 5 hours postoperation and after 6 hours postoperation, time until patient discharge, and cost of the procedure were examined.

Finally, all factors were combined in a multiple correspondence analysis. Multiple correspondence analyses are the categorical equivalent of principal component analysis in multivariate statistics. It produces a plot, which is a 2D representation of "n-space," where *n* is the number of variables. The 2 dimensions chosen are those that explain the most variance in the data. The closer the points are to this plot, the more highly they are associated with one another on a relative basis, while the further away from the origin the points are located, the more they are discriminating themselves from the rest of the data.

Data Availability Statement

The data sets generated during and/or analyzed during the study are available on Figshare [16].

Results

The descriptive statistics for the cohort of 77 patients in the series are presented in Table 1. The data indicate an approximate even distribution of patients across gender, age, and anesthesia method used for the procedure.

Results pertaining to incidence of vomiting up to 5 hours and after 6 hours postoperation are provided in Table 2. The odds ratios (ORs) for the incidence of vomiting based on administration of general anesthesia are also provided with 95% confidence limits.

For the case of <5 hours postoperation, the *P* values determined by the Fisher exact test were all less than .05 for the entire cohort as well as when stratified by gender and age. The null hypothesis was therefore rejected, and the probability of vomiting was determined to be greater when general anesthesia was used. The odds for vomiting within the first 5 hours postoperation when general anesthesia was used for the overall cohort was 8.1, with males exhibiting a maximum OR of 15.6 and females exhibiting a minimum OR of 4.4.

After 6 hours postoperation, the same null hypothesis was only rejected for the entire cohort, females, and the younger age bracket of 5-6–year-old patients. The OR spread for these 3 cohorts is less compared to the first 5 hours postoperation (OR 3.5, 5.7, and 5.0, respectively).

Table 1. Descriptive statistics of the patient cohort by gender, age, and anesthesia type used for the procedure (N=77).

Characteristic	Count, n (%)
Gender	
Female	38 (49.4)
Male	39 (50.6)
Age (years)	
5	17 (17.2)
6	17 (17.2)
7	24 (24.3)
8	19 (19.3)
Anesthesia type	
Spinal anesthesia	40 (52.0)
General anesthesia	37 (48.0)

Table 2. Statistical analysis of the effect of anesthesia on incidence of vomiting up to 5 hours postoperation and after 6 hours postoperation. The odds of vomiting when a general anesthetic was used is given with the 95% upper and lower confidence limits.

Null hypothesis and cohort	*P* value[a]	Odds ratio (95% confidence limits)
Probability of vomiting <5 hrs postoperation is greater for spinal than general anesthesia		
All	<.001	8.1 (2.9-22.4)
Gender		
Male	<.001	15.6 (3.2-77.2)
Female	.04	4.4 (1.1-17.8)
Age (years)		
5-6	.02	6.7 (1.4-32.3)
7-8	<.001	13.0 (2.9-58.9)
Probability of vomiting >6 hrs postoperation is greater for spinal than general anesthesia		
All	.008	3.5 (1.4-9.3)
Gender		
Male	.17	2.4 (0.62-9.0)
Female	.02	5.7 (1.4-23.5)
Age (years)		
5-6	.04	5.0 (1.1-23.2)
7-8	.12	2.6 (0.73-9.0)

[a]Fisher exact test.

The effect of anesthesia type on hospital discharge is summarized in Table 3. The ORs for same-day discharge were calculated based on the administration of spinal anesthesia. The *P* values from the Fisher exact test rejected the null hypothesis for the entire cohort, as well as for the female group and the younger age bracket. Thus, the probability of same-day discharge was greater when spinal anesthesia was used. This mirrors the result for the probability of vomiting after 6 hours postoperation. The OR values indicate that the younger age brackets were particularly more likely to be discharged on the same day when spinal anesthesia was used compared to the overall cohort (OR 6.8 vs OR 3.5).

A comparison of the cost of the procedure (in Bangladesh taka; 1 USD=84.75 BDT) when the different types of anesthesia were used is shown by the box plots in Figure 1. Results from the Shapiro-Wilk tests indicated that the data did not follow a normal distribution and thus a Wilcoxon test was used to test for a significant difference. The *P* value calculated was <.001, indicating that the costs encountered when using spinal and general anesthesia were significantly different. Use of spinal anesthesia was less expensive.

The effects of the adjuncts diazepam and ketamine hydrochloride on the spinal anesthesia group were also examined in terms of incidence of vomiting, but no significant differences were found up to 5 hours postoperation (Fisher exact test,

two-tailed; *P*=.26) or after 6 hours postoperation (*P*=.48). These adjuncts also did not affect the cost of the procedure (Student *t* test; *P*=.26) nor the speed of discharge (Fisher exact test, two-tailed; *P*=.48).

For the multiple correspondence analyses, the operation time and the theater time were binned into two categories: above and below the median value. The cost of the procedure was binned into "less expensive" (less than 15,000 Bangladesh taka) and "more expensive" (greater than 15,000 Bangladesh taka) categories. The resultant plot is shown in Figure 2.

The plot of these 2 dimensions explains 57% of the variance in the data and shows astonishingly well how "less expensive" and spinal anesthesia are associated (they lie practically on top of each other). Other factors found to be associated with the "less expensive" category included an operation theater time between 25-40 minutes (the shortest time bin), no vomiting during the first 5 hours, and female patients.

Table 3. Statistical analysis of the effect of anesthesia type on hospital discharge. The odds ratio of same-day hospital discharge when spinal anesthesia was used is provided with 95% upper and lower confidence limits.

Null hypothesis and cohort	*P* value[a]	Odds ratio (95% confidence limits)
Probability of same-day discharge is greater for general than spinal anesthesia		
All	.008	3.5 (1.4-9.3)
Gender		
Male	.11	2.9 (0.75-10.9)
Female	.04	4.4 (1.1-17.8)
Age (years)		
Age 5-6	.02	6.8 (1.4-32.4)
Age 7-8	.18	2.2 (0.62-7.6)

[a]Fisher exact test.

Figure 1. Comparison of the cost of laparoscopic appendectomies between procedures with general and spinal anesthesia (in Bangladesh taka; 1 USD=84.75 BDT).

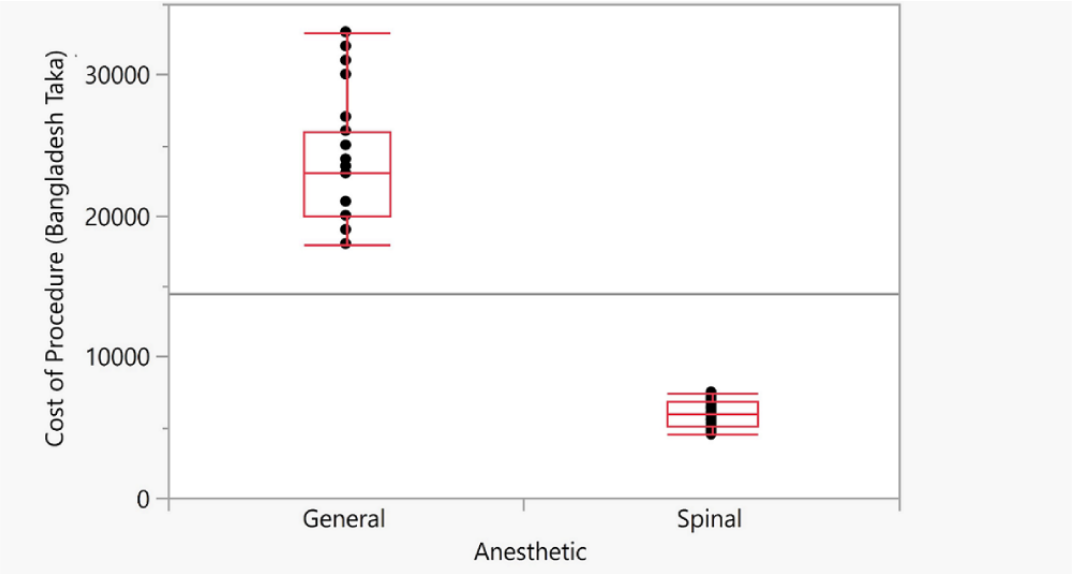
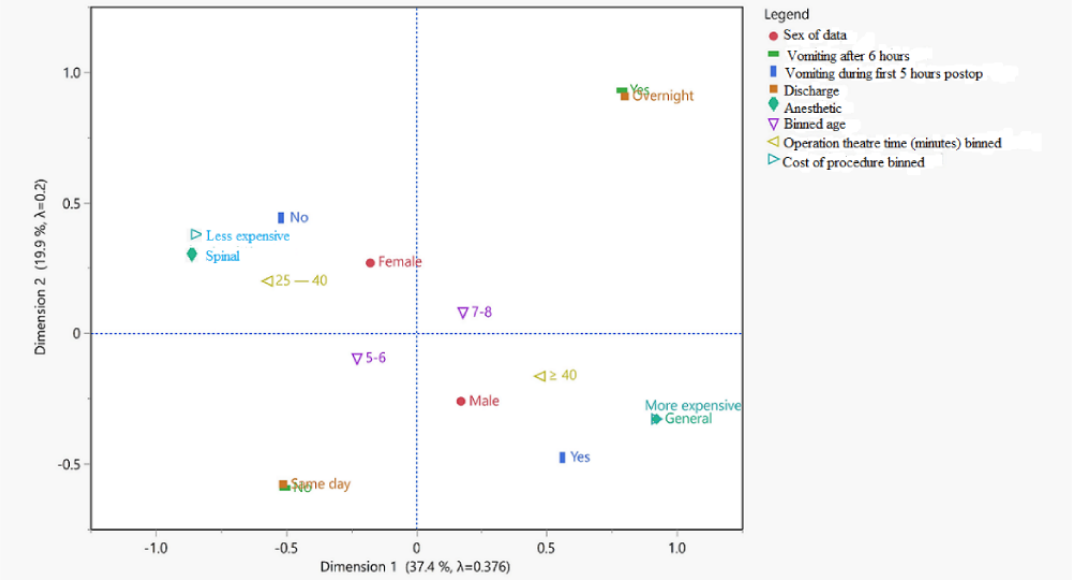


Figure 2. Multiple correspondence analysis plot from variables listed.



Discussion

Laparoscopic surgery is now the method of choice for lower abdominal procedures. Childers et al [17] reported that of the 9507 appendectomies conducted in children under the age of 18 years in the United States, 94.6% used laparoscopy. In 4 central European institutions, of the 519 pediatric appendectomies performed, 79.6% were conducted via laparoscopy [18]. In Germany, Gosemann et al [19] found that of 8110 pediatric appendectomies, 75% were performed using laparoscopy. In 2018, in a wide-ranging study, Tom et al [20] found that of the 58,511 appendectomies conducted in children's hospitals in the United States between 2003 and 2012, 70% were done using laparoscopy, compared to 53% of the ~1.2 million conducted at nonchildren's hospitals. Zani et al [21] summarized the results of the European Pediatric Surgeons' Association survey on the management of pediatric appendicitis, compiled from 169 respondents from 42 countries (24 European countries). For simple appendicitis, laparoscopy was the preferred method for 89%, while for perforated appendicitis, it remained the method of choice for 81%. In Japan, Fujishiro et al [22] found that of the 4489 pediatric appendectomies performed, 70.5% were performed laparoscopically. It is clear from these studies that for pediatric appendicitis, laparoscopy is the method of choice, which was also the conclusion of a review of pediatric appendicitis by Rentea et al [23]. However, in all of these studies, an important fact is conspicuously absent. No mention of the type of anesthesia administered during the procedure is provided. An Egyptian study of 390 complicated pediatric appendicitis cases was published by Khirallah et al [24], comparing laparoscopic (200 cases) and open appendectomies. All procedures were conducted under general anesthesia, and the authors concluded that the laparoscopic technique should be pediatric surgeons' first choice for appendectomy procedures. Thus, our study clearly addresses a paucity of data pertaining to the effect of the type of anesthesia on pediatric laparoscopic procedures in terms of postoperative patient vomiting, discharge time, and relative costs.

The results of the present study clearly showed that the use of spinal anesthesia reduced the likelihood of vomiting during both the first 5 hours and after 6 hours postoperation (Table 1). This mirrors the results of Verma et al [25] in their study of 102 pediatric patients aged 6 months to 14 years undergoing various surgeries, including herniotomy, appendectomy, genitourinary surgeries, and lower limb orthopedic surgeries, under spinal anesthesia. In this cohort, no incidence of vomiting was noted. Similarly, Ahmed et al [26] in their study of 78 children with a similar range of procedures reported 6 cases of nausea and 1 case of vomiting. Kokki and Hendolin [27] reported 10 patients experiencing nausea but no vomiting in a cohort of 52 patients between the ages of 7 and 18 years undergoing lower umbilical procedures with spinal anesthesia (bupivacaine in 8% dextrose). None of these studies stratified the incidence of vomiting by gender, so in that respect, the results of our study are, to the best of our knowledge, novel. However, the studies by Verma et al [25] and Ahmed et al [26] were largely male dominated (>80%); therefore, our observation that males are especially less likely to experience vomiting in the first 5 hours postoperation is not unexpected. Nonetheless, the entire subject of postoperative nausea and vomiting can be quite complex [28].

There is ample evidence for shorter hospital stays with a laparoscopic procedure [19,29-31] although the study by Fujishiro et al [22] contradicted this observation. They found no significant difference between laparoscopic and open appendectomies in terms of length of stay. The present results showed a definite trend for overnight stays when general anesthesia was used, whereas same-day discharges were highly associated with spinal anesthesia (Table 3).

Teja et al [32] have championed the need for more cost-effectiveness research in anesthesiology. They noted a paucity of cost-effectiveness data, particularly from a pediatric perspective. Although the research to this end is relatively simplistic and relates only to the cost of the procedures, a significant reduction in cost (by nearly a factor of 5; Figure 1) was found in this study when spinal anesthesia was used.

Imbelloni et al [7] reported a savings in anesthesia cost of 54% when the spinal method was used compared to historical data. This was pooled using a variety of pediatric procedures.

In summary, the results of this case series provide a clear indication that spinal anesthesia has advantages to general anesthesia in laparoscopic appendectomy procedures. The data provided strong evidence for more rapid hospital discharges and substantial cost savings, without compromising the outcome of the procedure and postoperative comfort of the patient.

Authors' Contributions

MJH, MKP, and AKN designed the study, performed the experiments, analyzed the data, and wrote the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

NSAID: nonsteroidal anti-inflammatory drug
OR: odds ratio

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Original Paper

A Physical Activity Mobile Game for Hematopoietic Stem Cell Transplant Patients: App Design, Development, and Evaluation

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Abstract

Background: Physical activity mobile apps may encourage patients with cancer to increase exercise uptake, consequently decreasing cancer-related fatigue. While many fitness apps are currently available for download, most are not suitable for patients with cancer due to the unique barriers these patients face, such as fatigue, pain, and nausea.

Objective: The aim of this study is to design, develop, and perform alpha testing of a physical activity mobile health game for hematopoietic stem cell transplant (HSCT) patients. The ultimate future goal of this project is to motivate HSCT patients to increase physical activity and provide them with a safe and fun way to exercise.

Methods: A mobile health game called Walking Warrior was designed as a puzzle game where tiles are moved and matched. Walking Warrior interfaces with an open-source step counter and communicates with a central online MySQL database to record game play and walking performance. The game came to fruition after following an iterative process model with several prototypes. Game developers and bone marrow transplant nurses were recruited to perform an expert usability evaluation of the Walking Warrior prototype by completing a heuristic questionnaire and providing qualitative suggestions for improvement. Experts also made qualitative recommendations for improvements on speed, movement of tiles, appearance, and accuracy of the step counter. We recruited 5 additional usability evaluators who searched for and compared 4 open-source step counter programs, then qualitatively compared them for accuracy, robustness, cheat proofing, ease of use, and battery drain issues. Patient recruitment is planned at a later stage in this project. This paper only describes software design, development, and evaluation, rather than behavioral evaluation (ie, impact on physical activity), which is the long-term goal of this project.

Results: Internal consistency and the instrument's reliability evaluation results from 1 clinical expert and 4 technical experts were deemed excellent (Cronbach α=.933). A hierarchical cluster analysis of the questionnaire item responses for similarity/dissimilarity among the experts indicated that the two expert groups were not clustered into two separate groups in the dendrogram. This indicates that the item responses were not affected by profession. Factor analyses indicate that responses from the 40-item questionnaire were classified into five primary factors. The associated descriptive statistics for each of these categories

were as follows (on a scale of 1 to 5): clarity and ease (median 4; mean 3.7, SD 0.45), appropriateness (median 4; mean 3.7, SD 0.49), game quality (median 3.5; mean 3.3, SD 0.42), motivation to walk (median 3; mean 3.1, SD 0.58), and mental effort (median 3.5; mean 3.1, SD 1.27).

Conclusions: The evaluation from experts and clinicians provided qualitative information to further improve game design and development. Findings from the expert usability evaluation suggest the game's assets of clarity, ease of use, appropriateness, quality, motivation to walk, and mental effort were all favorable. This mobile game could ultimately help patients increase physical activity as an aid to recovery.

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KEYWORDS

cancer; mobile app; gamification; bone marrow transplant; alpha testing; physical activity

Introduction

A hematopoietic stem cell transplant (HSCT) is the transplantation of stem cells, derived from bone marrow, peripheral blood, or umbilical cord blood, as a means of treatment for blood or bone marrow cancers. HSCT involves an intensive conditioning regimen that uses chemotherapy with or without total body irradiation; this is followed by a period of myelosuppression to create marrow space for the engraftment of the transplanted stem cells [1]. During the transplant process, many patients experience several physical and psychosocial complications and side effects, such as severe fatigue, loss of physical performance, infection, graft-versus-host disease, and distress [2]. Fatigue, a commonly reported symptom of patients who have undergone HSCT treatment, has multiple causes, including deconditioning, anemia, and medications. Regardless of the cause, fatigue impacts patients' well-being, ability to reintegrate into their normal lifestyle, physical recovery from transplantation, and overall symptom management [1].

The Center for International Blood and Marrow Transplant Research showed an increase of 39% in allogenic transplants in individuals aged 60 years and older in the United States. In 2018, there were nearly 4000 transplants in the United States [3]. At the same time, smartphone use by patients with cancer is being utilized in many studies, suggesting that mobile health (mHealth) can be an effective means of patient engagement [4]. According to the National Comprehensive Cancer Network (NCCN), of all nonpharmacologic interventions, physical therapies and some psychosocial interventions have the strongest evidence base for treating fatigue in HSCT patients [5]. These interventions align with recommendations from the Oncology Nursing Society (ONS). The ONS presents a number of evidence-based interventions for cancer symptoms, which are published through critical reviews. Their review on fatigue confirmed exercise/physical activity to be an effective intervention in the management of cancer-related fatigue for patients with many types of cancer including HSCT [6]. Several meta-analyses have been conducted to provide a comprehensive evaluation of the impact of increased physical activity upon cancer-related fatigue [7-9]. This evidence was effective in understanding the need for mHealth for HSCT patients to help increase their physical activity levels.

The need to create a motivational game that would engage HSCT patients to be physically active is important for this population; they carry a smartphone (our survey in 2017 at the Johns Hopkins Bone Marrow Transplant unit found that >80% of the patients owned a smartphone), and the majority of patients receiving transplants are under 60 years of age [3]. Transplant patients also vary in their health care settings between inpatient and outpatient status. Having an app on their smartphones to use wherever they are for physical activity engagement is an appropriate solution. A systematic review by Hernandez Silva et al [10] showed that many mHealth interventions have potential benefits, and the most promising improvements are in fatigue outcomes. mHealth gaming can be used in patients with cancer and has the potential to improve treatment outcomes [10,11].

Exercise is not only safe during cancer treatment but can also improve physical function and quality of life [5]. Too much inactivity can lead to loss of body function, muscle weakness, and reduced range of motion. Regular exercise during cancer treatment can help lower the risk of falls, blood clots, nausea, and fatigue [12]. The NCCN Clinical Practice Guidelines for Cancer-Related Fatigue advise starting slowly with a 10-minute walk and incrementally progressing with distance and time [5]. The goal is to reach 30 minutes of aerobic exercise, 5 days per week [5]. Unfortunately, patients may find it difficult to reach the recommended levels of physical activity [13].

Smartphones are increasingly becoming integrated into our society and can serve as a tool to improve health outcomes. Kamboj and Krishna [14] illustrated the positive health impacts of an innovative smartphone gaming app, Pokémon GO (Niantic Inc), in which users encounter Pokémon monster avatars when walking around as opposed to traditional stationary/seated games [14].

The study by Brassil et al [15] included hospitalized HSCT patients in a trial of an incentive-based mobility program to maintain or improve fatigue. Their findings suggest that participating in mobility programs may minimize fatigue [10,15,16]. These examples help to establish the concept of gamification [17]—the process of using "game design elements in non-game contexts"—in the application of achieving an incentive for ambulation [18].

The use of mobile device apps to promote fitness may be helpful in increasing physical activity levels [19,20]. While there are many fitness and physical activity apps currently available for download, most of them center on measuring and improving athletic performance. Content analyses of serious games for health is limited, but comparing these results to those of

nongamified health apps has shown that physical activity serious game apps demonstrate higher levels of behaviour theory [21].

Such apps are generally not well suited for most patients with cancer because they fail to address unique barriers, such as fatigue, pain, and nausea, that hinder this group from carrying out the recommended levels of physical activity [14]. We are aware of no mobile apps that promote physical activity specifically for HSCT patients. Therefore, innovative efforts are needed to develop and evaluate a mobile app that increases physical activity in this population. Meanwhile, we intend to design and develop software that is generic and suitable for a wide population (including patients with other types of cancer and people experiencing fatigue) to walk a medically prescribed number of steps.

Our intention is to develop a game, Walking Warrior (WW), to motivate HSCT patients to walk. Our rationale is as follows: (1) a large portion of HSCT patients have reported enjoying match-3 puzzle games such as Candy Crush, which is similar to our game; (2) continued game play requires walking: if patients want to play more, they will need to walk; (3) patients are advised that walking is part of their therapy so playing the game reinforces this behavior; (4) walking will allow players to unlock additional levels and allows them to earn higher scores; (5) game playing and walking performance data are automatically collected and displayed on a website that allows for patient self-tracking and provider review; (6) the game is mentally challenging, and this provides entertainment, opportunities for logical thinking, the element of chance, and high replayability; (7) the tiles that are moved in the puzzle are displayed as cell types and medications that are relevant to HSTC patients' condition and educates players, thereby enhancing their knowledge of the underlying biology and treatment they receive; (8) in addition to their automatically collected data, patients will participate in a survey that will serve as a tool for software evaluation and additional development, which shows that the individual patient's experiences and opinions are valued and will be integrated into the next phase of software development.

Methods

Overview and Planning

In this work, ideation, design, development, an expert heuristic usability evaluation (alpha testing), bug fixes, and prototypes of WW were conducted for HSCT patients. The purpose of combining a step counter with the game is to make engagement in physical activity more motivating and enjoyable [22,23]. Participants need to carry their phones to use the step counter app that runs in the background. The game progresses when the user walks the required number of steps and beats the puzzles (levels). Computer game developers, bone marrow transplant nurses, and nursing informatics students were recruited to evaluate the usability of WW and the step counter. The evaluations provide information to further improve game design and development to better suit patient needs.

The design and development process of WW took on a multidisciplinary approach with continuous systematic evaluations. The study was led by a computer science professor of nursing informatics, a nursing informatics student who is an oncology nurse, and an oncology nurse educator. The study team held meetings and communicated with computer programmers, an oncology research committee, domain experts of oncology, and domain experts of game design. The entire development process was based on a design that focused on the intended users, and prototype testing was performed throughout the life cycle.

To identify user preference for game type, a questionnaire was given to 30 HSCT patients. Inclusion criteria included users who (1) are >18 years of age, (2) are not working in health care, (3) have received HSCT therapy in the past, and (4) are currently playing a computer or mobile app game. Questions on the type of mobile games enjoyed by respondents, why they enjoyed it, and why they continue to play were asked. The majority of participants (n=21, 70%) preferred to play puzzle games, with half (n=11, 37%) preferring a match-3 puzzle game such as Candy Crush. Users of Candy Crush are not limited to any specific demographics; the game is played by users of all age groups, belonging to all ethnicities and religions, and in all 7 continents [24]. Therefore, WW was designed as a match-3 game for the enjoyment of the HSCT adult population and the game design was inspired by Candy Crush, but its rules, winning conditions, graphics, scoring, and sound effects are significantly different.

WW's main objective is to increase the physical activity level of HSCT patients, who are the intended users. Specifically, our short-term target population is HSCT patients who are >18 years old, received walking instructions from their clinician as part of their recovery from bone marrow transplant, and are willing to play a puzzle game using their own Android device. To achieve this, the game is designed for each level to be unlocked after the user walks a clinically designated number of steps. The game has a step counter that tracks the steps of the user as they walk and rewards them with a token that can be used to unlock levels in the game. The game screen includes 9×6 moveable tiles that are displayed as biological cells, including red blood cells, white blood cells, platelets, neutrophils, stem cells, and nerve cells. The game also includes bonus cells, magnesium and potassium pills, as well as bricks and concrete blocks for added variety and difficulty. Cells and pills are relevant to the patients' conditions and treatment. Each level has a customized goal that the player must attain to beat the level.

The targeted HSCT patient behavior change is use of our mobile health game, WW, as opposed to other apps. Through game design, we intend to prompt and motivate users to have increased physical activity in comparison to no app use. This may promote better engagement in patients' prescribed therapy and adoption of physical activity. In addition, by playing WW, they will automatically provide data about their walking and game-playing behaviors through WW's integrated step counter and the online database, which collects, stores, and displays the data. The database is designed to collect and display data to players and clinicians to instigate changes in behavior and physical activity level, motivate users, and track progress. This also serves as proof of game play and walking achievement, which are important for goal setting, goal achievements, self-monitoring,

and fast, automated objective feedback. In the future, various competitions will be open to users; their scores will be visible to all competitors, hence encouraging them to achieve high scores. This is often done in the gaming industry to generate significant interest in game play and social community building. Players may choose to release their scores for public view in the database with a push of a button. There is no personally identifiable information in the database; only usernames and performance data are stored.

Mobile Game Development and Prototypes

The game's initial user interface (UI) design was sketched freehand and consisted of a login screen, menu page, cell art, tutorial content, and a game screen. Gameplay was then mapped out in Lucid Chart (Lucid Software Inc) and graphic art was designed in Paint.NET (dotPDN, LLC). The paper-based design was evaluated, refined, and adjusted based on team members' feedback (Figure 1).

After several adjustments, the UI design was given to the programmers to be coded in JavaScript. A GitHub repository was created to store and share the source code for team members to view and test the game. WW functions on a web server, accessible through any device with an internet browser and an internet connection. Throughout development, the study team followed an iterative process model through a combination of design, testing, evaluation, and planning with each prototype version. During the testing process, team members navigated through the prototypes and reported bugs and recommendations for improvements. The iterative process ensured that with each new version, the identified problems would be fixed and requirements met (see Figure 2 for prototype versions).

Separate JavaScript, Java, and PHP files were created for this game. The JavaScript files are responsible for the game itself. They manage the levels, contain game logic, and load the main frame and tiles. JavaScript is a lightweight, interpreted, object-oriented language with first-class functions and is best known as the scripting language for webpages. Java files count the steps and rely on the mobile device's built-in accelerometers. Due to variations in mobile phone hardware and the limitations of open-source Java software, WW's step counter currently only works on modern Android devices. The PHP files handle user logins and access and store the data on a server. The steps, login credentials, game-play performance, account creation, and the date and time of the last game played are stored in a MySQL database, as shown in Figure 3. The MySQL database is an open-source relational database management system. The database is stored on a server where administrators and authorized users can check the status of important variables for each user at any time. All data transfers go through AJAX, which does not require refreshing the webpage to send data through PHP, which makes the user experience smooth.

Figure 1. The game's initial user interface design.

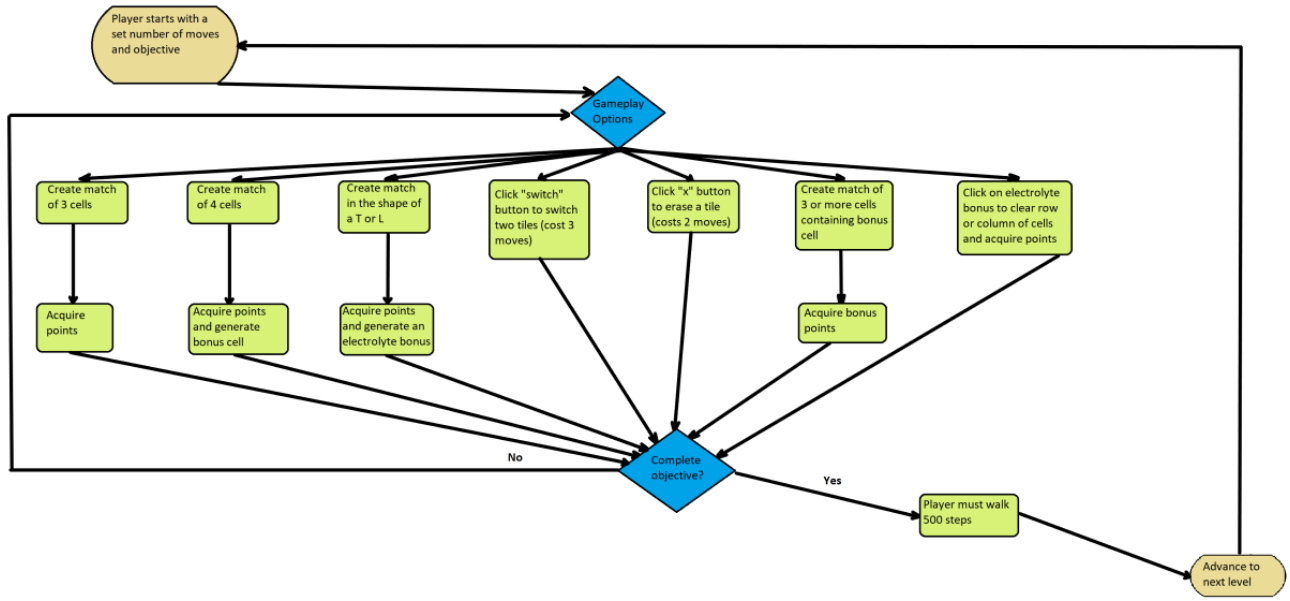

Figure 2. Prototype versions.

Figure 3. Screenshot of the MySQL database created to track patients' behavior.

Username	Tokens	Steps	Score	Highest Level	Created at	Last modified
Gergo	95	0	9645	5	2018-11-28 17:04:44	2019-02-19 08:14:23
Renato	1	0	0	1	2018-11-28 18:05:31	2019-01-30 12:25:28
Adrian	48	0	563	11	2018-11-28 18:23:08	2019-02-19 17:57:25
sawolfe89	1	0	1005	23	2018-12-12 14:57:59	2019-04-21 05:34:08
Renato93	3	0	0	1	2018-12-13 15:27:10	2019-01-30 12:25:28
Arpad	18	0	0	5	2018-12-15 18:47:00	2019-04-16 20:29:20

Expert Usability Evaluation and Qualitative Data Collection

A 40-item expert heuristic questionnaire was designed to evaluate and assess the usability of WW. Two experts assessed the face validity of this questionnaire. A total of 9 questions were derived from the Perceived Health Website Usability Questionnaire (PHWSUQ), which is an existing validated tool [25]. The PHWSUQ consists of 12 items related to three subscales: (1) satisfaction, (2) ease of use, and (3) usefulness. The PHWSUQ has reported excellent reliability with a Cronbach alpha of .93. In our study, only 9 of the 12 items of the PHWSUQ were used because 3 items were not applicable to game evaluation. Moreover, 31 new questions were added to determine clarity and ease, appropriateness, game quality, motivation to walk, and mental effort (Multimedia Appendix 1). These questions were unique to the target user population and to the specific game we developed. The validation of the 31 questions we designed was done by 2 experts, of whom one was familiar with our topic and evaluated the questions to assess whether they successfully captured the topic. The second expert, who specialized in question construction, ensured that our survey did not contain common errors such as confusing or double-barreled questions.

Participants of the expert heuristic usability evaluation of WW included 4 game development experts and 1 bone marrow transplant nurse. Each participant played the game for a minimum of 2 hours in at least one session and randomly tested as many features as they could. Evaluators took notes and filled out a survey. They evaluated the step counter for functionality,

robustness, and accuracy. They did not evaluate the step counter for its ability to motivate users or increase their physical activity level. This will be evaluated later with actual patients. The experts rated the questions on a scale of 1-5, where 1=strongly disagree, 2=disagree, 3=neutral, 4=agree, and 5=strongly agree. Participants also made comments and suggestions for improvement.

Step-counter software vary greatly due to the variations in hardware using different accelerometers, gyroscopes, GPS, sensitivity, and algorithms that classify smartphone moves into step events and nonstep events. This is in general a complex problem to investigate and address. We recruited 5 additional usability evaluators who were nursing informatics graduate students. They searched for and compared 4 open-source step-counter programs, then qualitatively compared them for accuracy, robustness, cheat proofing, ease of use, and battery drain issues. Generally, step counters lack perfection and have several usability and accuracy problems.

Behavioral evaluation (ie, impact on physical activity) will be done at a later stage of this project with HSCT patients.

Data Analysis

The qualitative analysis was performed after the project's nurse informaticist semantically merged, simplified, and summarized all the expert comments and requests into a list of nonredundant statements. These were discussed by the project team and given to the programmers for implementation.

Questionnaires were reviewed for reliability and validity of quality measures. A Cronbach alpha based on a 2-factor ANOVA (analysis of variance) was calculated for reliability, consistency, and reproducibility of the developed product. Descriptive statistics such as medians, means (SD), percentages of favorable and unfavorable ratings, and differential opinions between the bone marrow transplant nurse and computer game development experts were computed. Hierarchical cluster analysis and exploratory factor analysis were conducted to classify item responses for better interpretations. In addition, qualitative data from comments were summarized. All analyses were conducted using SAS (SAS Institute) and Microsoft Excel (Microsoft Corp).

Results

We recruited 1 clinical domain expert and 4 game developers for an expert heuristic evaluation of our WW game prototype. Their ages ranged between 28 to 60 years and comprised 3 females and 2 males, with a master's degree or higher. Analysis of the instrument demonstrated excellent internal consistency and reliability (Cronbach α=.933). Descriptive analysis showed that the overall game usability was favorable (>3) in all five categories, although two categories' means were close to neutral (3.1). Table 1 provides the expert evaluations of 40 item responses and associated descriptive statistics, which showed some mean differences and agreements/disagreements between the two expert groups (the bone marrow transplant nurse and the game developers). However, a hierarchical cluster analysis of these item responses for similarity/dissimilarity among the experts indicated that the two groups were not clustered into two separate groups in the hierarchical cluster dendrogram. This indicates that the item responses were not affected by their profession if we consider the entire survey. Exploratory factor analysis indicate that 40 items were classified into five prime factors based on similarity, and means for each of the five categories were calculated to summarize item responses (Table 1).

Qualitative data suggest that the game is casually fun, suitable for the target audience, and the overall concept of the game has high potential. Experts recommended improvements on speed, ease of movement of tiles by finger, graphical quality of tile appearance, and accuracy of the step counter. They also recommended the addition of a "pause" and "back" button, and the addition of a tutorial for users unfamiliar with matching puzzle games.

After additional heuristic evaluation of the step counters done by the 5 nursing informatics students, based on the factors discussed in the *Methods* section, the old step counter was replaced and a new step counter was integrated into WW. A limitation of the selected step counter is that it only works on modern Android devices, since the open-source iPhone versions of step counters did not perform well. Developing our own step counter with better performance than the current best open-source step counter would be too complex, time consuming, and require extensive understanding and exploitation of different hardware technologies, artificial intelligence, machine learning algorithms, and tuning. Further, it would take several years of additional development and testing, followed by pairing this software with individual walkers to learn about and classify their steps based on their training data. Even then it would remain vulnerable to changing walking patterns among users in the future.

Table 1. Heuristic questionnaire results (n=5; 1 bone marrow transplant nurse, 4 game developers/computer science technical experts).

Category[a]	Median	Mean (SD)	Nurse score–developer mean	Agree (%)	Disagree (%)
Clarity and ease		3.7			
Easy to read	2	2.4 (1.5)	–0.5	20	80
Easy to learn	5	4.2 (1.3)	–2.75	80	20
Easy to use	5	4.2 (1.3)	–2.75	80	20
Easy to navigate	5	4.6 (0.5)	–0.75	100	0
I made the desired moves with ease	5	4 (1.4)	–2.5	60	20
Clear results of my actions	4	4 (1.2)	–2.5	80	20
Clear display	4	4 (1.0)	0	60	0
Easy to understand how to play	5	5 (0.0)	0	100	0
Clear winning and losing criteria	4	3.6 (1.1)	–2	60	20
Understood how steps convert into tokens	4	3.2 (1.1)	–1.5	60	40
Recognized cells of the body	4	3.6 (1.1)	0.5	60	20
Recognized magnesium and potassium pills	3	3 (1.6)	–1.25	40	40
No problem accessing the step counter	2	2.8 (1.6)	–1	40	60
Appropriateness		3.7			
Appropriate flow	4	4.2 (0.8)	–0.25	80	0
Appropriate rules	4	3.8 (1.3)	–2.25	60	20
Appropriate winning and losing criteria	4	4.2 (0.4)	–0.25	100	0
Scores were assigned appropriately	4	4 (1.2)	–2.5	80	20
Appropriate amount of time to win a level	4	3.8 (1.3)	–2.25	60	20
Difficulty level appropriate for target patients	4	4 (1.0)	0	60	0
Increase in difficulty was appropriate	4	3.6 (1.1)	–2	60	20
Combos made the game more interesting	4	3.6 (1.1)	–0.75	60	20
The game was free of bugs and problems	3	3.2 (1.3)	–1.5	40	40
The step counter counted steps accurately	2	2.6 (1.5)	0.5	20	60
Game quality		3.3			
Good appearance	4	3.8 (1.1)	0.25	80	20
Good graphics	4	3.6 (1.1)	0.5	60	20
Graphics added life to the game	4	4 (1.0)	0	60	0
Pleasant music	3	2.8 (1.8)	0.25	40	40
The game was entertaining	3	3 (1.0)	–1.25	40	40
Had sense of immersion	3	3 (0.7)	1.25	20	20
Provided sensory curiosity	3	3 (0.0)	0	0	0
Felt satisfaction when beating levels	4	3.8 (1.6)	0.25	80	20
Found the game to be highly replayable	4	3.2 (1.3)	1	60	20
Found the game to be potentially competitive	3	3.2 (1.5)	–0.25	40	20
Motivation to walk		3.1			
The game encouraged me to walk	3	2.6 (1.5)	–2	40	40
This game will help me walk more	3	2.6 (1.5)	–2	40	40
Desire to reach the next level motivated me to walk	3	3.2 (1.5)	1	40	20

Category[a]	Median	Mean (SD)	Nurse score–developer mean	Agree (%)	Disagree (%)
The game made walking more fun	4	3.2 (1.6)	1	60	40
The game will motivate patients	4	4 (1.0)	1.25	60	0
Mental effort ("disagree" answers are desired)		3.1			
Required too much mental effort	2	2.2 (1.3)	2.25	20	60
Required too little mental effort	5	4 (1.7)	–3.75	80	20

[a]The heuristic questionnaire was organized into categories so statistical analysis could be calculated.

Discussion

Our findings from the expert heuristic questionnaire suggest that WW's clarity, ease of use, appropriateness, quality, motivation, and mental effort were moderately favorable. Experts offered many suggestions and recommendations that we used to improve the usability of the game. These resulted in bug fixes, modifications, and feature additions too numerous to individually mention here.

Although 2 experts assessed the face validity of the 40-item expert heuristic questionnaire we designed and used, it is not a measure with established psychometric properties. This is a limitation of our study. Nevertheless, an expert heuristic usability evaluation of games is an essential step in development. It is usually done as part of alpha testing before a game is given to the intended users for beta testing due to the large number of bugs and usability problems at this stage of development. It helps to significantly improve game quality without needing to recruit a large group of users who are not on the team. For complex games, this step is repeated many times by a small group of experts. Experts who understand both the subject domain and the game development process can identify most usability problems without prematurely recruiting a large sample of the intended users to confirm the bugs and usability problems the development team is already aware of. Recruiting intended users for usability evaluation is usually done during beta testing and/or after the game is given a "version 1.0" label, that is, when the game is no longer called a prototype but is referred to as a product. Development, however, often continues beyond version 1.0, and we plan to do so for WW as well based on data we receive from our intended users.

It is important to include experts from both domain expert backgrounds. Another limitation of this study is that we were only able to recruit 1 bone marrow transplant nurse to complete the expert heuristic usability evaluation of WW. Our research team included 2 additional bone marrow transplant nurses who participated in the software design but were not included in the expert heuristic evaluation to avoid potential biases in response.

After the above discussed expert heuristic usability evaluations, we expanded the testing team to include 30 graduate students in nursing informatics and in computer science at 3 universities. Various other volunteer testers were also recruited. A standard online Google Docs form was created to report bugs. Bugs can be reported by the push of a button in the game and are reviewed by the project leader and the programmers, and changes in the source code are made. Once the programmers have completed all known bug fixes and usability improvements, and fulfilled expert recommendations, we will perform a usability test with the target HSCT patient population at the Johns Hopkins Bone Marrow Transplant unit. The planned future human subjects protocol of this research has been approved by the Johns Hopkins Medicine Convened Institutional Review Board (IRB) and the University of Maryland, Baltimore IRB expedited review. Patients will be recruited, and informed consent will be obtained by study team members. No personal identifiable information will be collected for this study.

Future work will focus on evaluating suitability for the HSCT population. This will allow us to recruit adult bone marrow transplant patients to test the usability of the game using the System Usability Scale and a semistructured interview [26]. By determining the usability and user preferences of WW from HSCT patients, it will show us how to improve the game to better meet the needs of this patient population. Our ultimate goal is to increase patient awareness of the importance of physical activity and its effect on decreasing fatigue. If WW decreases fatigue by increasing the steps that patients walk, it may improve quality of life [12]. This game could ultimately help any patient needing to increase physical activity as an aid to recovery or even initiate a healthier lifestyle or serve as a form of entertainment. After HSCT patients pilot WW, we will adjust the game per their feedback and recommendations, and plan a rigorous evaluation that includes feasibility, acceptability, patient walking behavior, and measured impact on walking. Upon completion of these steps, we will consider releasing the game to the public as a therapeutic tool.

While our target population is HSCT patients, we have attempted to make the game generic enough for the wider public, which can be done by changing the graphics and the frequency and amount of steps needed to walk, which will allow individual users to set goals themselves rather than their clinicians. Ultimately, this mobile game with its associated step counter and database could help patients increase physical activity as an aid to recovery, which we expect to confirm in a quantitative way to support our goal in demonstrating their direct relationship.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Heuristic questionnaire.
[DOCX File , 17 KB - xmed_v2i2e20461_app1.docx]

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Abbreviations

ANOVA: analysis of variance
HSCT: hematopoietic stem cell transplant
IRB: institutional review board
mHealth: mobile health
NCCN: National Comprehensive Cancer Network
ONS: Oncology Nursing Society
PHWSUQ: Perceived Health Website Usability Questionnaire
UI: user interface
WW: Walking Warrior

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Original Paper

Machine Learning for Risk Group Identification and User Data Collection in a Herpes Simplex Virus Patient Registry: Algorithm Development and Validation Study

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Abstract

Background: Researching people with herpes simplex virus (HSV) is challenging because of poor data quality, low user engagement, and concerns around stigma and anonymity.

Objective: This project aimed to improve data collection for a real-world HSV registry by identifying predictors of HSV infection and selecting a limited number of relevant questions to ask new registry users to determine their level of HSV infection risk.

Methods: The US National Health and Nutrition Examination Survey (NHANES, 2015-2016) database includes the confirmed HSV type 1 and type 2 (HSV-1 and HSV-2, respectively) status of American participants (14-49 years) and a wealth of demographic and health-related data. The questionnaires and data sets from this survey were used to form two data sets: one for HSV-1 and one for HSV-2. These data sets were used to train and test a model that used a random forest algorithm (devised using Python) to minimize the number of anonymous lifestyle-based questions needed to identify risk groups for HSV.

Results: The model selected a reduced number of questions from the NHANES questionnaire that predicted HSV infection risk with high accuracy scores of 0.91 and 0.96 and high recall scores of 0.88 and 0.98 for the HSV-1 and HSV-2 data sets, respectively. The number of questions was reduced from 150 to an average of 40, depending on age and gender. The model, therefore, provided high predictability of risk of infection with minimal required input.

Conclusions: This machine learning algorithm can be used in a real-world evidence registry to collect relevant lifestyle data and identify individuals' levels of risk of HSV infection. A limitation is the absence of real user data and integration with electronic medical records, which would enable model learning and improvement. Future work will explore model adjustments, anonymization options, explicit permissions, and a standardized data schema that meet the General Data Protection Regulation, Health Insurance Portability and Accountability Act, and third-party interface connectivity requirements.

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KEYWORDS

data collection; herpes simplex virus; registries; machine learning; risk assessment; artificial intelligence; medical information system; user-centered design; predictor; risk

Introduction

Background

Patient data in medical registries are an important source of information for screening, treatment, and research purposes. However, the value of these registries can be severely limited by a lack of high-quality data, especially in diseases where there are low patient engagement and concerns around stigma and anonymity, such as herpes simplex virus (HSV) [1]. Improving the quality and quantity of data collection from patients with HSV and individuals who may be at risk of HSV would provide significant benefits for research and clinical care. There is an urgent need for a vaccine for HSV type 2 (HSV-2), and its research relies on a collection of relevant data [2]. Large data sets of high-quality data will enable researchers to gain new insights into HSV and clinicians to personalize care plans to improve individuals' health outcomes and quality of life. HSV registry database design poses unique data quality challenges related to the stigma of the HSV condition, increased privacy concern, and selection biases [3]. For example, the lack of data on people who are living with HSV without symptoms calls to a specific need to collect data outside of clinical settings from populations who have not developed symptoms and are not motivated to complete extensive questionnaires or, worse, take offence at being asked to do so. Therefore, nonintrusive and time-efficient methods are necessary to reliably identify high-risk groups.

New technologies, such as machine learning and artificial intelligence, are gaining traction in medical research as a means of collecting and analyzing data [4,5]. Machine learning has previously been applied to medical diagnosis and patient data insights in oncology [6], for the diagnosis of heart, liver, and diabetic diseases, as well as infectious diseases such as dengue, and hepatitis [7], to predict suicidal behavior using longitudinal electronic health record (EHR) data [8], and to classify whether patients have Alzheimer disease [9]. However, current applications of machine learning are usually limited to pre-existing, structured data sets and do not address the problems of first-person data collection from patients and the resulting limitations of data completeness, quality, and validity.

Machine learning–based systems are particularly useful for generating new knowledge and insights without having a priori hypotheses. The concept of "data farming" or "evidence farming" addresses the problems of collecting data directly from users [10]. Data can be "organic" —grown and harvested—if suitable environmental conditions are provided. These conditions are often met by websites and online platforms where patients provide their data, such as the online enterprise PatientsLikeMe.com [11]. Data collected from these platforms can include medical information like disease diagnosis and laboratory results, medications the patients are taking, and subjective data from self-report questionnaires.

Data generation platforms like these provide an opportunity to gather the large amounts of data needed to develop machine learning models. One type of decision support model, decision trees, can be applied to analyze the flows of user-generated content and to determine the strategy that is most efficient and most likely to successfully achieve a certain goal [12]. Decision tree analyses are widely used in health care, but primarily in a basic way, on highly structured data, without applications in real-time data collection situations [13]. A key limitation of data tree analyses is that they are very sensitive to the data they are trained on [14]. However, machine learning methods such as random forest, which are based on a collection of individual decision trees, can minimize the effect of this limitation [14].

Machine learning methods have great potential in the field of real-world data [15]. They have particular promise for analyzing large "data lakes" that have been created by aggregating information from hospital EHRs, including unstructured and semistructured patient-generated data. Machine learning methods can explore this data to identify clinically meaningful patterns. Because these data lakes can track patients longitudinally, they provide a large body of data that would not be available in the typical randomized controlled trial. Therefore, the application of machine learning to these data sets could reduce, or even eliminate, the need for certain traditionally conducted late-phase trials. Drugs that have successfully completed phase I and II trials, and have evidence supporting their efficacy and safety, could be given to patients and monitored in the context of patients' real-world experiences [16]. The application of machine learning methods to such real-world databases also provides an opportunity to easily identify potentially eligible patients for clinical trials, by filtering the database based on relevant criteria. The potential value of this real-world data highlights the importance of developing ways of collecting high-quality data from patient registry platforms.

Challenges of Developing Patient Registries

Patient registries collect longitudinal data about a specific population of interest to provide real-world evidence and insights into disease progression, factors affecting health

outcomes and quality of life, and the effectiveness of different treatments [17,18]. Previously developed patient-focused digital registries, such as ArthritisPower, have achieved significant results in terms of patient engagement [19]. The ArthritisPower registry platform has proven to be an effective means of engaging patients to participate in research and enabling patient-generated data capture; however, the registry is limited to users who have already received a physician diagnosis and are actively motivated to participate. In addition to increased patient engagement with research, the growing focus on patient-centered care led to new emphasis on the use of patient-reported outcome measures in clinical care and research, and patient-reported outcomes now constitute a key component of patient registries [20]. Validated questionnaires provide a useful means of collecting standardized data, but the inclusion of multiple questionnaires in a patient registry can result in a long and arduous process for patients [21]. However, self-reported registries have the benefit of privacy and anonymization, which is particularly important for health conditions that people are uncomfortable discussing with clinicians or researchers, and they have significant potential for developing large databases of evidence that can inform clinical care and provide new insights into the condition in question [22].

However, several challenges need to be addressed to develop a usable and effective patient registry [3]:

1. Efficient use of data: collecting sufficient and high-quality data is necessary to provide useful insights and allow for more targeted clinical trial selection and recruitment. However, this tends to require long patient questionnaires, which often results in high drop-out rates. Therefore, a critical challenge for digital patient data collection is to maximize the usefulness, quality, and information content of the collected data while reducing time and effort for users.
2. Patient-centric design: to be usable and effective, patient registry data collection processes need to serve the expectations and needs of the patients. Therefore, another key challenge is to ensure that patients, and their experience, are considered from the early stages of patient registry development.
3. Selection bias: direct data collection methods can increase the risk of selection bias in the data because subsets of users with certain characteristics are more likely to complete an extensive questionnaire (eg, more computer-literate users), have more time, have more frequent or severe symptoms, and/or are keen to be informed of relevant clinical trials. The challenge for patient registries is to minimize the risk of selection bias by facilitating and simplifying the data collection process.
4. Privacy concerns: common user concerns when it comes to digital data collection are related to privacy and control over data. This is especially true for sensitive or personally identifiable information. This is a key challenge that must be addressed to ensure the adoption and sustainability of any digital solution.

Aim and Objectives

The resolution of the first of the four challenges described above relies on the ability to reduce the drop-off rates by shortening the time and effort required to complete the questionnaire without critically affecting the quality and quantity of results. Similarly, the patient-centric design (challenge 2) requires consideration of user experience, which includes minimizing participant burden. This may also ultimately reduce selection bias (challenge 3) by increasing completion rates. Therefore, this project is aimed primarily at addressing the challenges associated with time-consuming questionnaires containing sensitive questions by creating a prediction model to reliably assess whether a particular person has an increased risk of HSV. We explored the applications of innovative machine learning methods to optimize the questions asked of participants while maintaining the high quality and relevance of collected data. The main objective was to use a random forest model to design an HSV patient registry that can use various lifestyle predictors for HSV infection (eg, sexual activity, number of partners) and recurrences (eg, diet, exercise, sleep) to select the most relevant questions for an HSV registry and improve data collection and analysis in medical registries. For future studies, we suggest integrating this approach with privacy-preserving and trust-enabling solutions to more comprehensively address the four challenges described above.

Review of Past Studies

Multiple studies in recent years have sought to create machine learning models based on data from EHRs and other sources applying the multifactor classification approach to assess and predict risk groups for medical conditions and complications and to identify major risk factors. Such targets include delirium occurrences [23], alcohol use disorder [24], mortality in patients with liver disease [25], cardio-cerebrovascular events [26], suicide attempts [27], metabolic syndrome [28], and postpartum depression [29]. Random forest has been discussed as one of the most efficient methods for creating risk prediction models [14,30,31] and has been applied in most of the studies reviewed.

However, the considerations of user-focused design in the context of optimizing direct data collection for an HSV medical registry introduce additional context to the classification problem, including the emotional sensitivity of some questions and the need to minimize the number of factors (questions) in the ensemble to increase completion rates and address the other limitations discussed above. This study aims to apply the random forest classification approach to enable more efficient data collection from the population while providing an effective tool for HSV screening.

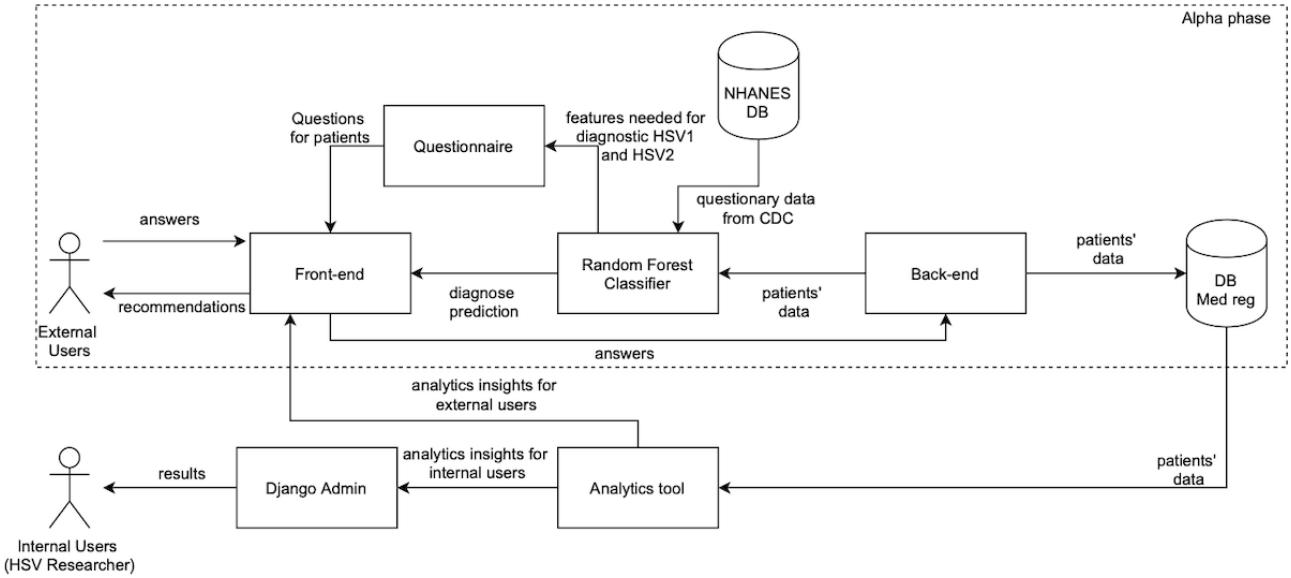
Overview of the Proposed Solution

We designed an algorithm to optimize data collection questionnaires for an HSV patient registry and predict HSV infection risk. Integrating a decision tree–based technology into a patient registry can reduce the number of questions users have to answer while increasing the data content and reducing informational entropy for each user's record. The model was trained using a pre-existing data set so that the question sets could be optimized to collect initial user data efficiently and

generate the most complete information to screen users' HSV risk. For nondiagnosed users, the model identifies risk groups based on the data provided. Data from users who are clinically diagnosed with HSV can be used to further train and improve the model.

HSV screening was chosen as the goal for the prototype solution to provide an efficient way of engaging users who otherwise might not be willing to participate in research or log HSV recurrence data. Three categories of users were considered when designing the system: two types of patient users (new and returning; external users) and HSV researchers (internal users). Since the barriers to user engagement and data collection are most pronounced when an external user starts using the system for the first time, an HSV preliminary screening tool was included to serve as an incentive to answer the list of questions and provide users with an assessment of their risk of HSV. The anonymous questionnaire was optimized to reduce information entropy and minimize the number of questions and their complexity while obtaining the maximum amount of information. The solution schema is represented in Figure 1.

Figure 1. Schema of the technological solution. HSV: herpes simplex virus, NHANES: US National Health and Nutrition Examination Survey, DB: database, CDC: Centers for Disease Control and Prevention, Med reg: medical registry.



Methods

Agile Development

The HSV patient registry development followed the agile framework defined by the UK Government Service Manual [32]. The alpha phase aims to develop the ideas formed in the previous discovery phase [3] and builds and tests prototype solutions. This involves examining the scope of the solution within the wider context of the users' journey and developing an online prototype that is accessible for various users.

Selection of a Database to Train and Test the Model

To develop and train the model, an initial data set that met the following requirements was needed:

- Open access, available without application or payment. This requirement is dictated by the fast iterative discovery approach that aims to maximize the speed and efficiency of the system development cycle
- A large number of patients included in the database; over 1000 rows are needed to provide sufficient data for machine learning model training and testing
- Clinically verified HSV diagnostic data
- Cross-referenced interviews and physical examination data
- An extensive list of demographics, lifestyle, and dietary variables
- High density of data points, meaning that most of the data fields are populated
- Verifiable data quality and reliability

The initial search was conducted via Google and patient registry lists using keywords related to human HSV patient databases and data sets. The data found on HSV patients consisted mostly of laboratory measurement data, which was not applicable for building a lifestyle-focused questionnaire. The US National Health and Nutrition Examination Survey (NHANES) was the only database identified that met all of the above requirements. Its data are in the public domain and can be used freely without obtaining copyright permission [33].

The NHANES Database

The NHANES database was a major program conducted by the US National Centre for Health Statistics (under the umbrella of the Centers for Disease Control and Prevention). It provides high-density population data, gathered by high-quality standards, and details the methodology and data provenance [34], where all data are anonymized and are open access for statistical analysis. The data set used in this project was representative of the US population in 2015-2016 [35]. Moreover, the NHANES collected demographic information, enriched by detailed dietary, examination, and laboratory data, all linked with unique participant IDs. The survey is unique in that it combines interviews and physical examinations. The NHANES interview included demographic, socioeconomic, dietary, and health-related questions. The examination component consisted of medical, dental, and physiological measurements, as well as

laboratory tests administered by highly trained medical personnel. All NHANES participants visited a physician. Dietary interviews, body measurements, blood sampling, and dental screening were included for all participants. Depending on the age of the participant, the rest of the examination included tests and procedures to assess the various aspects of health. HSV diagnosis was confirmed using diagnostic tests by physicians.

HSV-1 and HSV-2 Data Sets

Two data sets—concerning HSV-1 (HSV type 1) and HSV-2—were taken from the NHANES database and used to train and validate the model. The demographics of the validation data sets for HSV-1 and HSV-2 can be found in Figure 2. Males and females, aged 14-49 years, were represented in the data set. The HSV-1 data set contains data from 3386 participants: 1840 confirmed positive for HSV-1 and 1546 confirmed negative. The HSV-2 data set contains data from 2813 participants: 478 confirmed positive for HSV-2 and 2335 confirmed negative.

Figure 2. Demographics of the validation data set.

LBXHE1 - Herpes Simplex Virus Type 1

Variable Name: LBXHE1

SAS Label: Herpes Simplex Virus Type 1

English Text: Herpes Simplex Virus Type 1

Target: Both males and females 14 YEARS - 49 YEARS

Code or Value	Value Description	Count	Cumulative	Skip to Item
1	Positive	1840	1840	
2	Negative	1546	3386	
3	Indeterminate	7	3393	
.	Missing	317	3710	

LBXHE2 - Herpes Simplex Virus Type 2

Variable Name: LBXHE2

SAS Label: Herpes Simplex Virus Type 2

English Text: Herpes Simplex Virus Type 2

Target: Both males and females 18 YEARS - 49 YEARS

Code or Value	Value Description	Count	Cumulative	Skip to Item
1	Positive	478	478	
2	Negative	2335	2813	
3	Indeterminate	2	2815	
.	Missing	895	3710	

Data Set Preparation

A complete data set with questionnaires and results for the period 2015-2016 is available on the National Center for Health Statistics website [34]. The overall initial list of questions is listed in Multimedia Appendix 1 and comprises over 600 questions. For the model, a smaller number of questions that contained sufficient cross-referenced data points to allow for analysis (n=150) was selected (Multimedia Appendix 2) to avoid the influence of missing data on the prediction results and to exclude some of the potentially sensitive questions. The value distribution for the HSV diagnosis confirmation (y) is 2335 (negative) and 478 (positive).

Training and Testing Subsets

Using the data science method *train_test_split* from the *sklearn* Python library [36], the confirmed negative or positive cases reported in NHANES were randomly divided into two subdata sets for training and validation of the model with a ratio of 0.8 to 0.2. This ratio was chosen to keep the variance low and to leave enough data for training. The training data set was used to train the model, and the validation data set was used for accurate scoring. A threshold of 0.01 was experimentally defined to keep the list of questions as short as possible while maintaining good accuracy of the model. After checking feature importance values and determining that a *max_depth* value of 9 yields a threshold of feature importance less than 0.01, questions below the threshold were considered less relevant and were excluded.

Cross-validation With a Grit Search

GridSearchCV was employed on the training data with cross-validation to tune the random forest parameters for variable selection size, several trees to generate (n_estimators=550), and maximum tree depth (max_depth=9). GridSearchCV accuracy was compared to that of RandomizedSearchCV (n_estimators=300, maximum tree depth [max_depth]=9), with a better performance of GridSearchCV on test accuracy—GridSearchCV train accuracy: 0.978, test accuracy: 0.957; RandomizedSearchCV train accuracy: 0.978, test accuracy: 0.954. Considering the higher speed of performance for RandomizedSearchCV, it may be more appropriate to use RandomizedSearchCV in the future production implementations of the model.

Tools and Technology Stack for Model

A CART (classification and regression trees) random forest model was used to generate the main questionnaire. XGBoost approaches were also reviewed, but random forest performed better than XGBoost and with fewer complexities of implementation in production. Due to the high transparency and interpretability of CART models, a sequence of decision trees bagged into a random forest ensemble was chosen. The average decision tree plot, together with feature importance, was used to explore the full list of questions and define the shortest chain of interdependencies leading to HSV screening with the highest probability of accuracy.

The random forest ensemble was built from a sequence of decision trees using a bagging method [37]. Bagged decision tree ensembles are used to define entropy and information gain from previously selected features or discriminants [38]. Binary splitting on features with maximal informational gain leads to fewer nodes in the trees (ie, fewer relevant questions for diagnosing HSV). The model was designed to process the data in the following way:

1. The initial data set was divided into two subsets based on HSV type (1 or 2);
2. These data sets were randomly split by the data science method *train_test_split* from the sklearn Python library into a training set containing 80% of the samples and a validation set containing the remaining 20%;
3. The HSV-1 and HSV-2 training sets were processed by random forest classification estimators;
4. Accuracy on the training data sets was optimized by tuning the *max_depth* parameter (controls the total depth of the tree, that is, the number of binary splitting levels);
5. Accuracy was checked with validation subsets;
6. Values of *max_depth* gave the threshold of sufficient feature importance, and all questions below that level were excluded;
7. The final questions became the exhaustive list of features for the trained random forest classifier and used for the screening tool;
8. Given real-life data (questionnaire responses and clinical diagnosis verification), the model can improve its precision.

In this study, we designed and tested an algorithm that follows steps 1 to 7. Step 8, improvement of precision via integration within a live data collection system, is intended as a direction for future work.

Illustration of the Random Forest Decision Tree

The decision tree (here bagged into a random forest ensemble) does sequences of binary splitting (splitting the sets of questions into two subgroups that produce the greatest distinction between positive and negative HSV diagnosis) until the resulting number of splittings is sufficient to explain the general tendencies of the data set (until the model has learned hidden patterns in data). Splittings are performed on the most informative feature, that is, the data feature having the highest information gain. In this particular case, a depth of 9 hierarchical levels of splitting was enough for the model to learn the connections between the data features and HSV-1/HSV-2 diagnosis.

The decision trees in Multimedia Appendices 3 and 4 show the final iteration of the random forest training process. The best results were achieved after 9 levels of branching, and further learning (splitting) brought no meaningful improvements in classification.

Model Evaluation Metrics

The reduction in the number of questions needed to achieve high accuracy is an important success metric of the model. It can show the feasibility of using the model to reduce information entropy and encourage participants to complete the questionnaire. To validate the performance of the model, two key metrics were used: accuracy and recall score. Accuracy is the overall precision of the model in identifying HSV-positive patients from the questionnaire, whereas recall is a measure of the model's capability to identify true positives.

Recall score is an important metric because it is preferable to identify a noninfected as being in the risk group than vice versa. The lowest possible score is 0 (0%), the highest is 1 (100% probability of true prediction). The recall was calculated using the equation:

The resulting code can be found in a GitHub repository [39].

Results

Stage 1 Testing: NHANES Questions

The initial results of the random forest model computations are outlined in Table 1. As a result of the first stage of model development and testing, the number of questions was reduced from 150 to 62. The model selected a set of 62 questions that form shorter sequences for each user based on their age and gender. On average, a user would be asked 40 questions, with a minimum of 21 and a maximum of 62. It was estimated that it would take on average 25 minutes to answer all 150 questions depending on language and cognitive abilities, with the increased time required for sensitive questions. With only 40 questions, that would be reduced 3.75 times to less than 7 minutes. The final list of questions that could be presented to a user and the questionnaire flow can be found in Multimedia Appendix 5.

The confusion matrix for HSV-1 yielded 459 true positives, 81 true negatives, 8 false positives, and 15 false negatives.

Table 1. Stages 1 and 2 accuracy and recall scores.

Data set	Accuracy		Recall	
	Stage 1	Stage 2	Stage 1	Stage 2
HSV[a] type 1	0.61	0.91	0.83	0.88
HSV type 2	0.83	0.96	0.90	0.98

[a]HSV: herpes simplex virus.

Stage 2 Testing: NHANES Questions With Added Features

A lower accuracy score was found for the HSV-1 data set compared to the HSV-2 data set in stage 1. This meant that latent features inherited from NHANES were not strong enough to predict HSV-1 (Table 1). For example, the data set had limited symptom-related interview questions. Therefore, further research into HSV-1 and HSV-2 symptoms was conducted so that additional features could be introduced to the model and tested. A sample feature was added into the model based on literature suggesting that a significant proportion of people infected with HSV-1/HSV-2 virus types (up to 80%, depending on gender and virus type [40]) may experience more general symptoms like fever, muscle aches, and nausea. Therefore, a new question was added to the questionnaire for both HSV-1 and HSV-2 types: *Is your general feeling of discomfort or illness followed by one or more symptoms: fever, nausea, headaches, muscle pain, swollen lymph nodes, or malaise?* This additional feature was engineered for the data set, with a positive label in the 80% cases of the infected population. An additional question about symptoms with a high presence in HSV-infected people was introduced and improved the ability of the random forest model to train and test data predictions (Table 1).

Once the tool is in operation and is collecting real-world data (such that a significant number of participants answer the questionnaire and have their HSV status confirmed clinically), the model will gradually verify whether flu-like symptoms are a strong predictor of HSV. The model is intended to readjust the scoring method to exclude it as an important factor if this question turns out not to improve model accuracy.

Discussion

Principal Findings

This project has developed and successfully tested an optimization algorithm that minimizes the number of user-generated data points needed to accurately assess the risk of HSV-1 and HSV-2 infection. As a result of the implementation of the developed machine learning model, the algorithm was able to predict the HSV risk group attribution with high accuracy and recall scores, while the number of questions was reduced from 150 to 62. In the first stage of testing, the system was prototyped on the publicly available data of a small population of US citizens published in the NHANES database [3]. The second stage demonstrated how the same procedure could be repeated with additional variables (that are determined to be strongly linked to HSV infection) to achieve greater model accuracy.

Strengths and Limitations

A strength of the study is that it was conducted following the UK Government Service Manual for agile delivery [32] and was based on the principles established in a previously published discovery phase paper [3]. The project conducted fast technical prototyping to test the innovation's assumptions, for example, that it is possible to use machine learning methods to improve direct patient data collection for sensitive topics. The results of this study will therefore provide inputs for further development and beta system design improvements.

One limitation of the project is that the model was tested and trained using precollected survey data. These data are limited in both size and dimensionality and were relatively sparsely populated. Access to larger data sets with more symptom-related information would have been beneficial and likely would have enabled greater model accuracy.

Another limitation is that the model has not yet been trained and tested on real user data in the context of a patient registry or online questionnaire. It was designed to be used in a machine learning system with a feedback loop that enables verification of the predicted HSV risk level with subsequent clinically confirmed diagnoses. Without real-world data, this function could not be tested in this study.

Relation to Other Works

Many studies are applying decision trees and random forest machine learning models to patient databases to predict a variety of clinical risks [41-45]. However, there is only limited research

into the application of machine learning algorithms to produce or deliver adaptive or optimized questionnaires [46,47]. While adaptive questionnaires do already have a place in clinical evaluations, these tend to be based on predetermined rules [20]. However, these papers do not consider the implications of these models for the development of patient registries to support ongoing data collection that will enable model self-improvement.

Future Directions

The ultimate aim of this project is to increase the quality and quantity of data collected and improve the probability of users disclosing sensitive information and volunteering for clinical trials. The next step toward achieving a patient registry that meets these aims is to integrate the model into an independent backend module and connect it with a question-outputting and answer-collecting front end. This will enable further improvement of the model and testing of its self-improvement capabilities on real-world data. Once real users start using the screening tool and the tool predictions are verified by a clinician through diagnostic tests, the model will self-learn and verify or discard assumptions about relationships between the questions and HSV status. The model could also be improved by integrating more user data from EHRs to generate more insights regarding what questions can be more predictive of an individual's risk level.

Anonymization options, explicit permissions, and a standardized data schema that address the General Data Protection Regulation (GDPR), the Health Insurance Portability and Accountability Act (HIPAA), and the requirements of third-party interfaces (such as the Fast Healthcare Interoperability Resources [FHIR]) will be essential components for a platform based on the HSV screening tool. Some of the additional functionalities that could be considered for future research and system improvement are:

- Multiclass classification, where HSV-1 and HSV-2 data would be treated simultaneously: machine learning assembling would help researchers find additional patterns in the habits of patients with HSV in the generated response database;
- Adding descriptive user segmentation to the model: by defining the most recurring patient behavior and patients' profile type, the probability of gathering more relevant data could be improved.

Suggested Success Metrics for Future Work

According to the Gov.uk Service Design guidelines [32], the beta stage of the project will introduce and track key quantitative metrics of system performance. This tracking should include the following key metrics:

- Conversion rate: patients who visit the registry and proceed to start the questionnaire;
- Drop-off rate: patients who start the questionnaire and proceed to complete it;
- Retention rate: patients who complete the questionnaire and proceed to sign up to share personal data;
- Number of users who completed the screening questionnaire.

These metrics can be tracked by integrated database analytics and Google Analytics, which will also be important for accumulating user behavior data for future analytics and development.

Intended User Journey

The platform will be tailored for the two main groups of users: researchers and members of the public (which includes patients with a confirmed diagnosis and users who may wish to participate in the study or have concerns regarding the risks of HSV). Members of the public will be able to get an assessment of their risk of having HSV and will be encouraged to engage with further data sharing to obtain further health insights and support research endeavors. The system will be designed so that after new users receive the results from the screening tool, they will be asked whether or not they want to register and be added to the database. If they decide not to be added, their responses will be saved anonymously in the database and can be used as an additional source of insights into populations that would not provide any data that required registration, which will help address the challenge of selection bias.

If they do opt to register, users would receive access to dashboards that help them track their health and provide personalized insights, news, and advice. Consent processes would allow users to agree to notifications, give consent for trial involvement and use of data, and communicate with a clinician. The user responses will be recorded in the database and the model will self-improve based on the incoming data as each HSV screening tool result is compared to a clinically confirmed diagnosis.

Researchers will be able to use the registry to complement clinical research and facilitate patient recruitment for clinical trials. Researchers will need to register, be verified by the system administrator, and log in to their account before accessing pseudo-anonymized data (ie, data where personally identifiable information has been removed, but links to the original personal data are preserved). They will be able to filter user data to identify subsets of users with the characteristics they are investigating, send invitations to trial and research groups, and create further questions to identify trial eligibility. Introducing other potentially relevant variables into the questionnaire and model would also provide a means for researchers to test other assumptions of HSV on real users. The various user flows identified for the platform are listed in Multimedia Appendix 6.

Conclusion

This project successfully developed, trained, and tested a model to predict individuals' risk of HSV-1 and HSV-2 infection based on an optimized set of questions on demographics, lifestyle, and symptoms. Using machine learning to determine the questions with the best predictive value means that patients need to answer fewer survey questions. This solution will improve the user-centricity of patient registry systems and will address the challenge of collecting relevant, high-quality data from patients with a stigmatized health condition such as HSV. In the context of using the model within a patient registry platform that would enable ongoing data collection and feedback

process, the improved data collection process would lead to better research and patient outcomes by addressing the issues associated with data incompleteness, including selection bias and stigma. Future research and development of the system will use real-world data to improve the model, examine important anonymity, consent, interoperability, and data security concerns, and develop and evaluate a holistic patient registry system (with a front-end user interface and a back-end data architecture).

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Authors' Contributions

CL and EM conceived the study topic. SS and SG conducted the research and prototyped the model. SS prepared the first draft of the paper with revisions from MvV, EM, and CL, and the draft was revised and finalized by MM-I. All authors read and approved the final manuscript.

Conflicts of Interest

EM is the Editor-in-Chief of JMIRx Med.

Multimedia Appendix 1
Initial set of questions from NHANES.
[PDF File (Adobe PDF File), 346 KB - xmed_v2i2e25560_app1.pdf]

Multimedia Appendix 2
Questions selected to develop and train the model.
[PDF File (Adobe PDF File), 107 KB - xmed_v2i2e25560_app2.pdf]

Multimedia Appendix 3
Random forest decision tree for HSV-1.
[PNG File , 920 KB - xmed_v2i2e25560_app3.png]

Multimedia Appendix 4
Random forest decision tree for HSV-2.
[PNG File , 411 KB - xmed_v2i2e25560_app4.png]

Multimedia Appendix 5
Flow diagram and final selected questions.
[DOCX File , 56 KB - xmed_v2i2e25560_app5.docx]

Multimedia Appendix 6
The schema of user journeys.
[PDF File (Adobe PDF File), 20297 KB - xmed_v2i2e25560_app6.pdf]

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Abbreviations

CART: classification and regression trees
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resources
GDPR: General Data Protection Regulation
HIPAA: Health Insurance Portability and Accountability Act
HSV: herpes simplex virus
HSV-1: herpes simplex virus, type 1
HSV-2: herpes simplex virus, type 2
NHANES: US National Health and Nutrition Examination Survey

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Review

Mass Testing With Contact Tracing Compared to Test and Trace for the Effective Suppression of COVID-19 in the United Kingdom: Systematic Review

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Abstract

Background: Making testing available to everyone and tracing contacts might be the gold standard to control COVID-19. Many countries including the United Kingdom have relied on the symptom-based test and trace strategy in bringing the COVID-19 pandemic under control. The effectiveness of a test and trace strategy based on symptoms has been questionable and has failed to meet testing and tracing needs. This is further exacerbated by it not being delivered at the point of care, leading to rising cases and deaths. Increases in COVID-19 cases and deaths in the United Kingdom despite performing the highest number of tests in Europe suggest that symptom-based testing and contact tracing might not be effective as a control strategy. An alternative strategy is making testing available to all.

Objective: The primary objective of this review was to compare mass testing and contact tracing with the conventional test and trace method in the suppression of SARS-CoV-2 infections. The secondary objective was to determine the proportion of asymptomatic COVID-19 cases reported during mass testing interventions.

Methods: Literature in English was searched from September through December 2020 in Google Scholar, ScienceDirect, Mendeley, and PubMed. Search terms included “mass testing,” “test and trace,” “contact tracing,” “COVID-19,” “SARS-CoV-2,” “effectiveness,” “asymptomatic,” “symptomatic,” “community screening,” “UK,” and “2020.” Search results were synthesized without meta-analysis using the direction of effect as the standardized metric and vote counting as the synthesis metric. A statistical synthesis was performed using Stata 14.2. Tabular and graphical methods were used to present findings.

Results: The literature search yielded 286 articles from Google Scholar, 20 from ScienceDirect, 14 from Mendeley, 27 from PubMed, and 15 through manual search. A total of 35 articles were included in the review, with a sample size of nearly 1 million participants. We found a 76.9% (10/13, 95% CI 46.2%-95.0%; *P*=.09) majority vote in favor of the intervention under the primary objective. The overall proportion of asymptomatic cases among those who tested positive and in the tested sample populations under the secondary objective was 40.7% (1084/2661, 95% CI 38.9%-42.6%) and 0.0% (1084/9,942,878, 95% CI 0.0%-0.0%), respectively.

Conclusions: There was low-level but promising evidence that mass testing and contact tracing could be more effective in bringing the virus under control and even more effective if combined with social distancing and face coverings. The conventional test and trace method should be superseded by decentralized and regular mass rapid testing and contact tracing, championed by general practitioner surgeries and low-cost community services.

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KEYWORDS

COVID-19; SARS-CoV-2; test and trace; universal testing; mass testing; contact tracing; infection surveillance; prevention and control; review

Introduction

Background

The United Kingdom's Test and Trace program has been suboptimal in addressing the testing needs of those infected with SARS-CoV-2 and can hardly be expected to handle its new variant [1]. The panic over rising cases and a potentially more dangerous second wave led to the creation of the National Institute for Health Protection [2]. Other follow-up measures against rising cases have been the implementation of a national lockdown; a tier system; furlough and other support schemes; increased testing; and the approval of the Pfizer, Oxford AstraZeneca, and Moderna vaccines [3,4]. As part of the above, about 56 million tests were performed by January 10, 2021, with about 1.3 million vaccinated [5]. To meet testing needs, the United Kingdom plans to launch the £100-billion "moonshot" program. This program will perform optimally only if tests are delivered based on infections rather than on symptoms in controlling the pandemic [6,7]. According to the Director-General of the World Health Organization, "You cannot fight a fire blindfolded. And we cannot stop this pandemic if we don't know who is infected" [8]. Knowledge of infections could better inform public policy and facilitate the equitable rollout of vaccines. While we remain hopeful that vaccines will effectively speed up or provide herd immunity, it is important not to lose sight of other control measures like regular, widespread testing. Regular mass testing combined with contact tracing could be a novel control strategy not just to inform vaccination but also to guard against uncertainties arising from any new variant [9].

Research in Context

Prior to this study, 3 modeling studies implemented in the United Kingdom on mass testing were found. There was also 1 systematic review that evaluated the effectiveness of universal screening for SARS-CoV-2 compared to no screening [10].

This study is the first review, to the best of our knowledge, that sought to evaluate the benefits of mass testing and contact tracing (hybrid strategy) compared to test and trace, to control COVID-19 in the United Kingdom. The reported proportion of asymptomatic cases during mass testing was also explored.

There is an urgent need for a strategy that will identify SARS-CoV-2 carriers when their viral load is high and are most likely to be infectious. Real-time studies are needed to (1) obtain a true picture of disease burden, (2) validate various mass testing options for surveillance, and (3) better inform vaccination programs.

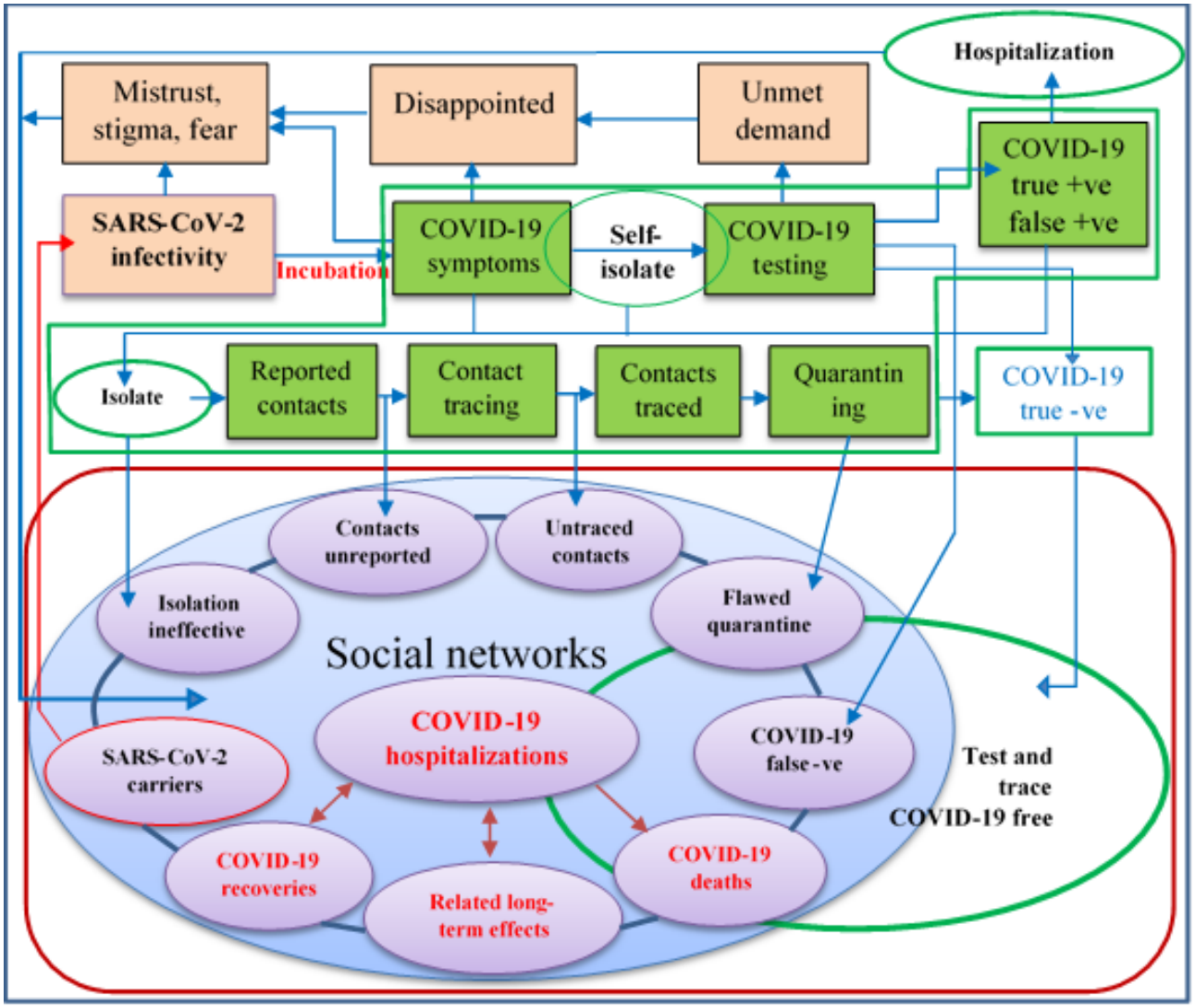
Conventional Test and Trace

Figure 1 shows the traditional test and trace system currently implemented in the United Kingdom, with several possible implications; readers should refer to the UK government website for further details on how the Test and Trace program works [11]. In the face of rising asymptomatic infectivity, the present delivery strategy can be categorized as "the cake not worth the candle," since the program fails to determine the true burden of the disease.

The following can generally be observed in the conventional system:

1. Individuals who are asymptomatic and presymptomatic are missed [12,13];
2. People are generally afraid of quarantine and may shy away from testing [14];
3. Decisions related to public safety (eg, getting tested) have been shifted to the public;
4. Operational false-positive estimates in the United Kingdom are currently unknown [15];
5. The proportion of daily asymptomatic cases is still not part of the reported national statistics and the true disease burden remains unknown [16];
6. Test and trace depend on self-reported contacts, which may be flawed;
7. Members of the public are hesitant due to data ethics–associated stigma [17];
8. The test and trace strategy is a shift away from universal health coverage in the midst of a pandemic [18];
9. Long travel and other factors are barriers to accessing sample collection centers;
10. There seems to be an apparent mix-up between "sample collection centers" and "testing centers."

Figure 1. The conventional test and trace system.



The "Infectivity Problem" of COVID-19

The "infectivity problem" can be summarized into (1) the test ramp-up controversy, (2) test and trace system leakages, (3) the time-to-test paradox, (4) inequitable test delivery, and (5) test and trace system delays.

Test Ramp-up Controversy

This refers to the heated discussion and lockdown-related antagonism expressed by the public regarding the undesired positive correlation, which was presumed inverse, between testing capacity and COVID-19 cases. The supposed endgame of test ramp-up was to contain the virus, but countries have found themselves in the opposite situation. This may be due to more cases now being detected as a result of increased testing or because testing is not comprehensive and early enough to outweigh viral shedding. This may culminate into the United Kingdom's "operation moonshot" controversy if the testing rate continues to be less than the infectivity rate [19].

Test and Trace System Leakages

Leakage refers to infectious individuals who are not detected. This includes those with either unreported symptoms or not presenting for testing despite being able to, those sent home due to an unavailability of tests, testing conducted on samples of compromised quality, unreported and untraced contacts, false negatives, and noncompliance to isolation and quarantine rules [20-22].

Time-to-Test Paradox

This refers to the conflicting interest of whether to test before symptom onset or upon reported symptoms. The Test and Trace program has been designed not to test people at the very early stages of infection for fear of missing out on the very cases it is meant to detect. The same is true when people are tested late [23,24]. A hidden "giant" within this paradox and a major contributor to transmissions is asymptomatic and presymptomatic infectivity. Research suggests that the serial interval of COVID-19 is shorter than the incubation period, indicating a possible infectivity multiplier effect before the onset of symptoms [25,26]. This is further compounded by the currently unknown operational false negatives [15].

Inequitable Test Delivery

This refers to testing that is not only being selective but is also not being delivered at the point of care. As a result, a major group of the public is eliminated. This has led to the lack of a comprehensive understanding of disease behavior.

Test and Trace System Delays

The problem includes delays in testing those reporting symptoms, test-to-results delays, and time lapses in contact tracing. These system delays have led to increasing infections in the face of delivering the highest number of tests in Europe [27]. A disease that is as deadly as the present one does not tolerate turnaround time and mitigation program mistakes, the biggest of which has been the neglect of asymptomatic infectivity.

Methods

Study Objectives

In this study, we compared the strategy of mass testing and contact tracing with the conventional test and trace method in the control of COVID-19 in the United Kingdom. Mass testing and contact tracing is one proactive way of testing individuals irrespective of symptoms to detect infections, track their contacts, and break the transmission circuit of SARS-CoV-2 in a timely manner [28,29].

This study's objective was twofold. We aimed (1) to evaluate the evidence of mass test and trace compared to conventional test and trace in the suppression of community transmissions of COVID-19 and (2) to find out the proportion of asymptomatic carriers during mass testing interventions.

The primary and secondary research questions are (1) is there evidence that testing irrespective of symptoms combined with tracing could suppress SARS-CoV-2 infections better than symptom-based testing and tracing? and (2) what is the proportion of asymptomatic carriers of SARS-CoV-2 reported during mass testing interventions?

Database Search

Search Strategy

A literature search was performed on September 9, 2020, and constantly refreshed through December 22, 2020. The search involved all articles in English published in 2020, including gray literature. Search terms in Google Scholar included "[UK] [effectiveness of mass testing] [COVID-19] [SARS-CoV-2] [contact OR tracing] [contact tracing] [effectiveness of test and trace] –Animals –Influenza –HIV –Cancer." The search was restricted to the year 2020.

An advanced search was performed in ScienceDirect for "[test and trace] OR [contact tracing] AND [COVID-19] AND [SARS-CoV-2] AND [asymptomatic] AND [symptomatic] OR [screening for SARS-CoV-2] OR [mass testing for SARS-CoV-2]" with article titles terms "[UK] AND [test and trace] OR [contact tracing] OR [community screening for SARS-CoV-2] OR [mass testing for SARS-CoV-2]." The search was restricted to the year 2020.

A search in PubMed included "(((((((mass testing for COVID-19 and "contact tracing") OR (mass testing for SARS-CoV-2 and "contact tracing")) OR ("test and trace")) OR ("mass testing" and "symptom-based testing")) NOT (Animals)) NOT (HIV)) NOT (Influenza)) NOT (Ebola)) NOT (Cancer)."

Finally, a search for "mass testing for COVID-19" AND "contact tracing for COVID-19" OR "mass testing for SARS-CoV-2" AND "contact tracing for SARS-CoV-2" was performed in Mendeley.

Eligibility Criteria and Exclusion

Eligibility

The population of interest included persons infected with SARS-CoV-2 who were either symptomatic or asymptomatic. The intervention of interest was mass testing irrespective of symptoms and tracing contacts. The comparison was a test and trace strategy based on symptoms. We were interested in studies evaluating effectiveness, cost-effectiveness, safety, acceptability, and equity under the primary research question, and the proportion of asymptomatic cases under the secondary research question. Studies that did not include contact tracing but compared testing irrespective of symptoms and symptom-based testing were also included under the primary research question.

Exclusion

Articles were excluded if they were published before the year 2020, were not in English, had inaccessible full texts, were not related to COVID-19, focused on nonhuman subjects, and were not related to mass testing. Given that this review was about detecting people currently infected, we excluded antibody studies. We also excluded editorials, theses, protocols, and news articles.

Selection and Publication Bias

The preferential publication of studies was counteracted by ensuring that our search included gray literature. Missing data effect verification was performed by searching for gray literature that sought to compare the effectiveness of the intervention to the control [30].

Data Management

Data Extraction

We performed a detailed screening of the extracted data for individual studies. Extracted data included the study date, author, setting, study design, study objective, type of intervention, outcome, type of participants, strategies used, assumptions, data analysis, results, study limitations, and bias.

Criteria for Grouping Studies

Following our study objective, studies for synthesis were grouped according to study outcomes. This was done to help capture the studies whose interventions were geared toward evaluating effects on outcomes of interest [31]. This also facilitated the synthesis of results according to the research questions.

Data Quality Assessment

Review findings were synthesized thematically. The quality of studies was critically appraised using the most recent tools based on study design, following the Public Health Ontario MetQAT (Meta Quality Appraisal Tool) 1.0 [32,33]. The methodology and risk of bias of modeling studies were assessed using the Relevance and Credibility Assessment of Modeling Studies tool proposed by Caro and colleagues [34]. Cohort studies were

assessed using the Critical Appraisal Skills Program (CASP) tool [35]. The Specialist Unit for Review Evidence (SURE) tool was used to assess cross-sectional studies [36]. Studies were grouped into 6 main categories according to study outcomes, as outlined in the eligibility criteria, for easy analysis and synthesis. The quality of evidence generated by different studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [37].

Standardized and Synthesis Metrics

The direction of effect was used as the standardized metric because there was a lack of precision, which was specific to the effect of the intervention and control in the results presented by different studies. This did not permit the calculation of summary statistics [38]. In light of the above, vote counting was the best match in synthesizing the results. A sign test was used to indicate whether there was evidence of an effect or not. Equivocal effects between the intervention and control were considered to be distributed around the null hypothesis of no effect. This study made use of Synthesis Without Meta-Analysis (SWiM) reporting guidelines to report review results [39].

Data Presentation and Visualization

Tabular and graphical methods were deployed in presenting the results of this study. For the primary objective, the GRADE summary of findings table was used to present the certainty of evidence and a bar chart to present the effect direction of studies. For the secondary objective, forest plots were used to present the proportion of asymptomatic cases of SARS-CoV-2, using an Excel model proposed by Neyeloff et al [40].

Criteria for Prioritizing Results

Concerning the primary question, the results of studies that evaluated the effectiveness of the intervention and control within the United Kingdom, with low risk of bias, were prioritized since this was in line with the review objective. Real-time studies were also prioritized as these are more likely to resemble reality.

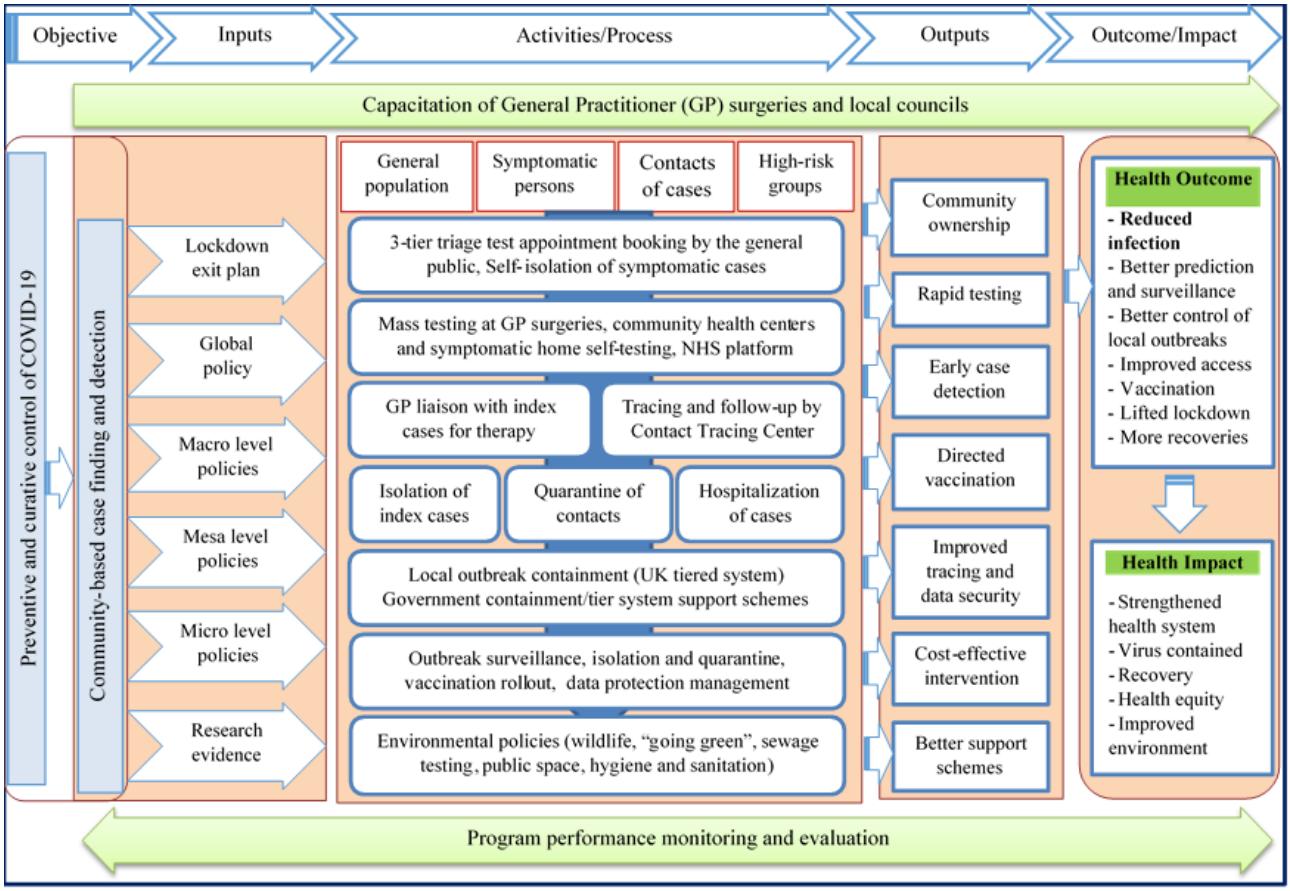
Heterogeneity Assessment

The heterogeneity of studies was assessed following the GRADE risk assessment factors [41]. The lack of a pooled effect size for modeling studies did not warrant us to perform a test for methodological diversity for the primary objective [42]. Regarding the secondary objective, however, variability was assessed by directly observing the confidence intervals on the plotted graphs.

Active Runs of the Intervention

The novel mass test and contact trace strategy (1) extends the present test and trace system to the general public and (2) moves it from laboratory-based to point-of-care settings, thereby enhancing acceptability, accessibility, and equity. A framework is used to explain how the novel strategy could be implemented. This framework is a modification of the one proposed by Lassi et al [43]. Community ownership in the implementation of this strategy requires each individual to be registered with a general practitioner (GP) surgery and the capacitation of GP surgeries to perform routine, open-invitation testing irrespective of symptoms. The strategy equally necessitates the availability of rapid easy-to-run, cost-effective tests and a succinct phasic exit strategy. Strategy inputs include macro policies (fiscal, support schemes, personal protective equipment, hygiene and sanitation, environmental, a tier system, vaccination development and approval, etc), mesa policies (GP capacitation, social gathering, at-risk group, vaccination, etc), and micro policies (testing, health status, personal hygiene, compliance to national guidelines, tracing app acceptability, etc). Routine health checks with GPs have hardly raised concerns around privacy due to trust. Patients find it more reliable and assuring if GPs run testing programs, offer direct vaccination and therapy to those that have tested positive, and request those with positive test results to report their contacts on the National Health Service (NHS) Contact Tracing platform. Through a shared platform, the Contact Tracing Center could be granted access to a limited data set or escalate reported contacts to the NHS Contact Tracing system. The contact tracing team liaises with index cases for the reporting of any additional contacts and calls all listed contacts for quarantine advice. Based on the data collected, the tier management team and environmental health officers work in synergy with local councils toward local containment strategies, similar to how the local outbreak in Leicester was managed. Figure 2 shows the workflow of the proposed intervention.

Figure 2. Framework for decentralized mass testing and contact tracing. NHS: National Health Service.



Results

Search Results

The search yielded 286 articles from Google Scholar, 20 articles from ScienceDirect, 14 articles from Mendeley, 27 articles from PubMed, and 15 articles from other sources, for a total of 362 articles. Altogether 64 eligible articles were screened for inclusion. Given the ambiguity in the use of contact tracing in most studies to include testing, studies evaluating the effectiveness of contact tracing were included, provided they had a component of mass testing. Considering the novelty of the term "test and trace" used in this study, it is commonplace to find contact tracing based on symptom testing used in studies to be likened to test and trace in this review. A total of 35 articles that met the eligibility criteria were included in the review. A flowchart of how articles were selected can be seen in Figure 3.

Table 1 shows a brief description of the included studies [44-78]. Detailed characteristics of the studies can be found in Table S1 of Multimedia Appendix 1. Table S1 of Multimedia Appendix 2 presents the characteristics of excluded studies [79-107].

Figure 3. Flowchart showing article counts at each stage as well as the number of included articles.

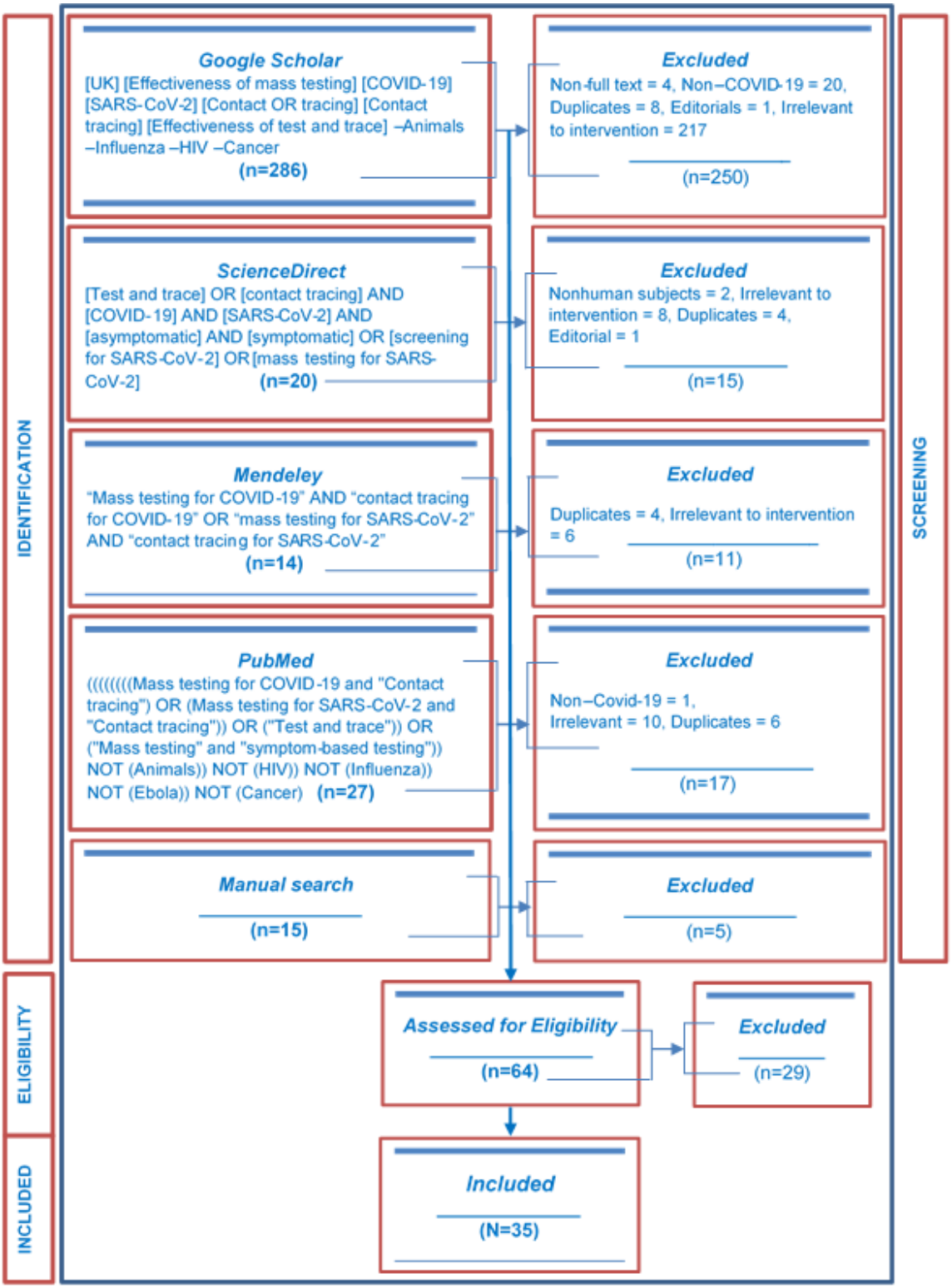


Table 1. Summary description of included studies.

Study	Description
Effectiveness	
Emery et al [44]	Asymptomatic transmissions among 3711 cruise ship passengers and crew, Japan
Grassly et al [45]	Percent reduction in reproduction number (hypothetical sample), United Kingdom
Tsou et al [46]	Outbreak containment using 393 COVID-19 cases, Taiwan
Mizumoto et al [47]	Asymptomatic cases among 3063 cruise ship passengers, Japan
Sasmita et al [48]	Infections using COVID-19 data, Indonesia
Moghadas et al [49]	A hypothetical population of 10,000 to measure required isolation and curtail silent transmission, Canada
Bracis et al [50]	SARS-CoV-2 transmissions projection using daily COVID-19 cases of King County from March 8-29, United States
Pollmann et al [51]	Impact of digital contact tracing (hypothetical sample)
Hill et al [52]	Reduction in infections using contact data from 2010, United Kingdom
Gorji et al [53]	Reduction in reproduction number (hypothetical sample), Switzerland
Alsing et al [54]	Intervention efficacy using commuter data from 2011, United Kingdom
Hagan et al [55]	SARS-CoV-2 prevalence among incarcerated persons in 6 jurisdictions, United States
Cost-effectiveness	
Paltiel et al [56]	Evaluate clinical and economic performance using a hypothetical cohort of 4990, United States
Asymptomatic proportion	
Porru et al [57]	Health surveillance among 5942 staff of a hospital, Italy
Nishiura et al [58]	Asymptomatic ratio among 565 passengers, Japan
Treibel et al [59]	Asymptomatic carriers among 400 health care staff, United Kingdom
Abeysuriya et al [60]	SARS-CoV-2 prevalence among 180 pregnant women, United Kingdom
Brown et al [61]	SARS-CoV-2 prevalence among 1152 health care workers in 6 hospitals, United Kingdom
Graham et al [62]	Infections, clinical features, and outcome among 464 residents and staff in care homes, United Kingdom
Arons et al [63]	Transmission and adequacy of symptom-based screening among 89 residents of a skilled nursing home, United States
Jameson et al [64]	Asymptomatic infections among 121 nonsymptomatic health care staff, United States
Callaghan et al [65]	Prevention effectiveness and prevalence of SARS-CoV-2 among 46 patients and 171 health care staff, United States
Louie et al [66]	Transmission monitoring among 734 persons, United States
Gudbjartsson et al [67]	Transmissions among 9199 targeted, 10,797 openly invited, and 2283 randomly sampled persons, Iceland
Reid et al [68]	Testing and cases among 5204 health care staff, Canada
Lavezzo et al [69]	Population exposure among 2812 residents before and 2343 residents after the lockdown, Italy
Kimball et al [70]	The utility of symptom screening among 76 older adults in a skilled nursing home, United States
Olalla et al [71]	Asymptomatic cases among 498 health care staff, Spain
Guery et al [72]	Infections among 136 nursing care home staff, France
Roxby et al [73]	COVID-19 morbidity among 142 staff and residents in a residential community, United States
Lytras et al [74]	SARS-CoV-2 prevalence among passengers repatriated from the United Kingdom (n=357), Spain (n=394), and Turkey (n=32) to Greece
Hoehl et al [75]	Infections among 125 passengers evacuated to Germany
Cao et al [76]	Prevalence among 9,899,828 residents in China
Baggett et al [77]	Infections among 408 homeless shelter residents, United States
Imbert et al [78]	Infections among 150 homeless shelter residents, United States

Of the 35 studies, 12 (34%) were models, 1 (3%) was a cohort study, and 22 (63%) were cross-sectional studies. In total, 11 studies were implemented in the United States [50,55,56,63-66,70,73,77,78], comprising a sample population of 23,088 participants. Of the 35 studies, 7 (20%) were implemented in the United Kingdom [45,52,54,59-62], with a sample size of 2196 in addition to the real-world data sets that were used in the modeling studies. Three of the studies (8%) were implemented in Japan [44,47,58], with a sample size of 7339. Two of the studies (6%) were implemented in Canada [49,68], with an overall sample size of 5204 subjects (one of the studies used a hypothetical sample). Two studies (6%) were implemented in Italy [57,69], with an overall sample of 11,097 subjects. One study (3%) was implemented in each of the following countries: Taiwan (n=393 subjects) [46], Indonesia [48] using COVID-19 data, Switzerland [53], Spain (n=498 subjects) [71], Germany (n=125 subjects) [75], Greece (n=783 subjects) [74], France (n=136 subjects) [72], Iceland (n=22,297 subjects) [67], and China (n=9,899,828 subjects) [76]. The studies by Moghadas et al [49], Pollmann et al [51], Hill et al [52], and Paltiel et al [56] made use of hypothetical samples.

Methodological and Risk of Bias Assessment

The methodology and risk of bias assessment was organized according to study design and using the most comprehensive assessment tools. This review made use of the "whole study" assessment method and deployed study design–specific tools, due to the lack of a standardized tool for nonrandomized controlled studies [33,108]. This review's critical appraisal is also in line with the PHO MetQAT 1.0 quality appraisal tool [32].

Modeling Studies

The Relevance and Credibility Assessment for Modeling Studies tool was used to evaluate the methodology and risk of bias of modeling studies [34]. A total of 12 (34%) modeling studies [44-54,56] were included and assessed for risk of bias. Of the 12 studies, 5 (42%) were judged to be at low risk of bias, 4 (33%) to be at moderate risk of bias, and 3 (25%) to be at high risk of bias. The main concerns regarding the risk of bias included inappropriate population and setting: no real-world data set leading to either an unreported or inadequately reported validation process of models. There were issues with either the model validation process or the use of a real-world data set across 7 of the 12 studies (58%) that were rated to be either at moderate or at high risk of bias. Above all, the models were based on a series of assumptions, most of which may not work in real life. A summary of the risk of bias assessment of modeling studies is presented in Table 2. A more detailed risk of bias assessment of models can be found in Table S1 of Multimedia Appendix 3.

Table 2. Risk of bias of modeling studies.

Study	Relevance	Credibility	Overall risk
Effectiveness			
Emery et al [44]	Insufficient	Insufficient	Low
Grassly et al [45]	Sufficient	Sufficient	Low
Tsou et al [46]	Insufficient	Insufficient	High
Mizumoto et al [47]	Insufficient	Insufficient	Moderate
Sasmita et al [48]	Insufficient	Insufficient	Moderate
Moghadas et al [49]	Sufficient	Insufficient	High
Bracis et al [50]	Insufficient	Sufficient	Low
Pollmann et al [51]	Insufficient	Insufficient	High
Hill et al [52]	Sufficient	Sufficient	Low
Gorji et al [53]	Insufficient	Insufficient	Moderate
Alsing et al [54]	Sufficient	Insufficient	Low
Cost-effectiveness			
Paltiel et al [56]	Insufficient	Insufficient	Moderate

Cohort Study

The single cohort study [57] included in the review was rated to be at moderate risk of bias, principally due to unsuitable population and setting. This study was implemented in Italy. The study's risk of bias was assessed using the CASP checklist for cohort studies [35]. In this study, contact tracing was limited to control. There could have been issues surrounding participant selection due to unreported eligibility criteria. In addition, no details were provided about loss to follow-up and how this was managed. Table S1 of Multimedia Appendix 4 provides a detailed risk of bias assessment for this study.

Cross-sectional Studies

The risk of bias assessment of cross-sectional studies was conducted using the SURE tool [36]. A total of 22 cross-sectional studies were assessed: 5 (23%) were judged to be at low risk of bias, 1 (4%) at moderate risk of bias, and 16 (73%) to be at high risk of bias. The authors of 10 (45%) studies failed to clearly state their study design. The study population

and setting were unrepresentative in up to 82% (n=18) of the studies. Contact tracing as part of the intervention was lacking in 27% (n=6) of studies. The authors in 15 of the 22 studies (68%) did not justify their sample size. The fair selection of participants was not clear in 73% (n=16) of studies due to unreported eligibility criteria. Statistical methods used in study analysis were unreported in 45% (n=10) of studies, while the reporting of statistical analysis was judged to be inadequate in 18% (n=4) of studies. Nine studies (41%) did not provide technical details regarding sample collection and management. Additionally, only 50% (n=11) of studies provided technical details about testing. Unreported blinding was observed in 95% (n=21) of studies. Seven studies (32%) did not report limitations, leading to possible study bias. Lack of participant characteristics was also observed in 32% (n=7) of studies. Bias due to conflicting interests was judged to be possible in 18% (n=4) of studies since the authors' conflicts of interest were not declared. Table 3 displays a summary of the risk of bias rating for cross-sectional studies. A detailed examination of how cross-sectional studies were assessed is found in Table S1 of Multimedia Appendix 5.

Table 3. Risk of bias of cross-sectional studies.

Study	Overall risk
Effectiveness	
Hagan et al [55]	High
Asymptomatic proportion	
Nishiura et al [58]	High
Treibel et al [59]	High
Brown et al [61]	Low
Graham et al [62]	Low
Abeysuriya et al [60]	Low
Arons et al [63]	High
Jameson et al [64]	High
Callaghan et al [65]	High
Louie et al [66]	Moderate
Gudbjartsson et al [67]	High
Reid et al [68]	High
Lavezzo et al [69]	Low
Kimball et al [70]	High
Olalla et al [71]	High
Guery et al [72]	High
Roxby et al [73]	High
Lytras et al [74]	High
Hoehl et al [75]	High
Cao et al [76]	Low
Baggett et al [77]	High
Imbert et al [78]	High

Synthesis of Results

Is There Evidence That Mass Testing and Contact Tracing Could Suppress the Community Spread of SARS-CoV-2 Infections Better Than Test and Trace?

Vote counting was deployed as the method to synthesize results, in line with the direction of effect that was used. Studies were prioritized based on their degree of bias in the reported evidence. The GRADE diagram for assessing the quality of evidence was used to grade the evidence presented by the different studies [109].

Effectiveness

Of the 12 studies categorized under this outcome, 4 (33%) were at high risk of bias, 3 (25%) were at moderate risk of bias, and 5 (42%) were rated as low. A total of 9 (75%) studies [44,46,47,49,51-55] were voted in favor of the intervention (95% binomial exact [BE] CI 42.8%-94.5%, *P*=.15). Three of the 12 (25%) studies [45,48,50] showed an unfavorable direction of effect and were voted in favor of the control (95% BE CI 5.5%-57.1%, *P*=.15). The body of evidence presented by the 11 modeling studies [44-54] for this outcome was downgraded by three levels to "very low." First, studies were downgraded

one level because they were neither randomized controlled trials nor real-time studies. An additional two levels of downgrading were due to serious study bias, interstudy variation, imprecision, and indirectness. The evidence from the lone cross-sectional study by Hagan et al [55] was downgraded by three levels to "very low" as well. It was downgraded by one level because the study was not a randomized controlled trial and was further downgraded by two levels due to methodological issues, imprecision, and indirectness.

Cost-effectiveness

The single study found for this outcome [56] was voted in favor of the intervention. This study was judged to be at high risk of bias. The quality of evidence was downgraded by one level given that it was not a randomized controlled trial. Being a model based on assumptions, coupled with study limitations, imprecision, and indirectness, the evidence was further downgraded by two levels. The evidence was classified as very low.

Safety

We found no study addressing this outcome. There have been mixed views regarding the safety of mass testing and contact tracing. Some argue that rapid mass testing will lead to false positives and negatives, thereby causing misinformation [79,110]. Others see both rapid mass testing and contact tracing as safety nets against virus spread [111-114]. Both nasopharyngeal and oropharyngeal swaps appear to be slightly invasive. There also exists a body of evidence regarding safety and security concerns from the public on contact tracing [115-117].

Acceptability

Again, no study was found regarding this outcome. Altmann and colleagues [111] found a high level of acceptance for app-based contact tracing. Their investigation was done across different countries including the United Kingdom [111]. It was also reported that there is a higher preference for government contact tracing applications than those managed by private companies [22].

Equity

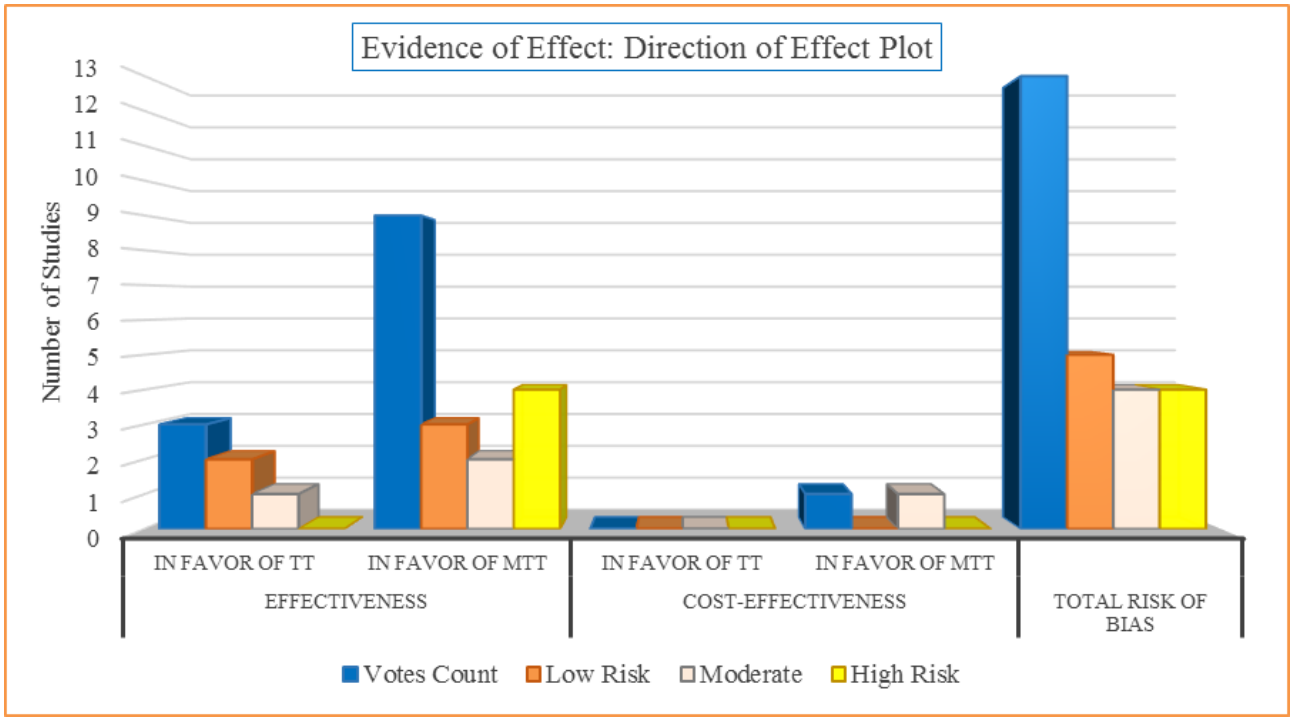
There was no study evaluating this outcome. It remains, however, clear that the test and trace system is not equitable [18]. Testing that is delivered near the patient and at a walkable distance increases equity [118,119].

Binomial Test and 95% CI

A total of 13 studies were retained to assess the primary objective. Statistical synthesis for the primary objective was based on the binomial probability test and BE CIs performed in Stata 14.2 (StataCorp LLC). Of the 13 studies, 10 (76.9%) favored the intervention (95% BE CI 46.2%-95.0%, *P*=.09), with just 3 (23%) studies voted in favor of the control (95% BE CI 5%-54%, *P*=.09). The above indicates that the intervention is a better strategy than the control in the suppression of SARS-CoV-2 transmissions. The probability that the above estimate is true if the conventional Test and Trace program was truly better than mass testing and contact tracing is just 9%. The 76.9% (10/13) favorable direction of effect is a clear enough majority vote to indicate that mass test and trace is truly more beneficial.

Assuming that the true probability of both mass testing with contact tracing and test and trace being equivocal is .50 under the null hypothesis (H_0: mass test and trace=test and trace), this study observed 10 out of 13 votes (76.9%), which is well above the expected binomial probability mean of 6.5 (SD 1.803) votes. Of the 10 studies, 4 (40%) in favor of the intervention were judged to be at high risk of bias, 3 (30%) at moderate risk of bias, and 3 (30%) at low risk of bias. A total of 23% (n=3) of the retained studies had representative samples and settings. Two of 3 studies (67%) implemented in the United Kingdom [52,54] voted in favor of the intervention were judged to be at low risk of bias. The effect direction plot of different studies, together with the associated risk of bias, is shown in Figure 4.

Figure 4. Evidence of effect attributable to the intervention (mass testing and contact tracing, MTT) and control (test and trace, TT) for the primary objective.



The results of 6 studies [44,47,52-54,56] were judged to be at low to moderate risk of bias. These studies were prioritized in concluding that the mass testing and contact tracing strategy was more effective in the suppression of community transmission of SARS-CoV-2 and the control of COVID-19 than conventional test and trace. The studies by Emery et al [44], Hill et al [52], and Alsing et al [54] were judged to be at low risk of bias. Two of these (ie, [52,54]) were both representative of the population and evaluated mass testing and contact tracing as a hybrid strategy, in line with the primary objective. Emery et al [44] failed to consider contact tracing but compared the effectiveness of testing based on symptoms and testing irrespective of symptoms. We concluded that the direction of effect will not be different if contact tracing were to be integrated since contact tracing is contingent on testing.

The generated GRADE evidence profile was used to present the synthesis findings regarding the primary objective (Table 4). Table S1 of Multimedia Appendix 6 provides details of how the evidence for different outcomes under the primary objective was graded.

Table 4. Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile: certainty of evidence for the primary objective.

Outcome	Studies, n	Quality of evidence factors					Direction of effect SOF[a]			Quality of evidence[b]
		Limitation	Heterogeneity	Indirectness	Imprecision	Publication bias	TT[c], n	MTT[d], n	Direction[e]	
Effectiveness										
Model	11	Serious	Serious	Serious	Serious	Unlikely	3	8	↑	Very low
Cross-sectional study	1	Not serious	Unlikely	Serious	Serious	Unlikely	0	1	↑	Very low
Cost-effectiveness										
Model	1	Serious	Unlikely	Serious	Serious	Unlikely	0	1	↑	Very low

[a]SOF: summary of findings.

[b]Quality of evidence graded as either "very low," "low," "moderate," or "high."

[c]TT: test and trace.

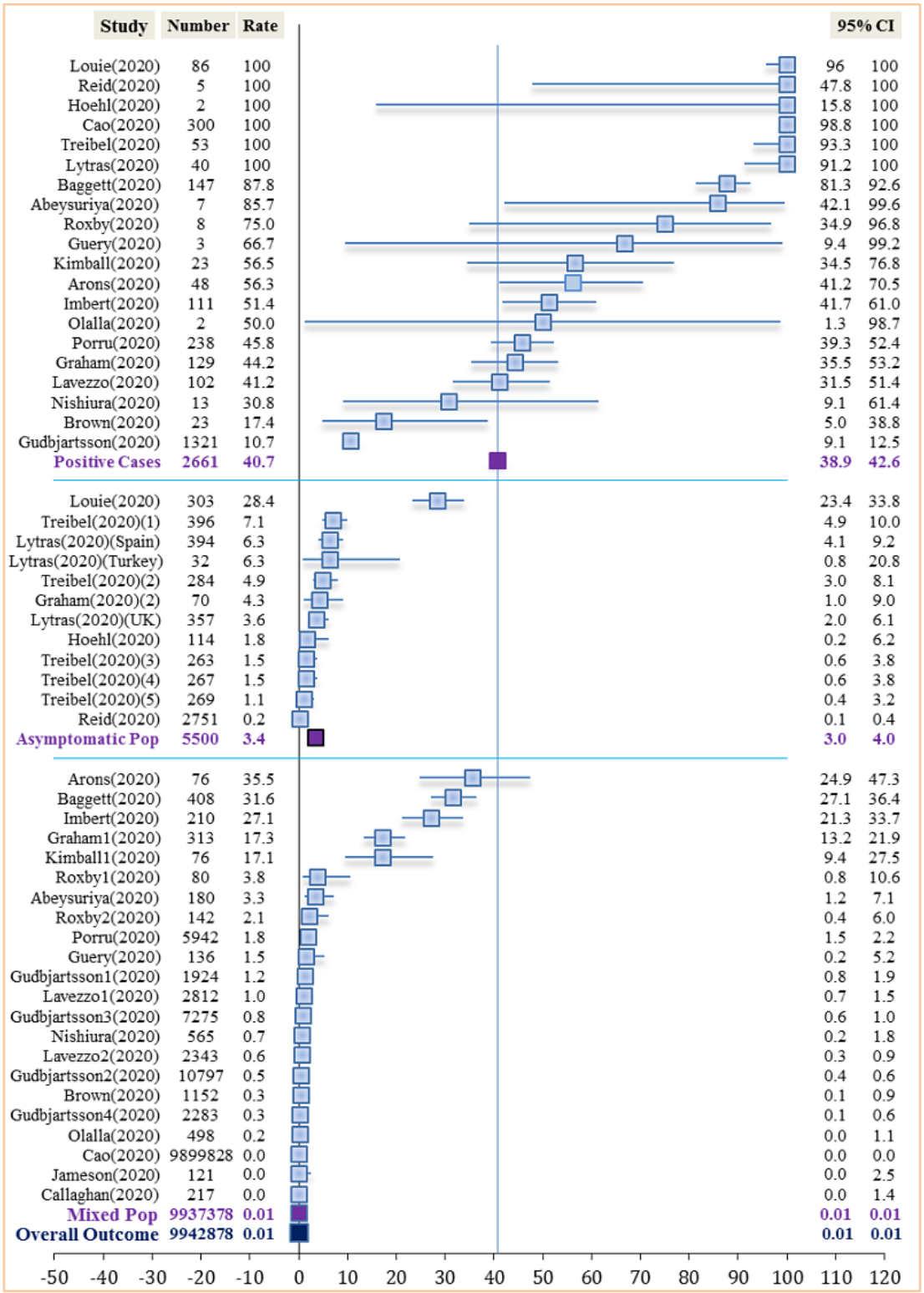
[d]MTT: mass testing and contact tracing.

[e]↑MTT is better than TT; ↓TT is better than MTT; ↔ MTT and TT are equivocal.

What Is the Proportion of Asymptomatic Cases of SARS-CoV-2 Reported During Mass Testing Interventions?

A total of 21 cross-sectional studies and 1 cohort study [57-78] were retained under the secondary objective. There was limited precision in effect estimates with just 27% (6/22) of studies providing data on CIs for the proportion of asymptomatic carriers. Of the 22 studies, 7 (32%) were judged to be at low to moderate risk of bias. A graphical presentation of the asymptomatic proportion from the 22 studies (34 reports) can be seen in Figure 5. The sampled population ranged from 76 to 9,899,828 subjects, with a median sample of 395.5 subjects. The number of detected positive SARS-CoV-2 cases and asymptomatic carriers ranged from 0 to 1321 and from 0 to 300, respectively. Likewise, the mean number of positive cases and asymptomatic carriers were 120.9 (SD 280) and 49.3 (SD 71.1), respectively.

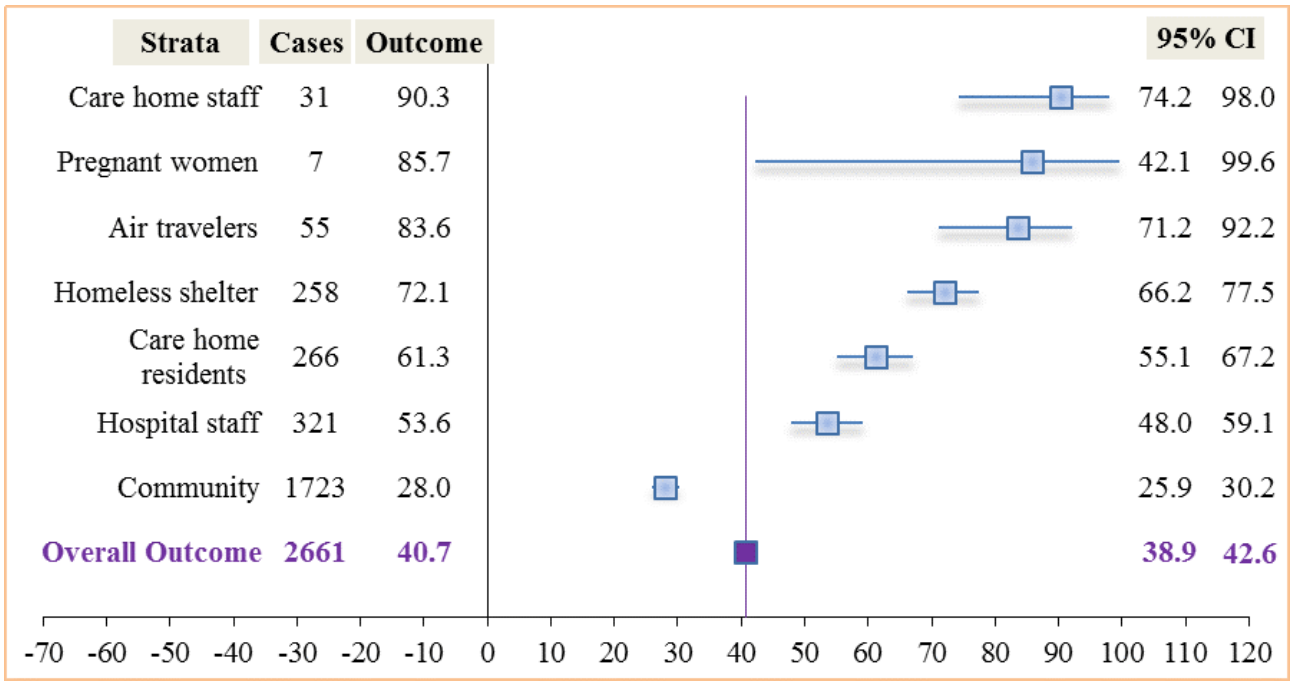
Figure 5. Asymptomatic SARS-CoV-2 carriers among detected cases, in asymptomatic and mixed-sample populations.



Outcome Among Stratified Positive Cases

The proportion of asymptomatic cases among those testing positive ranged from 28% (483/1723, 95% CI 25.9%-30.2%) in the community (testing of residents) to 90.3% (28/31, 95% CI 74.2%-98.0%) among care home staff. The overall proportion was found to be 40.7% (1084/2661, 95% CI 38.9%-42.6%) (Figure 6). Two studies [64,65] with sample sizes of 121 and 217 subjects, respectively, detected neither cases nor found any asymptomatic carriers and were excluded in the evaluation of asymptomatic carriers among persons who tested positive.

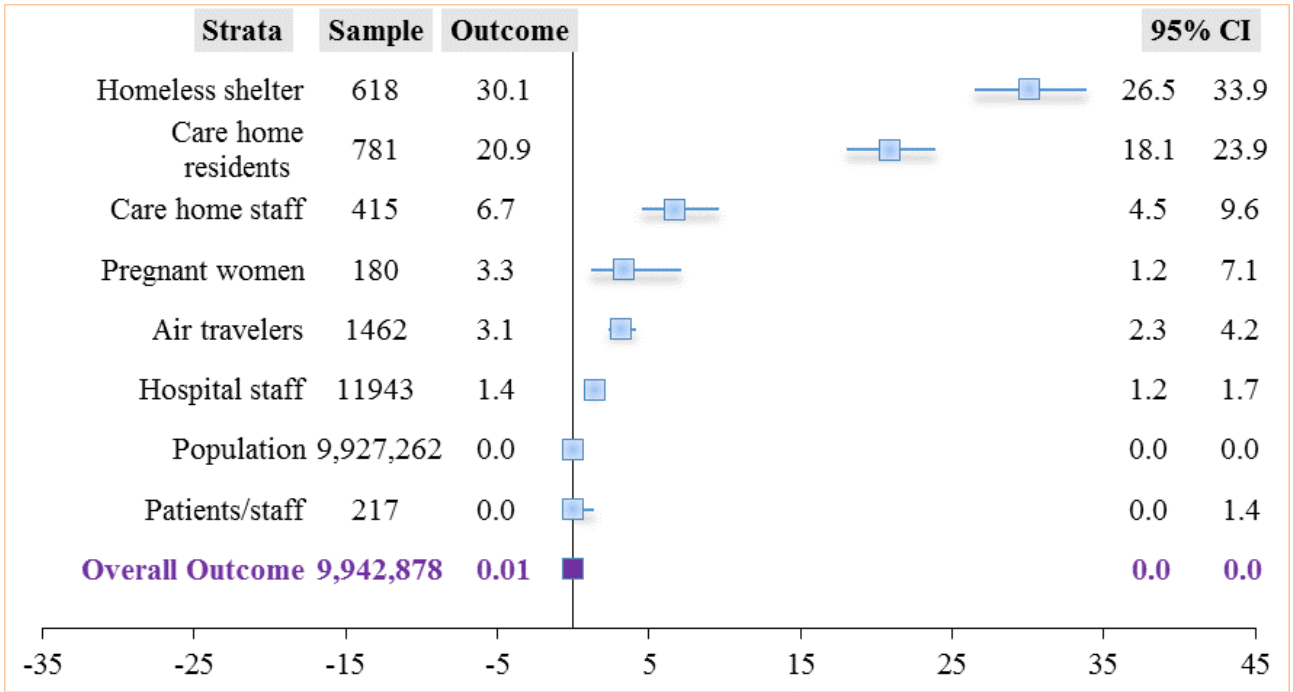
Figure 6. Asymptomatic SARS-CoV-2 carriers among stratified positive cases.



Outcome Among Stratified Sample Populations

The prevalence of asymptomatic SARS-CoV-2 cases was highest among homeless shelter residents (186/618, 30.1%; 95% CI 26.5%-33.9%), followed by care home residents (163/781, 21%; 95% CI 18%-24%), and lowest among hospital patients (0/217, 0%; 95% CI 0.0%-1.4%). The overall prevalence for all studies was 0.01% (1084/9,942,878; 95% CI 0.0%-0.0%). Excluding screening in the general population in the studies by Cao et al [76], Gudbjartsson et al [67], and Lavezzo et al [69], overall asymptomatic SARS-CoV-2 prevalence for all other settings was found to be 3.8% (601/15,616, 95% CI 3.5%-4.2%). Figure 7 shows the outcome prevalence in various specific sample populations.

Figure 7. Asymptomatic SARS-CoV-2 carriers in the stratified overall sampled population.

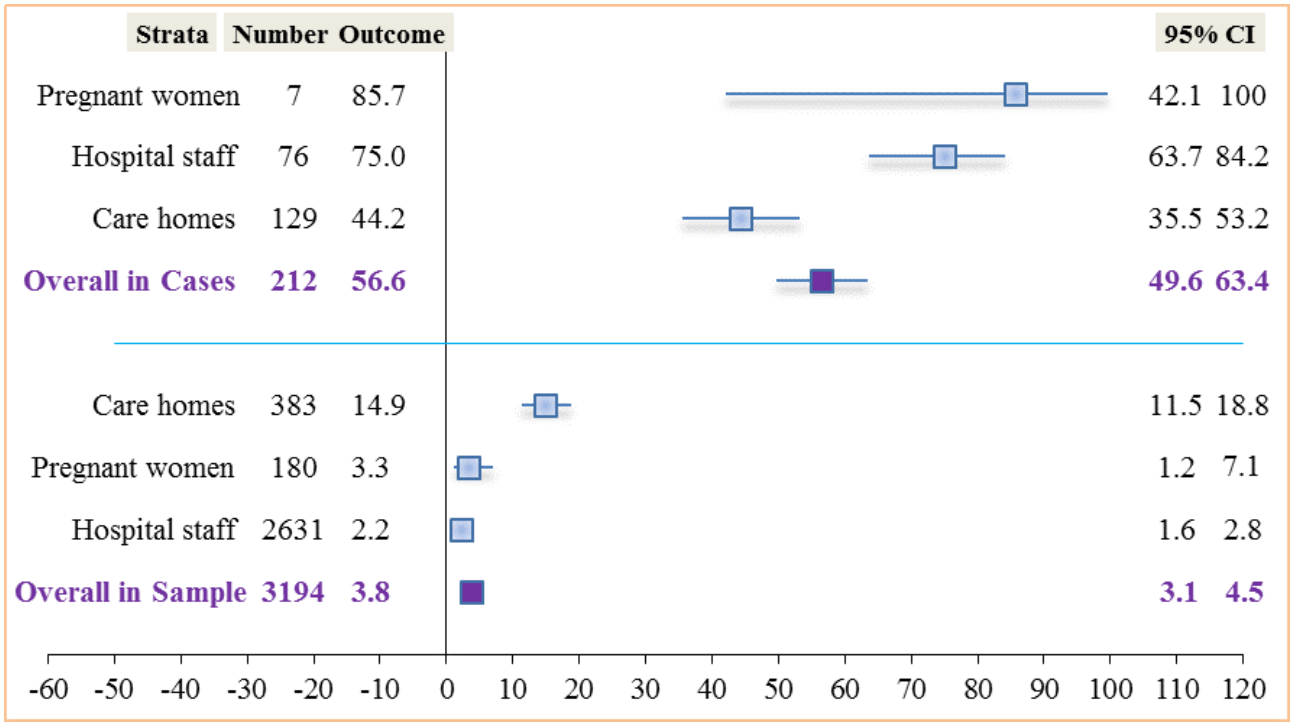


The prevalence among asymptomatic populations from 6 studies [59,62,66,68,74,75] was 3.4% (189/5500, 95% CI 3%-4%). The prevalence in a mixed population from 17 studies [57,58,60-65,67,69-73,76-78] averaged 0.009% (895/9,937,378, 95% CI 0.0%-0.0%) (Figure 5).

Outcome Within the United Kingdom

Four studies [59-62] evaluated the outcome within the United Kingdom. Treibel et al [59] and Brown et al [61] evaluated the outcome among hospital staff, Graham et al [62] evaluated it in care homes, and Abeysuriya et al [60] among pregnant women at term. The overall asymptomatic SARS-CoV-2 proportion among detected cases in the United Kingdom was found to be 56.6% (120/212; 95% CI 49.6%-63.4%). The proportion of asymptomatic cases among those tested positive ranged from 44.2% (57/129; 95% CI 35.4%-53.2%) in care homes to 85.7% (6/7; 95% CI 42.1%-100%) in pregnancy. Figure 8 shows the relationship of asymptomatic proportion among detected cases and in the sampled population in different settings within the United Kingdom.

Figure 8. Asymptomatic SARS-CoV-2 carriers among cases and in the sampled population in the United Kingdom.



The overall prevalence of asymptomatic cases within the United Kingdom was found to be 3.8% (120/3194; 95% CI 3.1%-4.5%) with rates ranging from 2.2% (57/2631; 95% CI 1.6%-2.8%) among hospital staff to 14.9% (57/383; 95% CI 11.5%-18.8%) in care homes. Figure 8 demonstrates a higher overall rate among detected cases in the United Kingdom (120/212, 56.6%) compared to that of all studies (z=4.52, *P*<.001). We found in this review that asymptomatic cases were 1.4 times (56.6%/40.7%) more likely to be detected among positive cases in the United Kingdom than all studies put together. The overall SARS-CoV-2 prevalence rate in the United Kingdom (120/3194, 3.8%) was similar to that of all studies put together (601/15,616, 3.8%), excluding studies undertaken at the population level.

All unreported and unsuitable CIs were generated in Stata 14.2 (BE) and exported to Excel. The rule of three was applied to the studies by Jameson et al [64] and Callaghan et al [65] due to zero-outcome events in their sampled populations.

Interstudy Variability

Variations among studies included in the primary objective were mainly due to the study population and setting, assumptions, and model structure. We observed that only 3 of 13 studies (23%) synthesized under the primary objective were representative of the population. Apart from deploying different model types, some studies made use of real-time COVID-19 data sets, whereas others used historic data sets or relied on hypothetical samples. This increased variability and reduced the generalizability of the results. However, 2 of the 3 (66.7%) studies implemented in the United Kingdom were in favor of the intervention.

An observation of plotted graphs under the secondary objective showed high heterogeneity when measuring the outcome among detected SARS-CoV-2 cases, mainly due to methodology (Figure 5). Some studies were implemented at the population level while others purposefully used asymptomatic populations. Additionally, a limited number of studies provided details on the type of test used as well as how test samples were managed (Table S1, Multimedia Appendix 7). However, there was observed minimal heterogeneity among studies when stratified, mostly stemming from the study implemented among pregnant women; this was a single study by Abeysuriya et al [60], with a small sample of 180 pregnant women at term. The median age of these women was just 29.9 years (SD 7.4). This is contrary to the belief that infections are more prevalent in older populations. A stratification of the different studies by setting produced similar rates for studies implemented in the United Kingdom and all studies pooled together, excluding population-level studies. Excluding the largest citywide study

(n=9,899,828 subjects) [76] from this review increased the overall SARS-CoV-2 prevalence in the sampled population to 1.8% (784/43,050; 95% CI 1.7%-1.9%).

Discussion

Principal Findings

Although considered low-level evidence, our review synthesis has shown a clear majority vote of 76.9% (10/13; 95% BE CI 46.2%-95.0%, *P*=.09) in favor of mass testing and contact tracing.

We also found an overall proportion of asymptomatic carriers among detected positive cases to be 40.7% (1084/2661; 95% CI 38.9%-42.6%) for all studies, compared to 56.6% (120/212; 95% CI 49.6%-63.4%) within the United Kingdom when stratified. The proportion of asymptomatic cases across studies ranged from 28% (483/1723) among cases detected in the general population to 90% (28/31) among care home staff with positive tests. In addition, asymptomatic SARS-CoV-2 prevalence was highest among residents in homeless shelters (186/618, 30.1%) and lowest among hospital patients (0/217, 0.0%). The overall prevalence of asymptomatic cases in the sampled population was 0.01% (1084/9,942,878; 95% CI 0.0%-0.0%) compared to 3.8% (120/3194; 95% CI 3.1%-4.5%) within the United Kingdom.

Comparison With Prior Work

Studies that were in favor of the control in this review assumed that mass testing was not feasible, as acknowledged by Peto [80]. Evidence from countries that embarked on mass testing, including Taiwan, Germany, Ireland, China, and India, suggests that regular mass testing and contact tracing could be a game changer. The analysis by Peto et al [80, 112] showed that mass testing and contact tracing is by far more cost-effective than the present test and trace method, which is in line with the second outcome. Maslov [79] shares an opposing view in that even the slightest false positives will render random mass testing an unreliable policy. While Maslov [79] seems to be concerned with the inherent moral decadence of unjust isolation, it is better to be on the safe side than to be amid false negatives and contented asymptomatic carriers. Symptomless testing to identify asymptomatic carriers is crucial because Viswanathan and colleagues [10] also acknowledged that strategies based on symptom screening could miss between 40%-100% of infected persons. A study among pregnant women at term in East London by Abeysuriya et al [60] found the sensitivity of testing based on symptoms to be as low as 14.3% (95% CI 0.36%-57.87%). Paying attention to asymptomatic infections as cases that could be missed has also been underscored by Byambasuren et al [120]. This is concordant with the key messages and objectives of the European Centre for Disease Prevention and Control that countries should test the whole population in high-transmission settings [121].

The 40.7% (1084/2661) asymptomatic proportion among positive cases found in this review is in line with the 40%-45% proportion estimated by Oran and Topol [122]. Clarke and colleagues [123] reported a similar rate of 40.3% among hemodialysis patients. This proportion is also similar to that reported in Spain (40.5%) by Albalate and colleagues [124]. The asymptomatic proportion among detected positive air travelers (46/55, 83.6%) we found in this review is higher than the 76.6% reported by Al-Qahtani et al [125], perhaps due to more awareness as the study was implemented at a much later date. Yanes-Lane et al [126] reported an asymptomatic proportion of positive cases among care home residents (54%), which is just slightly lower than the 61.3% (163/266) reported in this review. Notwithstanding the overarching reported high infectivity from asymptomatic individuals, we report rates in this review ranging from 0.003% (300/9,899,828) to 1.2% (24/1924) in the population. This is contrary to the rates (1.5%-2.8%) reported by Wu and McGoogan [127]; this higher rate could have been because testing was initially done among symptomatic individuals since asymptomatic proportions normally remain higher among index cases. In this review, we estimated that the proportion of asymptomatic SARS-CoV-2 carriers among cases in the general population was 28% (483/1723) (Figure 6), in agreement with the community asymptomatic proportion of 28% reported in Beale et al [128]. In contrast, Petersen and colleagues [129] reported a community asymptomatic proportion that was 3 times higher (76.5%-86.1%). This population-level study was undertaken in the United Kingdom, contrary to those included in this review that were conducted in Iceland, Italy, and China. The largest population sample in this review, from Cao et al [76], was a study done immediately after the lockdown, which could be the reason behind the low rate of asymptomatic cases.

Limitations

A substantial number of included studies were models, which normally rely on assumptions that may not be achieved in real life. Expert knowledge was needed to evaluate the validation process of models. This might have affected the results. The fact that this review went through a single reviewer could have introduced some bias in study selection and analysis. The variability in the understanding of mass testing by different researchers might have affected the analysis as well. In addition, review results could have been affected by differences in sample handling and testing methods, coupled with the lack of provision of technical details about testing. This review was language biased since the literature search was limited to English articles. This review was not registered with PROSPERO (International Prospective Register of Systematic Reviews) per standard systematic review practice.

Public Health Implications

Controlling a virus whose manifestation changes over time and increasingly without signs is not about the number of tests but about who needs to be tested. The pertinent questions relate to when people should be tested, where they should be tested, and how often. An appropriate public health strategy that will get the right people tested, at the right time, in the right place, and at regular intervals requires a community-based and participatory approach that will not be without a greater cost burden. At the center of such a strategy is overcoming the challenges related to the scarcity of supplies and waiting time, through the development of rapid tests [130]. Among others, winning public confidence; ensuring data security, acceptability of the contact

tracing apps, and equity of testing and contact tracing; use of rapid tests; capacity building and system strengthening; effective monitoring of isolation/quarantine and program sustainability are some factors to be considered. More real-time research is needed regarding the effectiveness of mass testing and contact tracing to obtain a better picture of disease burden and mitigation strategies.

Conclusions

We sought to critically evaluate the evidence that mass testing and contact tracing is a better strategy for controlling local transmissions of SARS-CoV-2 in the United Kingdom compared to the conventional test and trace method. We have demonstrated a very low level of promising evidence that mass testing and contact tracing could be more effective in bringing the virus under control and even more effective if combined with social distancing and face coverings. The implementation of test and trace should be done at mass irrespective of symptoms with the local community, through GP surgeries, community health centers, and local councils [131]. The proposal is for the present Test and Trace program to be superseded by a decentralized and continuous mass testing program with rapid tests, championed by community services with low resource needs [81]. The following recommendations could therefore be useful:

- Capacitate GP surgeries and community health services to deliver mass testing at the point of care [132];
- The government should work in synergy with local councils for surveillance, isolation, and quarantine [132]. This resulted in major success in Germany [133,134];
- Regular organizational and company-wide testing for the safe resumption of economic activities [135];
- Testing should be a border control measure for all travelers [82,83];
- Testing of prisoners, detainees, and all those in congested accommodations [49]. A good example is the Lesbos camp testing [136,137];
- Sewage and environmental testing should be part of mitigation strategies.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Characteristics of included studies.
[PDF File (Adobe PDF File), 474 KB - xmed_v2i2e27254_app1.pdf]

Multimedia Appendix 2
Characteristics of excluded studies.
[PDF File (Adobe PDF File), 306 KB - xmed_v2i2e27254_app2.pdf]

Multimedia Appendix 3
Quality assessment of modeling studies.
[PDF File (Adobe PDF File), 400 KB - xmed_v2i2e27254_app3.pdf]

Multimedia Appendix 4
Quality assessment of the cohort study.
[PDF File (Adobe PDF File), 429 KB - xmed_v2i2e27254_app4.pdf]

Multimedia Appendix 5
Quality assessment of cross-sectional studies.
[PDF File (Adobe PDF File), 363 KB - xmed_v2i2e27254_app5.pdf]

Multimedia Appendix 6
Certainty of evidence for the primary objective.
[PDF File (Adobe PDF File), 369 KB - xmed_v2i2e27254_app6.pdf]

Multimedia Appendix 7
Details of mass testing.
[PDF File (Adobe PDF File), 474 KB - xmed_v2i2e27254_app7.pdf]

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Abbreviations

BE: binomial exact
CASP: Critical Appraisal Skills Program
GP: general practitioner
GRADE: Grading Recommendations Assessment, Development, and Evaluation
MetQAT: Meta Quality Appraisal Tool
NHS: National Health Service
PROSPERO: International Prospective Register of Systematic Reviews
SURE: Specialist Unit for Review Evidence
SWiM: Synthesis Without Meta-Analysis

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Original Paper

Impact of COVID-19 Testing Strategies and Lockdowns on Disease Management Across Europe, South America, and the United States: Analysis Using Skew-Normal Distributions

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Abstract

Background: As COVID-19 infections worldwide exceed 6 million confirmed cases, the data reveal that the first wave of the outbreak is coming to an end in many European countries. There is variation in the testing strategies (eg, massive testing vs testing only those displaying symptoms) and the strictness of lockdowns imposed by countries around the world. For example, Brazil's mitigation measures lie between the strict lockdowns imposed by many European countries and the more liberal approach taken by Sweden. This can influence COVID-19 metrics (eg, total deaths, confirmed cases) in unexpected ways.

Objective: This study aimed to evaluate the effectiveness of local authorities' strategies in managing the COVID-19 pandemic in Europe, South America, and the United States.

Methods: The early stage of the COVID-19 outbreak in Brazil was compared to Europe using the weekly transmission rate. Using the European data as a basis for our analysis, we examined the spread of COVID-19 and modeled curves pertaining to daily confirmed cases and deaths per million using skew-normal probability density functions. For Sweden, the United Kingdom, and the United States, we forecasted the end of the pandemic, and for Brazil, we predicted the peak value for daily deaths per million. We also discussed additional factors that could play an important role in the fight against COVID-19, such as the fast response of local authorities, testing strategies, number of beds in the intensive care unit, and isolation strategies adopted.

Results: The European data analysis demonstrated that the transmission rate of COVID-19 increased similarly for all countries in the initial stage of the pandemic but changed as the total confirmed cases per million in each country grew. This was caused by the variation in timely action by local authorities in adopting isolation measures and/or massive testing strategies. The behavior of daily confirmed cases for the United States and Brazil during the early stage of the outbreak was similar to that of Italy and Sweden, respectively. For daily deaths per million, transmission in the United States was similar to that of Switzerland, whereas for Brazil, it was greater than the counts for Portugal, Germany, and Austria (which had, in terms of total deaths per million, the best results in Europe) but lower than other European countries.

Conclusions: The fitting skew parameters used to model the curves for daily confirmed cases per million and daily deaths per million allow for a more realistic prediction of the end of the pandemic and permit us to compare the mitigation measures adopted by local authorities by analyzing their respective skew-normal parameters. The massive testing strategy adopted in the early stage of the pandemic by German authorities made a positive difference compared to other countries like Italy where an effective testing strategy was adopted too late. This explains why, despite a strictly indiscriminate lockdown, Italy's mortality rate was one of the highest in the world.

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KEYWORDS

COVID-19; testing strategy; skew-normal distributions; lockdown; forecast; modeling; outbreak; infectious disease; prediction

Introduction

The study and development of models of infectious disease dynamics plays a fundamental role in the management of an unknown outbreak. Nevertheless, such models often create controversy about how, when, and whether there could be a useful tool in aiding policy decisions [1]. In the COVID-19 crisis, it appears that some articles were written to address local authorities rather than to scientifically discuss the real situation of the spread of the outbreak in each country.

It is clear that the timelier the action of local authorities, the more effective the result. The number of confirmed cases is a reliable number only if a testing strategy is adopted. Without it, we do not know in which stage of the disease the country is in at a given time. Many European countries had a similar weekly transmission rate in their *apparent* early stage of the disease, but, for example, for Italy and Spain, as well as Germany and Austria, it led to completely different outcomes. As we shall see in detail later, the massive testing strategy adopted by German and Austrian authorities created a positive difference in favor of these countries.

Often, countries are compared to each other by using their total confirmed cases. This is obviously misleading due to their varying population sizes. Nevertheless, the total confirmed cases per million (TCCpM) could also be misleading. Let us for example consider the following values taken from Worldometer [2] on May 30: Belgium, Spain, the United Kingdom, Italy, Iceland, and Singapore had a TCCpM value between 4000 and 6000. Are they in a similar situation in their management of the COVID-19 pandemic? The answer is found by examining their values for total deaths per million (TDpM), which are 815, 580, 566, 551, 29, and 4, respectively. This demonstrates clear differences in how each country was impacted by the outbreak. New Zealand, Australia, South Africa, and South Korea also have a mortality rate comparable to Singapore, but their TCCpM is approximately 300, which is well below that of Singapore. It is important to observe that, without a vaccination, *immunization* also plays a fundamental role. Hence, in the previous cases, Iceland and Singapore obtained the best results in combating the COVID-19 outbreak, whereas European countries exhibited the worst outcomes. The best way to fight the outbreak is to reach the *maximum number of immunizations together with a minimum number of deaths per million*. This point should be highlighted in scientific discussions and in the information disseminated by the media.

If a country does everything well, mortality is controlled over time. If the action of local authorities in adopting mitigation measures and testing strategies is not effective, health care systems become overwhelmed, and the mortality rate increases to critical levels. During the outbreaks in Italy and Spain, the untimely prevention and isolation measures and a weak testing strategy led to collapsed health care systems and a high mortality rate, despite lockdowns where people were only permitted to leave their homes for shopping (food and other necessities), for medical issues, and to travel to and from work only when necessary. Brazil, in time, banned international travel; canceled football matches; closed its land borders; shut down all nonessential public services (eg, all universities and primary and high schools) and private businesses, with employees working from home; and restricted commerce to supermarkets, pharmacies, restaurants (for takeaway or delivery only), gas stations, and other critical services. Despite its ineffective testing strategy when facing the outbreak, the timely action seems, at the moment, to yield good results in terms of deaths if we compare the early Brazilian stage of the disease to the European one where strict lockdowns were adopted. However, since Brazil is a big country, caution is needed when speaking of "good results." Indeed, while some Brazilian states plan to relax the quarantine rules, others, which are facing a health system collapse, are planning, following the European example, a strict lockdown with a ban on unnecessary movement of people and vehicles.

We also find other approaches worldwide. By quickly implementing public health measures, Hong Kong demonstrated that COVID-19 transmission can be effectively contained without resorting to the strict lockdown adopted by China, the United States, and Western Europe. The Hong-Kong TCCpM is approximately 145 and the mortality rate is 0.5 (TDpM). As one of the most heavily affected epicenters during the severe acute respiratory syndrome (SARS) epidemic in 2003, Hong Kong was better equipped to face the COVID-19 outbreak compared to other countries. Improved testing, greater hospital capacity to handle novel respiratory pathogens, and a population that understood the need to improve personal hygiene and maintain physical distancing made the difference.

In Europe, one country stands out in its approach to tackle COVID-19. In Sweden, individuals took responsibility for social distancing. High schools and universities were closed, but primary schools, gyms, restaurants, and bars remained open, with social distancing rules enforced, and gatherings were restricted to 50 people. Sweden's mortality rate per 1 million

inhabitants was lower than that of Italy, Spain, and the United Kingdom but higher than its neighbors Norway, Finland, and Denmark. Nevertheless, hospitals have not, at the moment, been overwhelmed as in Italy and Spain. There is no debate over how to reopen society, and whether there will be a second wave, because society has largely remained open, and the local consequences of a lockdown have been avoided. As remarked by its local authorities, Sweden opted for a marathon-style response instead of a sprint-like one to close its first COVID-19 wave.

To understand the *mathematical* reason behind lockdowns, a brief discussion of the basic reproduction number, the so-called R_0 number, is warranted [3]. It refers to the number of infected people caused by 1 infected person at the beginning of an outbreak, before widespread immunity starts to develop and/or any attempt is made to reduce transmission. The subscripted 0 refers to the lack of immunity in the population. The R_0 should not be confused with R_t, which is the number of persons infected, at any given time, by an infected individual. It decreases as immunized people increase, either by vaccination, natural immunity, or through death of infected persons. In the case of COVID-19, there is no vaccine as of the writing of this paper. Therefore, immunity to the infection in a large percentage of people (provided that the disease does not spread rapidly within the population), the so-called *herd immunity* [4], can only be achieved through two chains: natural immunity or death. When the number of susceptible people decreases, as people die or become immune by exposure, the R_t number decreases, and the sooner people recover or die, the smaller the R_t value becomes. The basic R_0 predicts the ratio of immunization that a population requires to achieve herd immunity.

The critical immunity threshold for random vaccination (assuming 100% vaccine effectiveness) is $(R_0-1)/R_0$ [4]. For a basic R_0 of 2.5 (the COVID-19 reproduction number estimated by Li et al [5] for Wuhan was 2.2), the critical immunity threshold is thus given by 3⁄5 (ie, 60%) of the population. For R_0=5, the threshold increases to 4/5 (ie, 80%) of the population. At any time, the effective reproduction number (R_t) can be expressed in terms of the R_0 and the percentage of immunized people in the population at that time, $P\text{imm}(t)$, by $R_t=R_0[1-P\text{imm}(t)]$. Mitigation and isolation strategies are often used to *artificially* reduce the reproduction number. For example, in Iran, the R_0 was 4.9 in the first week [6]. After the closure of schools and universities, the R_t was 4.5, and after a reduction in work hours, this decreased to 4.3 [6].

Without a vaccine, immunization at a much-delayed speed, ensuring that health services are not overwhelmed, is the only way to manage the pandemic. Isolation (or lockdown when necessary) is the main tool to allow those experiencing the most acute symptoms to receive the medical support they need. Nevertheless, what mitigation measures should be adopted continues to be a matter of discussion; they certainly cannot be implemented without *massive testing* strategies. Indeed, testing is not only important because it shows, at any given moment, the real situation of the outbreak, it is also essential to sensitize and empower people.

A recent study from King's College London [7], based on data from a survey of 2250 UK residents aged 18-75 years, classified the population according to their response to the COVID-19 crisis and lockdown measures. Three groups were identified: accepting (44%), suffering (47%), and resisting (9%). In the resisting cluster, with an average age of 29 years of which 64% were male, 58% thought that "too much fuss" was being made about the risk of coronavirus (around 6 times higher than in the other two groups); 76% opposed official guidelines, such as meeting friends or family outside their home (41%) or going outside when having coronavirus-like symptoms (35%). The researchers also observed that, contrary to what was observed in the resisting group, where young people dominated the sample count, people aged 55-75 years made up the largest portion of the accepting group. Women constituted nearly two-thirds of the suffering cluster, whereas men represented almost two-thirds of the resisting group. Worldwide, people spent weeks without seeing friends and/or family, without school or university, holidays, sports, or even being able to go to work. So, stress, anxiety, depression, and fear of the pandemic are common responses to lockdown measures during the COVID-19 pandemic [8,9].

Methods

Overview

In the early stage of the pandemic, the mitigation strategies adopted by local authorities could be monitored using countries' weekly transmission rate. At the end of the outbreak, they can be evaluated by studying the *skew-normal* distributions that fit the daily confirmed cases and deaths curves of each country. In this paper, we analyzed in detail the testing strategies of various countries during the early stage of the COVID-19 pandemic and fitted the pandemic curves by skew-normal distributions to show how massive testing strategies are more effective than the containment measures (ie, full lockdowns) implemented in some countries.

Data

We collated data collected by the global repositories Worldometer [2], the World Health Organization (WHO) [10], and GitHub [11].

The number of intensive care unit (ICU) beds in European countries was obtained from Rhodes et al [12]; updated counts were obtained for Germany from Brandt et al [13]. For the United States, counts were taken from Halpern and Tan [14], who reported 96,596 ICU beds (292 beds per 1 million inhabitants), with the following distribution: metropolitan, 94%; micropolitan, 5%; and rural, 1%. For Brazil, data were obtained from the Associação de Medicina Intensiva Brasileira [15]—46,000 ICU beds (216 beds per 1 million), subdivided into the five regions of Brazil: North (4%, 90 beds per 1 million), Northeast (19%, 150 beds per 1 million), Central-West (10%, 250 beds per 1 million), Southeast (52%, 270 beds per 1 million), and South (15%, 220 beds per 1 million).

Skew-Normal Distributions

The normal distribution [16] is one of the most important probability distributions in the field of statistics because it fits

many natural phenomena. It describes how the values of a variable are symmetrically distributed around its center, μ, and shows how the probabilities for extreme values further away from the mean go rapidly to zero in both directions. It is also known as the Gaussian distribution or the bell curve. Normal distributions are often used to fit data because, in many cases, the average point of a random variable, with a finite mean and variance, is itself a random variable whose distribution, as the number of data points increase, converges to a normal distribution. Normal distributions have also been used to fit curves pertaining to the COVID-19 pandemic. Nevertheless, their use led to misleading predictions regarding the end of the outbreak in many countries. Although we always expect uncertainties with forecasts, we must try to minimize them so that our predictions can be as close as possible to reality. It is well known that the curves of epidemiological models are *asymmetric*. So, why not use asymmetric distributions to fit the data? In particular, why do we not use skew-normal distributions in the place of normal distributions?

It is clear that before reaching the peak, normal distributions can be used to estimate the pandemic curves of daily confirmed cases per million (DCCpM) and daily deaths per million (DDpM). Indeed, eventual asymmetries can only be seen after a country has reached its peak. However, to estimate the end of the outbreak, skew-normal distributions, as we shall see later, are fundamental to obtain the correct answer. Skew-normal distributions contain an additional parameter (with respect to normal distributions) that measures the asymmetry of the curves (for a detailed review, see [17-21]). A negative value of this parameter indicates that the left tail is longer (the peak is found at the left of μ), and a positive one indicates that the right tail is longer (the peak moves to the right of μ). As seen in Multimedia Appendix 1, the blue line represents a Gaussian distribution centered at μ=0 (σ=3). The red line is a skew-normal distribution with a negative parameter (s=−2), and the green line represents a skew-normal distribution with a positive parameter (s=3).

The explicit analytical formula of the skew probabilities' density functions, used in this paper to fit the DCCpM and DDpM curves of 12 European countries and the United States, is given by:

where $a=c$ for the confirmed cases, $a=d$ for the deaths, and *Erfc* is the complementary error function:

The skewness of the distribution is defined by:

where

and s is limited to (−1,1). The mean value is given by $mean=\mu+\sigma\delta$, and the mode (maximum) has not an analytic expression but, as shown by Azzalini [21], an accurate closed form, given by:

Three fitting parameters were obtained, for both the TCCpM and the TDpM data, by modeling their curves by the respective cumulative skew-normal distributions:

The cumulative skew-normal distribution can be expressed in terms of the complementary error function and the T-function, introduced by Owen [22] in 1956:

The TCCpM and TDpM curves were modeled by using the *NonlinearModelFit* calculation of the computational program Wolfram Mathematica (Wolfram Research) [23].

The ρ Factor

Recalling that herd immunity and low mortality are *both* fundamental for tackling the outbreak, we introduce the ρ factor, which can be used to easily compare countries. If two countries have the same TCCpM value, the one with the greater tests per confirmed case (TpC) value should have a lower number of infected people in its population with respect to the other. A lower ρ value implies a better rating:

Results

Mortality Rate

Based on data collected from global repositories, Table 1 displays statistics for 12 European countries, 10 South American countries, and the United States, as of May 30, 2020.

On May 30, 2020, the total death count was greatest for Italy (TDpM=551.1), the United Kingdom (TDpM=566.0), Spain (TDpM=579.6), and Belgium (TDpM=814.9). In these countries, the TpC number was similar (14.9 for Belgium and Spain, 15.3 for the United Kingdom, and 16.4 for Italy), and their TCCpM ranged from 3845.7 (Italy) to 5111.7 (Spain). The mortality rate was 16.2% for Belgium, 11.3% for Spain, 14.3% for Italy, and 14.1% for the United Kingdom. Ireland and Switzerland, which had a TpC ratio of 13.0 and 12.8, had a lower mortality rate (6.6% and 6.2%, respectively). The United Kingdom and Ireland had a similarly low number of ICU beds (the WHO suggests a number between 100 and 300 beds per 1 million population as adequate) but a differing mortality rate. The same occurred for Italy (125 beds per million) and Spain (97 beds per million), and Switzerland (110 beds per million). Belgium, despite an adequate number of beds per million (159), had the worst mortality rate.

Sweden and the Netherlands had a TpC ratio of 6.2 and 7.1, respectively; that of the United States was 9.1. For these countries, the mortality rate was 11.8% (Sweden), 12.8% (Netherlands), and 5.9% (United States). Here, the great difference in the number of ICU beds and the temporal shift at the beginning of the outbreak (allowing for better preparation of the health care system) clearly played a fundamental role.

Table 1. The total deaths per 1 million inhabitants, the total confirmed cases per million, tests per confirmed case, population size in millions, population density per km2, and the number of intensive care unit (ICU) beds per million for 12 European countries, 10 South American countries, and the United States, as of May 30, 2020.

Country	Total deaths per million	Total confirmed cases per million	Tests per confirmed case	Population size in millions	Population density	ICU beds per million
Belgium	814.9	5016.0	14.9	11.6	376	159
Spain	579.6	5111.7	14.9	46.8	96	97
United Kingdom	566.0	4024.0	15.3	67.8	274	66
Italy	551.1	3845.7	16.4	60.5	200	125
France	439.8	2842.5	7.5	65.3	119	116
Sweden	435.1	3674.6	6.4	10.1	23	58
Netherlands	348.0	2705.1	7.5	17.1	421	64
Ireland	336.9	5087.6	13.0	4.9	70	65
United States	313.7	5351.2	9.8	330.8	36	292
Switzerland	223.1	3586.6	12.8	8.6	208	110
Ecuador	189.4	2191.5	2.9	17.6	63	N/A[a]
Portugal	136.9	3157.2	24.7	10.2	112	42
Brazil	135.8	2346.7	1.9	212.4	25	216
Peru	132.9	4731.6	6.5	32.9	25	N/A
Germany	101.8	2186.0	21.6	83.8	233	339
Austria	74.2	1853.9	26.9	9.0	76	218
Chile	52.2	4966.4	5.9	19.1	23	N/A
Bolivia	26.5	819.8	3.0	11.7	10	N/A
Columbia	17.5	526.3	12.0	50.8	41	N/A
Argentina	11.7	359.5	9.6	45.1	16	N/A
Uruguay	6.3	234.6	53.3	3.5	20	N/A
Paraguay	1.5	135.8	30.1	7.1	17	N/A
Venezuela	0.5	51.4	669.0	28.4	35	N/A

[a]N/A: not applicable.

For Brazil, which had the lowest TpC value (1.9), the mortality rate was 5.8%, similar to the United States. It is clear that for all the countries, due to the fact that there was a good number of asymptomatic people, an increasing number of tests should decrease the mortality rate—that is, when the TpC number resembles Spain's value, the mortality rates of Sweden, the Netherlands, the United States, and Brazil should further decrease. Portugal (TpC=24.7), Germany (TpC=21.6), and Austria (TpC=26.9) had the largest TpC numbers and exhibited a very low mortality rate of 4.3%, 4.7%, and 4.0%, respectively.

It should be noted that when comparing the mortality rate percentage, we must consider the number of tests done per confirmed case. To correctly interpret any data, we need to know how much testing for COVID-19 has been done by the country. Without complete data, it becomes difficult to assess which countries are doing well and understand how the pandemic is spreading. When discussing the total deaths per 1 million population, the number of tests is not important. In this case, we have to consider the stage of the outbreak. For example, the South American countries are in a stage of infection different to that of the European countries, which are closing their first COVID-19 wave. Looking at the total deaths per 1 million population, a particular case is called to our attention. In Table 1, of the first 4 countries listed, Italy had the highest TpC number (16.4), and the value for Germany was 21.6. Considering that both countries are closing their first wave of the pandemic, how can their large difference in TDpM (Italy: 551.1 vs Germany: 101.8) be justified?

To answer to this question, we looked at the data reported in Table 2 and collected for Austria, Germany, and the 4 countries with the greatest TDpM numbers in Table 1 (Belgium Spain,

Italy, and the United Kingdom) according to the Our World in Data repository [24].

Table 2. Tests per million, total confirmed cases per million, and tests per confirmed case for Austria, Germany, Italy, the United Kingdom, Spain, and Belgium on different dates.

Country and date	Tests per million	Total confirmed cases per million	Tests per confirmed case
February 27			
Austria	50	0.33	151.5
Italy	200	10.83	18.5
March 8			
Austria	500	11.56	43.3
Germany	1490	12.41	120.1
Italy	830	121.9	6.8
Belgium	350	17.24	20.3
March 15			
Austria	910	95.56	9.5
Germany	3010	69.15	43.5
Italy	2070	409.04	5.1
Belgium	1070	76.38	14.0
March 22			
Austria	2370	398.00	6.0
Germany	7170	296.81	24.2
Italy	4270	977.49	4.4
Belgium	2220	293.19	7.6
March 29			
Austria	5160	976.44	5.3
Germany	11,490	740.99	15.5
Italy	7510	1614.69	4.7
Belgium	4000	934.14	4.3
April 5			
Austria	12,040	1339.00	9.0
Germany	16,360	1194.79	13.7
Italy	11,440	2131.37	5.4
Belgium	6320	1697.5	3.7
April 13			
Austria	16,480	1560.11	10.6
Germany	20,890	1552.17	13.5
Italy	17,320	2636.63	6.6
United Kingdom	5420	1307.09	4.1
Spain	19,900	3634.59	5.5
Belgium	9900	2636.98	3.8

Massive Testing Strategy

On March 8, Belgium, Austria, and Germany had a similar TCCpM value (between 10 and 20) but a different TpC number: 20.3, 43.3, and 120.1, respectively. This indicates that when the pandemic was in its initial stage reaching the TCCpM value of 10-20, the testing strategy in Austria was twice as effective as that of Belgium, and Germany showed a massive testing strategy 6 times more effective than Belgium and twice as effective compared to Austria. On March 8, the pandemic in Italy was at an advanced stage, with a TCCpM value of 121.9.

To compare the testing strategy of Italy with that of Germany, we have to go back to February 27 when Italy's TCCpM was 10.83. The TpC number of Italy, when the disease reached 10-20 TCCpM, was similar to Belgium. An easy way to compare testing strategies is by normalizing the TpC to one of the compared countries. This allows us to yield an effectiveness factor (EF) with respect to that country. For example, by choosing Italy as the normalizing country, the EF for Belgium, Austria, and Germany is 1.1, 2.3, and 6.5, respectively. Table 3 reports the EFs generated when repeating this for other intervals of TCCpM.

Table 3. The effectiveness factor of the testing strategy of Italy, Belgium, Austria, and Germany.

Intervals of total confirmed cases per million	Effectiveness factor			
	Italy	Belgium	Austria	Germany
10-20	1.00 (18.5)	1.10 (20.3/18.5)	2.34 (43.3/18.5)	6.49 (120.1/18.5)
250-450	1.00 (5.1)	1.49 (7.6/5.1)	1.18 (6.0/5.1)	4.75 (24.2/5.1)
900-1200	1.00 (4.4)	0.98 (4.3/4.4)	1.20 (5.3/4.4)	3.11 (13.7/4.4)
1300-1700	1.00 (4.7)	0.78 (3.7/4.7)	1.91 (9.0/4.7)	2.87 (13.5/4.7)

In Figures 1 and 2, we show the temporal behavior of the TCCpM and TDpM curves for the United States and for countries in Europe and South America. The data of Table 1 and the plots of Figures 1 and 2 are periodically updated online [25].

Lastly, it is worthwhile to discuss the situation in Venezuela (Table 1, last row), whose TDpM was 0.5, TCCpM was 51.4, and TpC was surprisingly 669. Due to its socioeconomic and political crisis, Venezuela was isolated from the world even before the COVID-19 outbreak and was the first nation in South America to impose a strict lockdown. This may explain the lack of widespread transmission in Venezuela. With respect to the high number of tests, it is important to observe that Venezuela performed a substantial number of rapid blood antibody tests (manufactured in China) checking for proteins developing after someone is infected [26]. Few nasal swab exams were used by local authorities. It is important to recall that only swab-test positives are added to the official statistics of confirmed cases. Inclusion or exclusion of antibody tests explains why, for example, the total number of confirmed cases reported for Spain by Worldometer [2], where antibody tests are considered, and in GitHub [11], where they are not, differ.

Figure 1. Curves of the total confirmed cases per 1 million inhabitants (TCCpM) for (A) 12 European countries and the United States and (B) all South American countries, on day 130 (May 30, 2020). A stabilization point is seen in almost all European countries. This has not yet occurred in South America where the outbreak is delayed with respect to Europe. Among the 12 European countries analyzed, the higher TCCpM numbers belong to Spain, Ireland, and Belgium, followed by Italy and Switzerland. The United States overtook the European countries with the highest TCCpM numbers, the United Kingdom overtook Italy, and Sweden sits between Switzerland and Italy.

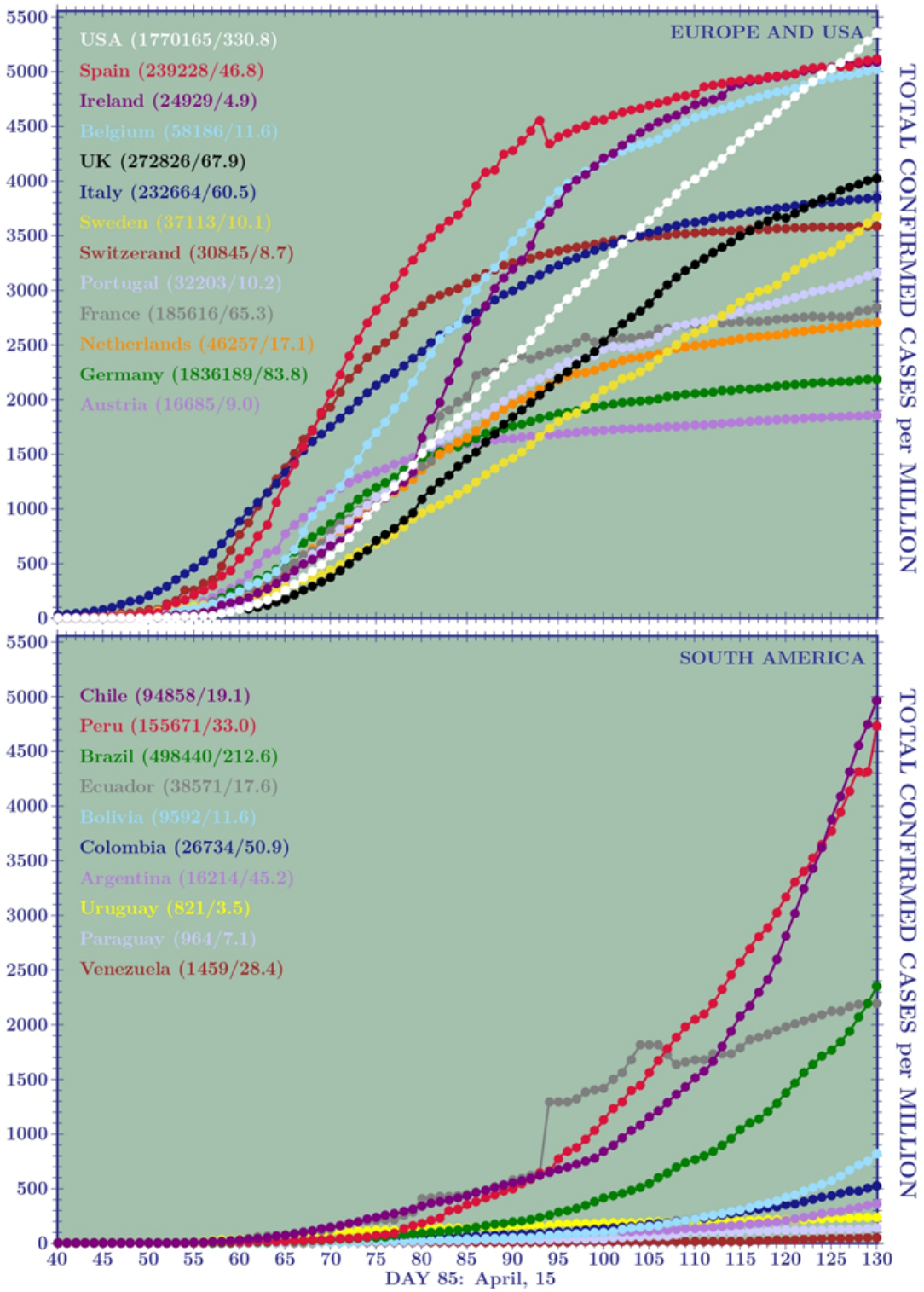
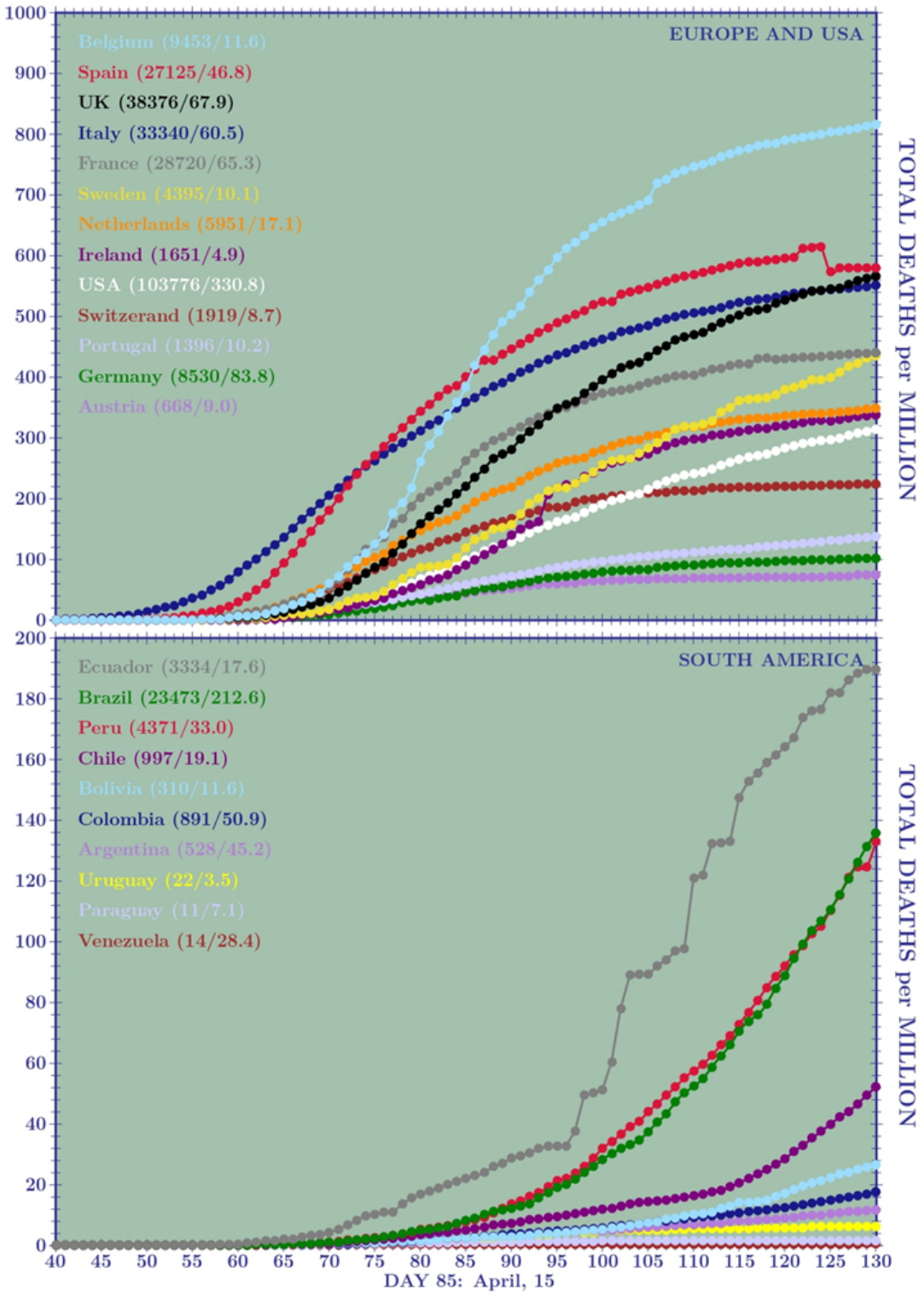


Figure 2. Curves of the total deaths per 1 million inhabitants (TDpM) for (A)12 European countries and the United States and (B) all South American countries, on day 130 (May 30, 2020). Among the 12 European countries analyzed, the higher TDpM numbers belong to Belgium, Spain, the United Kingdom, and Italy. The Spain anomaly is due to the lower number of deaths on day 125 (26,837) with respect to deaths on day 124 (28,752). Among the South American countries, Ecuador shows the more critical situation, followed by Peru and Brazil with nearly the same number of deaths per million and very similar curves.



Weekly Transmission Rates

We now discuss the weekly rate of DCCpM and DDpM. Before introducing what, for simplicity, we refer to as alpha (α) [27] and beta (β) factors, we first compare the outbreak in different countries. We shall analyze, as an illustrative example, Germany and Italy, the United States, and Brazil. In these countries, the outbreak did not start at the same time. Hence, we compared them with each other to see when they reached the same number of TCCpM. Let us consider the moment at which they reached 10 TCCpM. This happened for Italy on February 27 (TCCpM=10.83), for Germany on March 7 (TCCpM=9.53),

for the United States on March 15 (TCCpM=10.69), and, finally, for Brazil on March 24 (TCCpM=10.58). To see how the outbreak was spreading in these countries, we can compare their DCCpM numbers. This can be done by averaging the weekly data from February 27 for Italy, March 7 for Germany, March 15 for the United States, and March 24 for Brazil. This comparison can be also done for a TCCpM value of 100 (Table 4).

Table 4. The weekly transmission rate of daily confirmed cases per million and tests per million for Italy, Germany, the United States, and Brazil upon reaching 10 and 100 total confirmed cases per million.

Country	Total confirmed cases per million	Date	7-day moving average[a]	Tests per million
α factor				
Italy	10.83	Feb 27	3.63	200
Germany	9.53	Mar 7	2.15	1490
United States	10.69	Mar 15	2.81	120
Brazil	10.58	Mar 24	1.76	N/A[b]
β factor				
Italy	97.24	Mar 7	18.06	700
Germany	110.47	Mar 17	27.57	3010
United States	100.61	Mar 22	25.07	760
Brazil	97.58	Apr 11	7.55	300

[a]Daily confirmed cases per million/7.

[b]N/A: not applicable.

Figure 3A is a plot of the α factor for 12 European countries and the United States. The weekly transmission rate of DCCpM were greatest for Ireland and Spain (~200 and 180, respectively), followed by Belgium and Switzerland (both ~130), with the first three countries closing their first wave of the pandemic with a TCCpM around 5000. Italy and Germany showed a maximum rate of approximately 100 and 70, respectively, and a final TCCpM of around 4000 and 2000, respectively. Figure 4A demonstrates that all the European countries, with the exception of Sweden, present the same curves for their initial weekly transmission rate. In particular, the α factor of the United States followed, up to 1000 TCCpM, the same curve as Italy. So, why do the European countries exhibit a different behavior in the successive stages of the outbreak?

The answer once again comes from the testing strategy adopted by local authorities and can be seen by observing Table 4. Italy (on February 27) and the United States (on March 15) reached TCCpM values of 10.83 and 10.69, respectively, with an α factor of 3.63 for Italy and 2.81 for the United States. Due to the fact that, at that time, Italy and the United States tested 200 and 120 inhabitants per million, respectively, their initial-stage behavior was comparable. The plots in Figure 3A, as well the amplification done in Figure 4A, are not normalized. Hence, Germany's curve is similar to those of Italy and the United States. Nevertheless, looking at the last column of Table 4, we immediately see a great difference in the testing strategy of Germany (1490 tests per million) compared to Italy (200 tests per million) and the United States (120 tests per million), leading to a German relative factor with respect to Italy of (2.15/3.63) × (200/1490) ≈ 0.29/3.63, and to the United States of 0.17/2.81. Reaching 100 TCCpM, the German effective factors become 6.41/18.06 and 6.96/25.07.

Data on the testing strategy adopted by the different countries are often available. Hence, when the plots given in Figures 3A and 4B are used to compare countries to each other, they have to be appropriately normalized by the tests per million relative ratio.

We recall one more time that the success of a country in combating the pandemic is not to reduce the TCCpM but to reduce its TDpM. Immunization also plays a fundamental role in disease management. Obviously, reducing infections also has an effect on decreasing the rate of mortality. However, it is possible to find many examples in which a large TCCpM value does not necessarily imply a large TDpM value (see, for example, Ireland's curves in Figure 3).

Figure 3. The weekly spreading rate for (A) daily confirmed cases per million (DCCpM; α factor) and (B) daily deaths per million (DDpM; β factor), calculated for 12 European countries and the United States when these countries reach the same value for total confirmed cases (TCCpM) and total deaths per million (TDpM). For the factor, the number of tests per million should be considered as normalization, but this number is not always available. The curves show a clear asymmetry. They allow for the prediction of a final TCCpM greater than 5000 for Ireland, Spain, and Belgium; around 4000 for Italy and the United Kingdom; and around 2000 for Austria and Germany. For total deaths, Belgium exhibited the worst result (around 800), followed by Spain, the United Kingdom, and Italy (around 600). Austria and Germany had lower mortality rates.

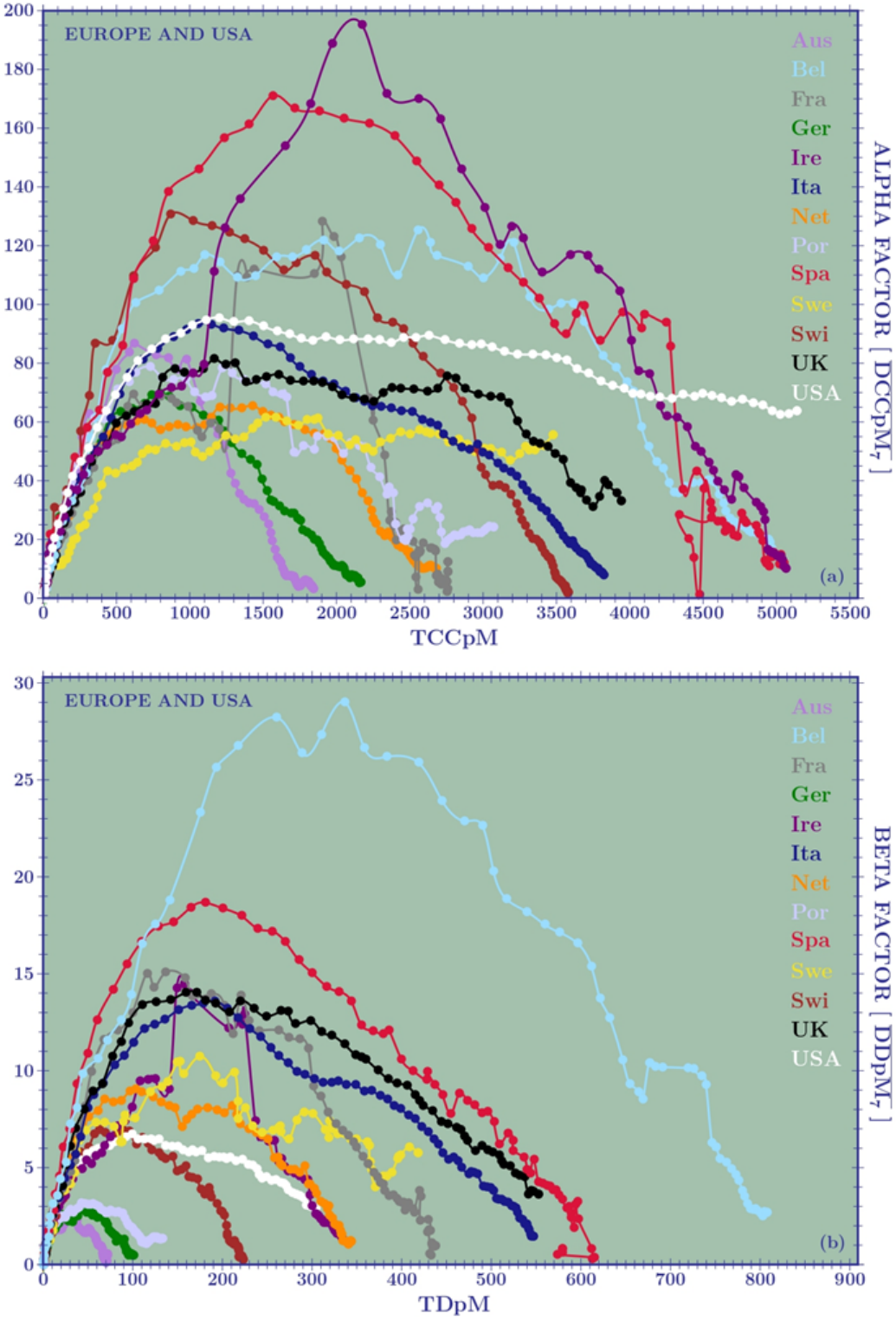
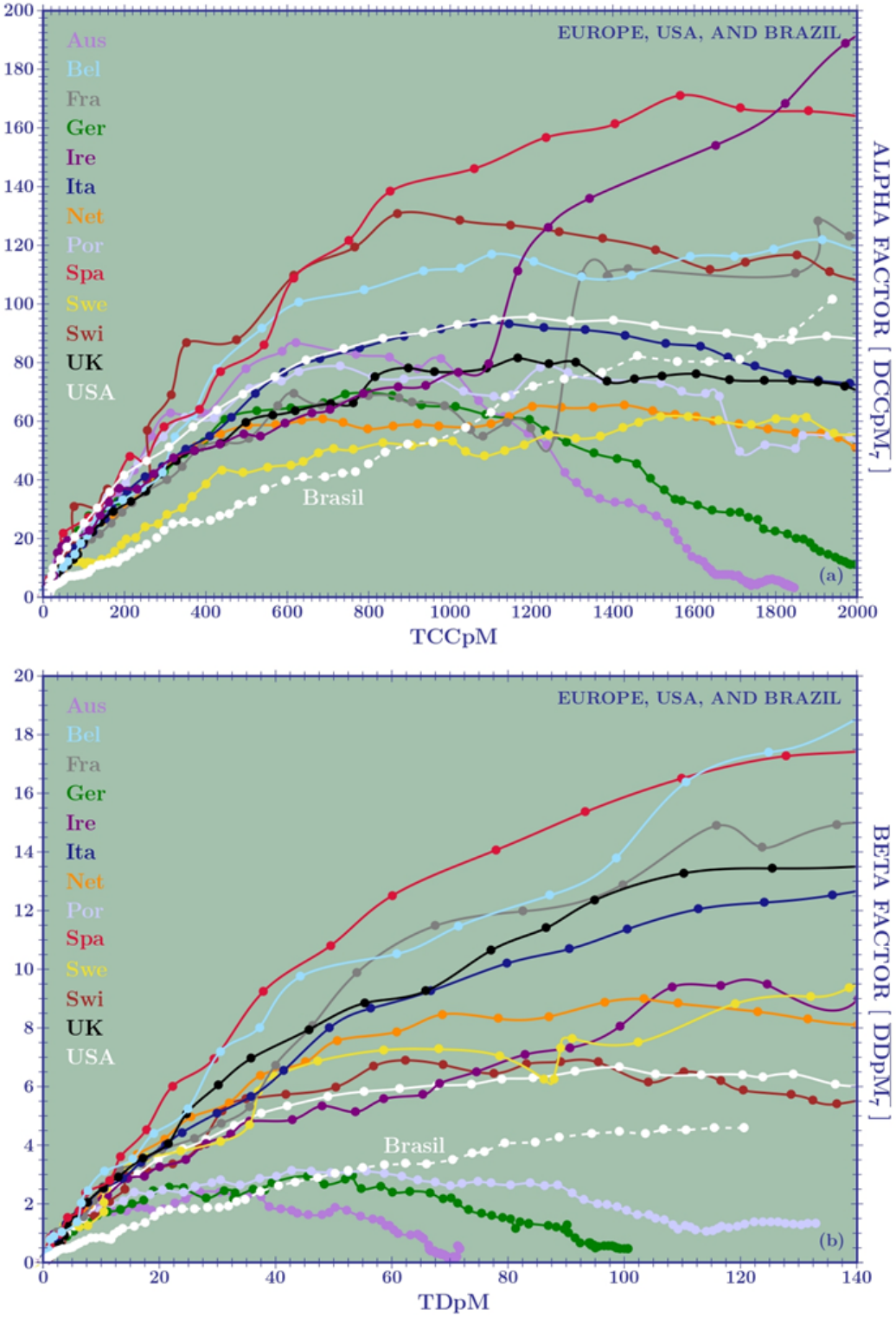


Figure 4. The weekly spreading rate at the beginning of the outbreak for 12 European countries, the United States, and Brazil. (A) Confirmed cases: Brazil, with an initial behavior similar to Sweden, shows a steep increase in its curve, overtaking most European countries and the United States. (B) Deaths: the Brazilian curve overtakes those of Austria, Germany, and Portugal (which have the lowest mortalities) but remains below all other European countries and the United States. DCCpM: daily confirmed cases per million, DDpM: daily deaths per million, TCCpM: total confirmed cases per million, TDpM: total deaths per million.



Next, we analyzed the weekly transmission rate for DDpM, the so-called β factor, which was done analogously to what has been done for the DCCpM. Table 5 takes Italy, Germany, the United States, and Brazil as illustrative examples.

In this case, the comparison can be done directly without any testing normalization. Obviously, subnotification of deaths has to be considered as well, but, at the moment, we have no reliable information on this. Between 10 and 20 TDpM, Table 5 shows the worst β factors for Italy and the best ones for Brazil. Nevertheless, the increasing rate for Italy, Germany, the United

States, and Brazil show a factor of 1.6, 1.4, 1.6, and 2.1, respectively. In Figure 3B, we see that Ireland, despite its high values for TCCpM and peak in DCCpM, will close its first wave of the pandemic with a TDpM value between 300 and 400, well below Belgium (TDpM=800) and Italy, Switzerland, and Spain (TDpM range 550-650). The plots also show good results for Austria (TDpM<100), Germany (TDpM~100), and Portugal (TDpM=150).

In Figure 4B, which is an amplification of Figure 3B, Brazil overtakes the curves of Austria, Germany, and Portugal (meaning that its final TDpM will be greater than 200) but is still under that of other European countries and the United States.

Table 5. The β factor for Italy, Germany, the United States, and Brazil upon reaching 10 and 20 total deaths per 1 million population.

Country	Total deaths per million	Date	7-day moving average[a]
10 total deaths per million			
Italy	10.43	Mar 10	2.52
Germany	10.98	Apr 1	1.72
United States	10.34	Mar 29	2.24
Brazil	10.08	Apr 17	0.85
20 total deaths per million			
Italy	20.93	Mar 13	4.00
Germany	18.90	Apr 5	2.44
United States	19.68	Mar 1	3.51
Brazil	20.18	Apr 17	1.75

[a]Daily total deaths/7.

Analysis of Skew-Normal Distributions

The three fitting parameters, with their respective 95% CIs, are shown in Tables 6 and 7 for 10 European countries. The cumulative density function and probability density function for these countries, which are closing their first pandemic wave, are displayed in Figures 5 and 6. The DCCpM plots in Figure 6 clearly show their asymmetric nature. This explains why forecasts based on normal distributions, due to the lack of profile asymmetry, leads to misleading results.

Table 6. The fitting parameters (center, standard deviation, and skewness) of the skew-normal distributions for the countries in Figures 5 and 6 for total confirmed cases per million.

Country	Parameter			Total confirmed cases per million (95% CI)
	μ_c(95% CI)	sig_c (95% CI)	s_c (95% CI)	
Ireland	73.4 (1.4)	19.2 (0.1)	1.6 (0.3)	5040 (39)
Belgium	63.7 (0.4)	26.5 (0.1)	3.3 (0.3)	5014 (25)
Spain	57.8 (0.5)	22.6 (0.1)	4.6 (0.8)	4977 (26)
Italy	50.9 (0.2)	32.3 (0.1)	5.1 (0.3)	3889 (10)
Switzerland	54.8 (0.2)	20.1 (0.1)	4.5 (0.5)	3551 (10)
Portugal	60.2 (0.4)	32.4 (0.1)	8.2 (2.2)	3133 (32)
France	70.8 (6.2)	14.4 (0.3)	0.8 (0.9)	2723 (24)
The Netherlands	62.1 (0.4)	25.9 (0.1)	2.8 (0.2)	2684 (12)
Germany	56.9 (0.4)	24.3 (0.1)	5.0 (0.9)	2136 (11)
Austria	55.4 (0.6)	17.3 (0.1)	4.9 (1.7)	1777 (11)

Table 7. The fitting parameters (center, standard deviation, and skewness) of the skew-normal distributions for the countries in Figures 5 and 6 for total deaths per million.

Country	Parameter			Total deaths per million (95% CI)
	μ_d (95% CI)	sig_d (95% CI)	s_d (95% CI)	
Belgium	71.2 (0.4)	21.8 (0.5)	3.7 (0.4)	810 (4)
Spain	59.8 (0.4)	26.1 (0.6)	7.0 (1.6)	600 (4)
Italy	54.3 (0.2)	33.7 (0.3)	5.8 (0.4)	562 (2)
France	66.6 (0.4)	22.6 (0.6)	4.4 (0.6)	436 (2)
The Netherlands	64.8 (0.2)	28.0 (0.4)	4.3 (0.3)	354 (1)
Ireland	82.3 (2.6)	16.1 (2.0)	1.2 (0.5)	330 (4)
Switzerland	64.7 (0.2)	21.8 (0.3)	3.2 (0.2)	223 (1)
Portugal	66.2 (0.4)	34.8 (1.1)	5.9 (0.9)	143 (2)
Germany	70.4 (0.4)	24.9 (0.6)	3.1 (0.3)	102 (1)
Austria	66.9 (0.4)	20.2 (0.5)	2.8 (0.3)	71 (1)

The greatest asymmetries are found in the skew-normal distributions of Portugal for confirmed cases (γ_c=0.94) and of Spain for deaths (γ_d=0.92). The most symmetric distributions belong to Ireland (γ_c=0.33 and γ_d=0.20) and France (γ_c=0.08), each with a profile very similar to Gaussian distributions.

By using the fitting parameters of the skew-normal distributions, we can also obtain information about the mean values of the DCCpM and DDpM curves. For example, for Germany, Spain, Italy, and Belgium, we find μ_c=75.9, 75.4, 76.1, and 83.9, respectively, showing that the epidemic began in the same period in the first three countries and a week later in Belgium. It is also interesting to calculate the shift between the mean values of deaths and confirmed cases ($\Delta mean=\mu_d-\mu_c+\sigma_d\delta_d-\sigma_c\delta_c$). For Germany, this value was 13.4. For Spain, Italy, and Belgium, it is lower: 5.0, 4.7, and 2.5, respectively. This indicates that in Spain, Italy, and Belgium, only people with moderate or severe symptoms were being tested; this serves as additional evidence of the different testing strategies adopted in the early stage of the outbreak by Spain, Italy, and Belgium vs Austria and Germany.

Figure 5. Skew-normal cumulative distribution functions for 10 European countries that have closed their first pandemic wave. TCCpM: total confirmed cases per million, TDpM: total deaths per million.

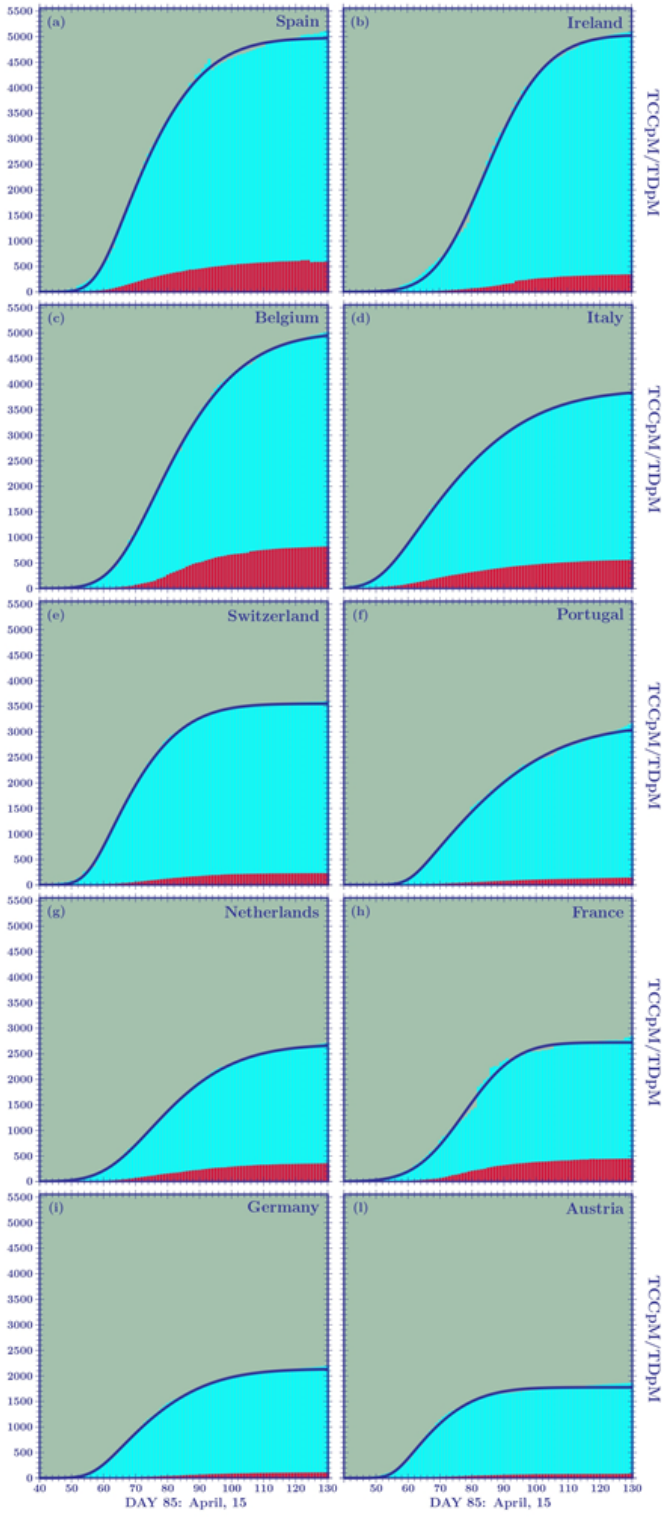
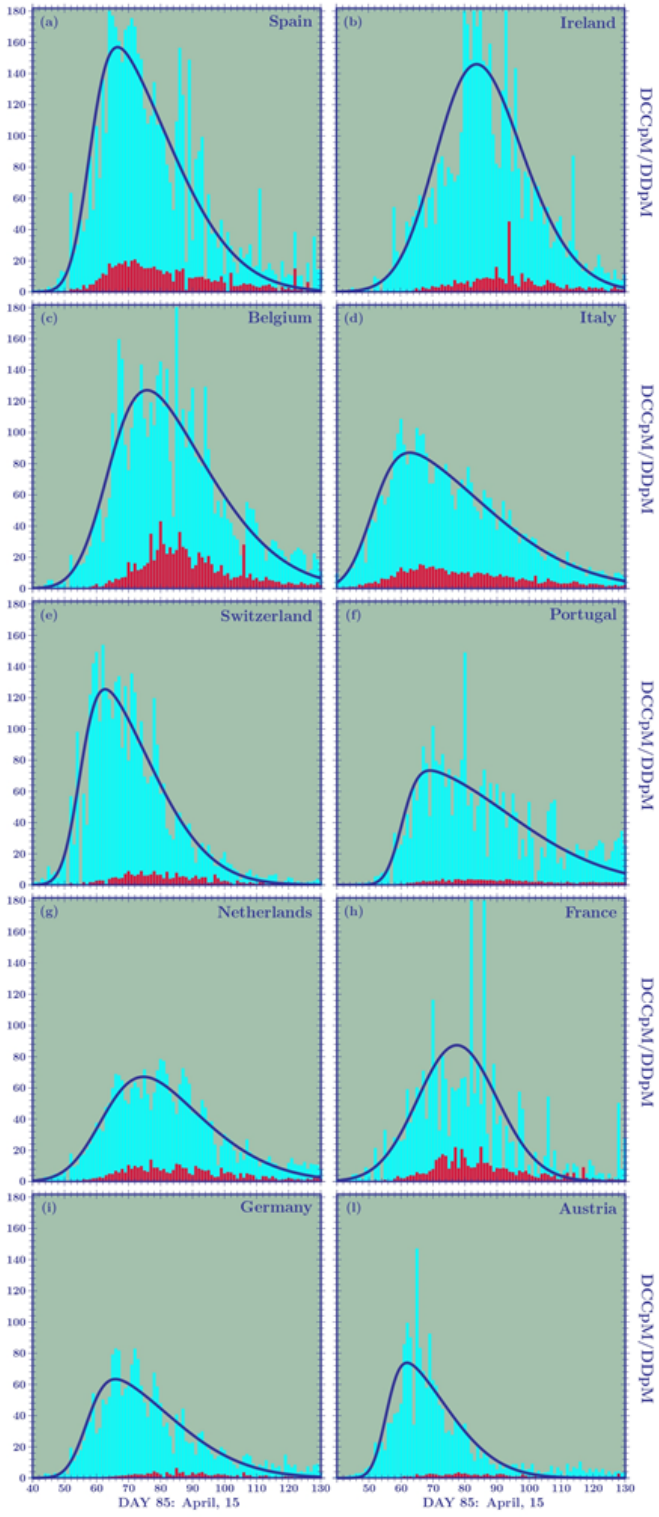


Figure 6. Skew-normal probability distribution functions corresponding to the cumulative distribution functions plotted in Figure 5. DCCpM: daily confirmed cases per million, DDpM: daily deaths per million.



We observed that, among the distributions plotted in Figure 6, that of the Netherlands shows a smooth growth and a peak (comparable to that of Germany) and is lower than all the other distributions. The Netherlands attempted to adopt a different form of lockdown. In contrast to most other European countries, where people were virtually housebound, the Dutch authorities opted for what they called an "intelligent" lockdown. The Dutch position, in many aspects similar to the Swedish one, reflects the idea that immunization also plays a fundamental role in managing the pandemic. Despite its differing approach with respect to the strict lockdowns of Belgium (TDpM=814.9), Spain (TDpM=579.6), the United Kingdom (TDpM=566.0), Italy (TDpM=551.1), and France (TDpM=439.8), the Netherlands seems to have made the right choice, closing their first wave of the outbreak with a smaller number of deaths per million (TDpM=348.0).

The United Kingdom, Sweden, the United States, and Brazil

In Figures 7 and 8, we plot the cumulative density function and probability density function skew-normal distributions for the United Kingdom, Sweden, and the United States. The fitting parameters modeling the TCCpM and TDpM curves are given in Tables 8 and 9.

Figure 7. Skew-normal cumulative distribution functions for the United Kingdom, Sweden, and the United States.

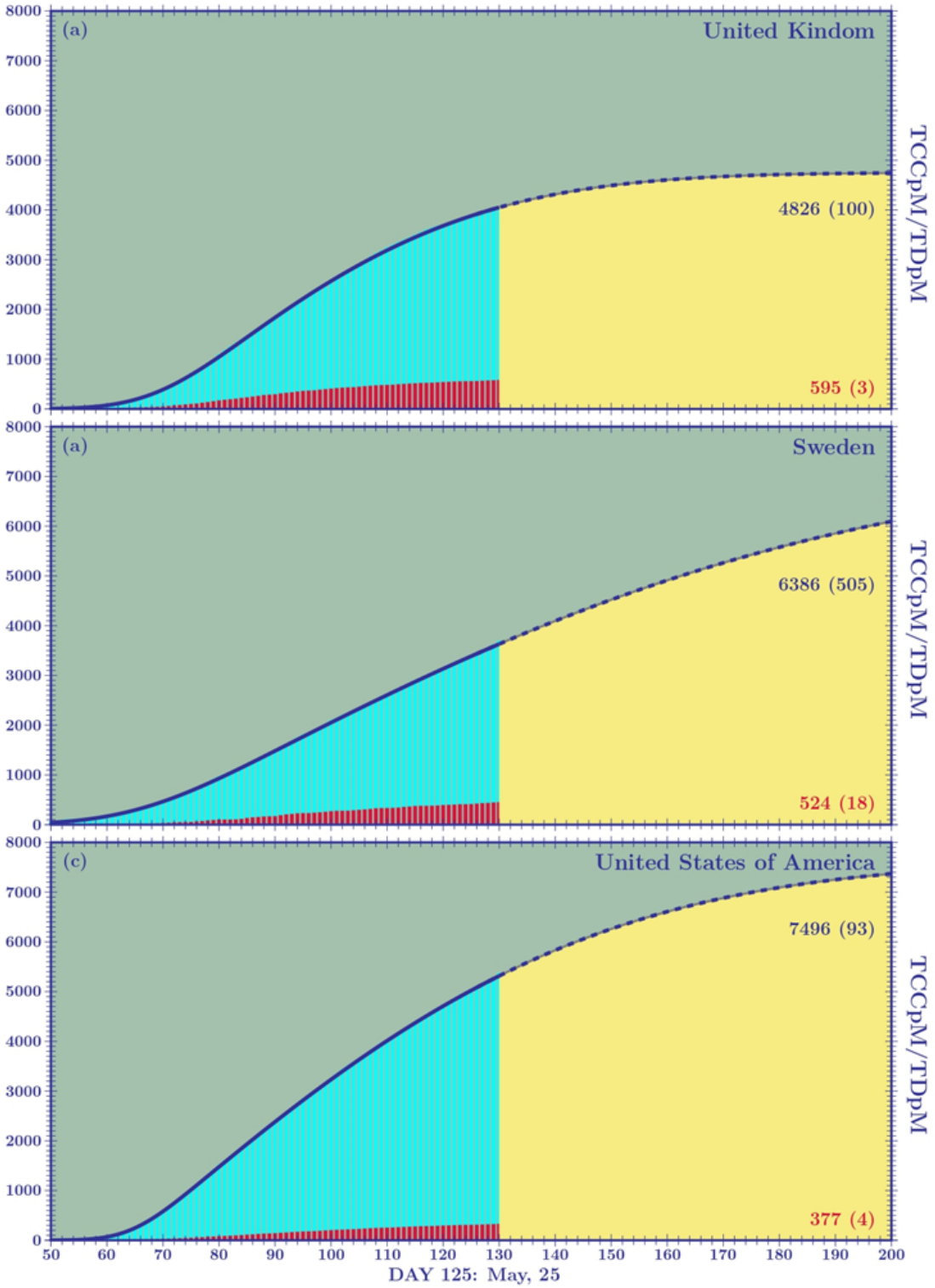


Figure 8. Skew-normal probability distribution functions corresponding to the cumulative distribution functions plotted in Figure 7. DCCpM: daily confirmed cases per million, DDpM: daily deaths per million.

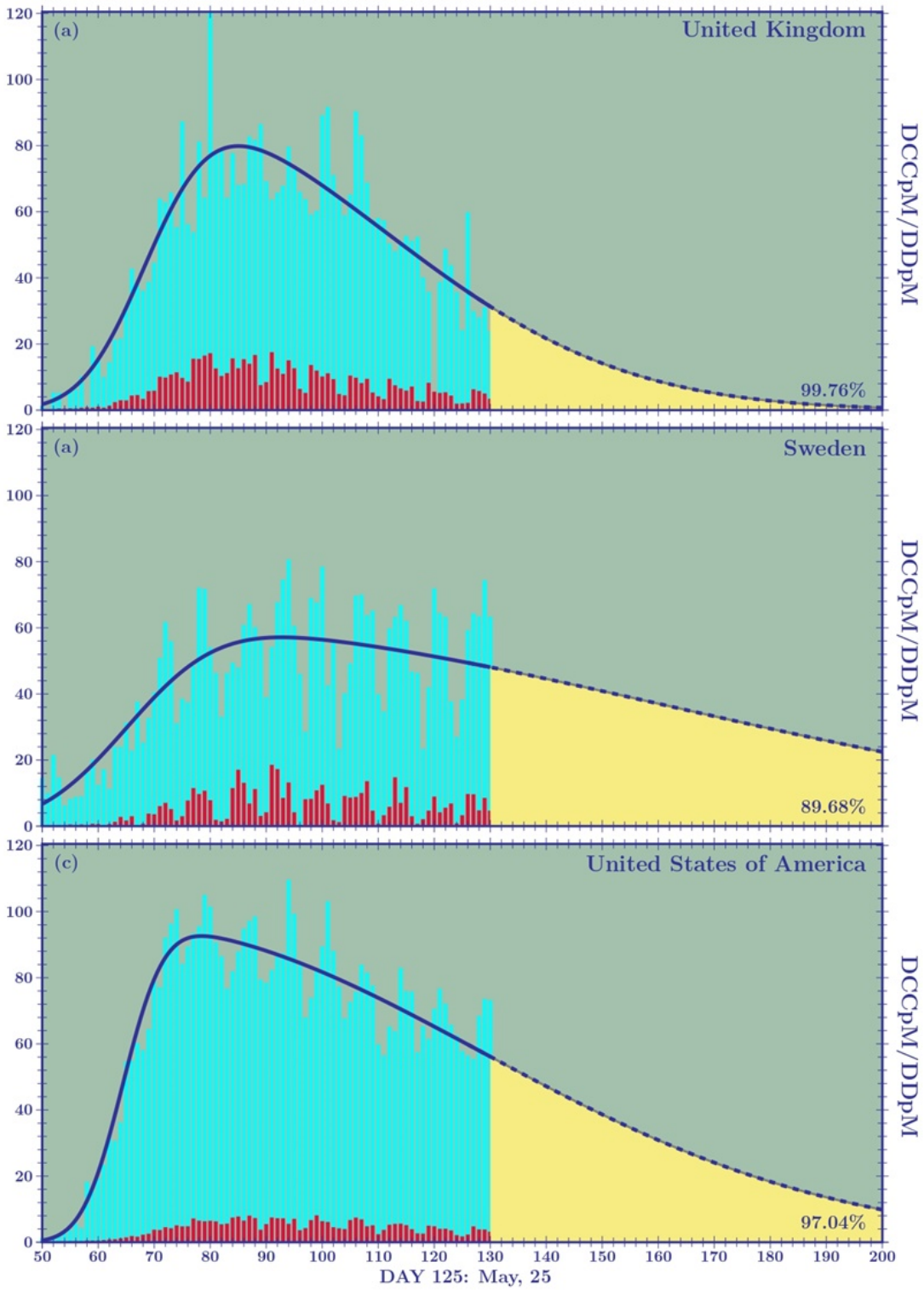


Table 8. The fitting parameters (center, standard deviation, and skewness) of the skew-normal distributions of the United Kingdom, Sweden, and the United States for total confirmed cases per million.

Country	Parameter			Total confirmed cases per million (95% CI)
	μ_c(95% CI)	sig_c (95% CI)	s_c (95% CI)	
United States	64.4 (0.1)	63.6 (0.1)	11.1 (0.6)	7618 (90)
Sweden	65.3 (0.6)	95.8 (1.1)	7.6 (1.2)	7253 (675)
United Kingdom	68.6 (0.4)	42.4 (0.1)	4.6 (0.4)	4753 (78)

Table 9. The fitting parameters (center, standard deviation, and skewness) of the skew-normal distributions of the United Kingdom, Sweden, and the United States for total deaths per million.

Country	Parameter			Total deaths per million (95% CI)
	μ_d (95% CI)	sig_d (95% CI)	s_d (95% CI)	
United States	69.5 (0.2)	31.9 (0.5)	5.4 (0.4)	595 (4)
Sweden	72.3 (0.6)	43.5 (2.8)	5.7 (1.0)	524 (18)
United Kingdom	70.6 (0.2)	43.2 (0.8)	6.4 (0.4)	377 (4)

The curves of the United Kingdom and Sweden, in terms of the DCCpM and DDpM skewness and DDpM standard deviation, are similar to that of Italy and Portugal, respectively. The difference is found in the standard deviation of DCCpM. The *c value* for the United Kingdom (c=42.4) is greater than that of Italy (c=32.3), and the c of Sweden (c=95.8) is the highest among all the countries studied in this paper. Sweden's high standard deviation is a clear consequence of the milder mitigation measures adopted by local authorities. Contrary to what will happen in other European countries, where once the first phase of the pandemic is closed and a new wave is expected to come, Sweden will probably face a single long period of the pandemic.

The greater standard deviations of the DCCpM curves of the United Kingdom and Sweden, with respect to those pertaining to their DDpM, leads to mean values of DDpM lower than those of DCCpM (United Kingdom: μ_d=94.5, μ_c=101.7; Sweden: μ_d=106.5, μ_c=141.1), which is contrary to what has been seen for other European countries. This result confirms what we discussed in the *Introduction*, that is, when speaking of COVID-19 numbers, it is fundamental to look at the deaths per million. Predictions of the critical peak region for the DDpM curves are clearly more important than the ones for the DCCpM curves. When the DDpM curves cannot be modeled, because one of the three parameters oscillates, we can resort to what we call dynamical prediction. This happens, for example, for Brazil, where the peak still shows an oscillating behavior. This point will be revisited later.

The skew-normal predictions can be complemented by the graphical analysis of the α and β factors given in Figure 3 . For example, Figure 3A shows a closing curve for the United Kingdom (black line) between 4000 and 5000 TCCpM, and this is in agreement with the skew-normal prediction (4753, SD 78). For the United Kingdom, with a population of 68 million people, a TCCpM of 5000 means 340,000 confirmed cases at the end of the first pandemic wave. For Sweden (yellow line), the factor does not yet show a decreasing trend. This means that the skew-normal forecast yields a TCCpM value greater that 7000 (7253, SD 675) corresponding to 70,000 confirmed cases (considering that the Swedish population is 10 million inhabitants), which could represent a lower limit. As observed before, the number of total infected people is only one of the analyses that needs to be done to assess how a country has tackled the epidemic. When looking at the skew-normal predictions for the total deaths in the United Kingdom and Sweden, we find values around 600 (595, SD 4) and 500 (524, SD 18), respectively. This predicts approximatively 40,000 and 5000 deaths for the United Kingdom and Sweden, respectively.

For the United States, the skew-normal prediction for the TCCpM results in a value of approximately 7500 (7618, SD 90); this means that for a population of 330 million people, there will be 2.5 million confirmed cases at the end of the first pandemic wave. Interestingly, the TCCpM of the United States and Sweden is similar despite differing mitigation measures. However, as observed earlier, when we compare the total confirmed cases between two countries, we must normalize using their TpC ratio, which in this case is 2/3 (Table 1).

The United States and the United Kingdom similarly adopted strict lockdowns. The factor of the United States (Figure 3B, white line) predicts, at the end of the first wave, a TDpM of 400 (130,000 deaths) compatible with the skew-normal prediction (377, SD 4). The United Kingdom should close its first wave with a TDpM of 600. This difference could be explained by the difference in the number of ICU beds per 1 million for the two countries (66 for the United Kingdom and 292 for the United States). Sweden, if the prediction is confirmed, should close with a TDpM of 500 without resorting to a strict lockdown and despite its very low number of beds per 1 million (58), which is certainly a win for the Swedish authorities. It should be noted that most European countries are now entering the second phase of COVID-19, and as mitigation measures are relaxed, their response will resemble the Swedish approach.

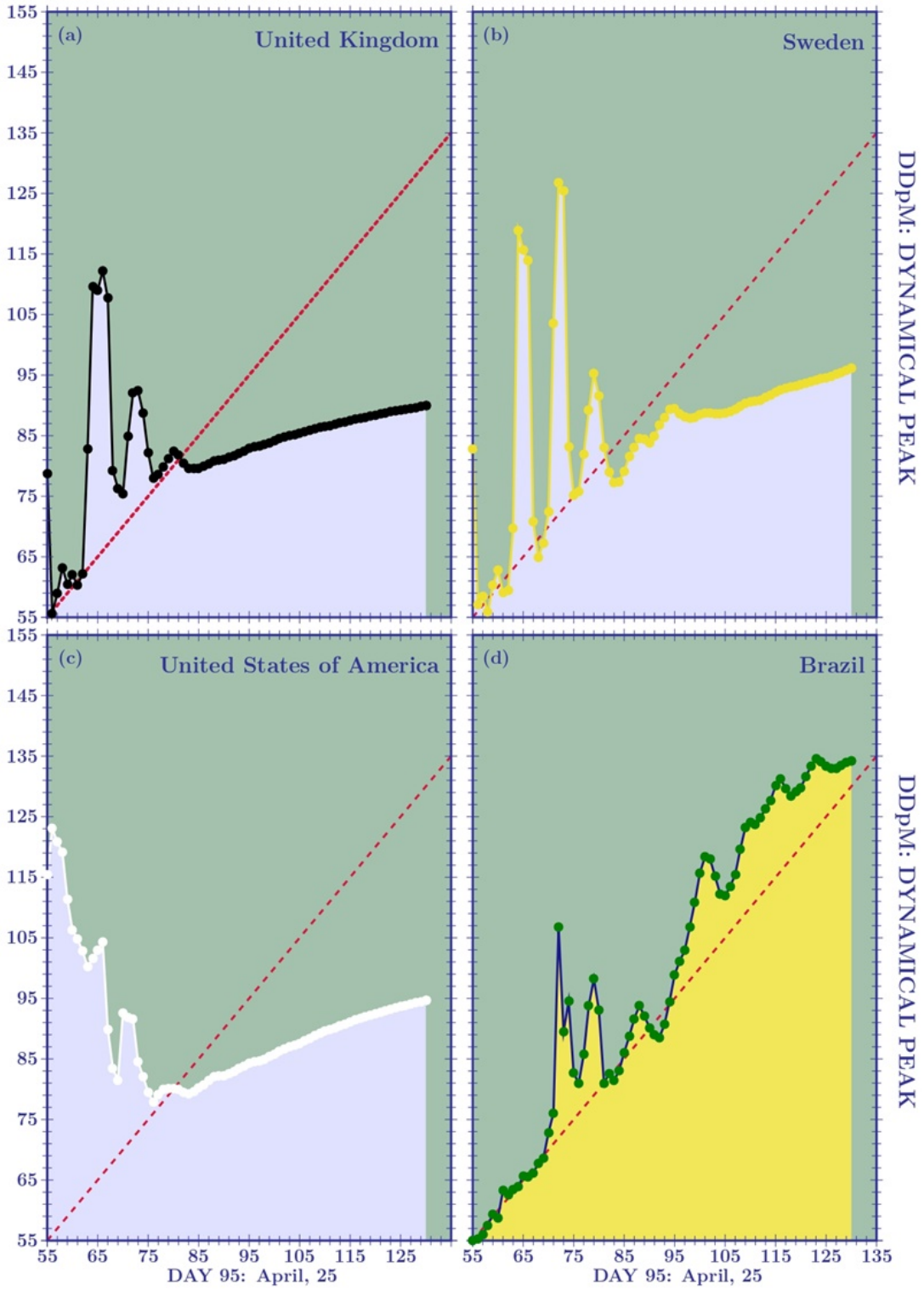
For Brazil, it is not yet possible to model the DCCpM and DDpM curves because the skew-normal parameters are still in their oscillating phase. However, the α and β factors can be

used to compare the epidemic curves of Brazil with those of the European countries when they were in the same stage of the outbreak. In particular, the Brazilian DDpM weekly spreading curve (Figure 4B) overtakes those of Austria, Germany, and Portugal, but it is lower than those of other European countries like Spain, Italy, and the United Kingdom.

Dynamical Predictions

To make some reliable predictions for Brazil, let us examine the dynamical peak (Figure 9). Until the peak is reached, we cannot speak of asymmetric distributions; hence, the standard normal distribution must be used to obtain *dynamical* predictions. The idea behind dynamical predictions is simple: in the initial stage of the disease, the daily updated data lead to forecasts that change drastically from one day to the next. For example, on day 65 (March 26), the peak of the DDpM curves for the United Kingdom, Sweden, and the United States was predicted to occur on day 103 (May 3), day 109 (May 9), and day 116 (May 16), respectively (Figure 9). Five days later, the peak of the DDpM curves was predicted on day 92 (the United Kingdom and the United States) and day 127 (Sweden). In Figure 9, the dashed red line (day of the prediction coinciding with the prediction of the peak) represents the critical line. When the prediction curve crosses such a line, it tends to stabilize (see the United Kingdom, Sweden, and the United States). For Brazil, the oscillating peak is getting closer to the critical line. For a symmetric distribution, after the crossing point, we should, theoretically, have a horizontal line. Therefore, the inclination of the dynamical curve, after the crossing point with the critical line, is an indication of the breaking of symmetry in the distribution. For example, the DDpM skew-normal curves of the United States and Sweden should have greater asymmetry compared to the United Kingdom. This is confirmed by the standard deviations provided in Table 4.

Figure 9. The dynamical curve for the peak of daily deaths per million (DDpM). The oscillatory behavior tends to stabilize when the curve crosses the critical (dashed red) line. After stabilization, the inclination is an indication of the breaking of symmetry in the distribution.



The dynamical analysis of Brazil's peak shows that the country is approaching its DDpM peak. To see when this will happen, let us consider the number of deaths on May 30 (day 130), that is, 28,834. If we go back to day 80 (April 10), we find 1057 deaths. Table 10 displays the number of deaths every 5 days starting on April 10.

The ratios between the number of deaths every 5 days (eg, 1.64=1736/1057) can be modeled using a linear fit: $yd=2.4-xd/100$. Solving for xd and setting $yd=1$, we find that $xd=140$, which predicts the peak of the DDpM curve to fall around June 10. Considering the increase of the last 10 days, this indicates a peak of around 200 TDpM, a number comparable to that of the most critical European countries (Figure 3B) but with a number of DDpM at a peak lower than those of these countries (Figure 4B) and similar to the Dutch and Swedish peaks. Recalling that the Netherlands is closing its first

pandemic wave at around 400 and the prediction for Sweden is around 500, for Brazil this means approximately 80,000 deaths if the mitigation measures remain similar to the current ones (which are comparable to the Netherlands' approach). Relaxing the mitigation rules (resembling Sweden's approach) will probably result in surpassing a TDpM value of 600, that is, exceeding 120,000 deaths.

Looking at the TDpM situation across the five regions of Brazil, we find (on May 31) a very heterogeneous situation, with the Central-West (TDpM=23) and South (TDpM=18) regions well below the national value of 140, the Northeast (TDpM=155) and Southeast (TDpM=157) regions with a TDpM comparable to the national one, and the Northern (TDpM=309) region surpassing the national one. In São Paulo State (TDpM=166), São Paulo City (11.8 million inhabitants) has a TDpM of 357 whereas Campinas (1.2 million inhabitants) has a TDpM of 63. This large heterogeneity indicates the impact of varying local mitigation measures when combating the long epidemic wave.

Table 10. The number of deaths every 5 days, starting on April 10, and ratios between the number of deaths every 5 days, for Brazil.

Day	Deaths, n	Ratio
80	1057	N/A[a]
85	1736	1.64
90	2587	1.49
95	4057	1.57
100	6006	1.48
105	7938	1.32
110	11,123	1.40
115	14,962	1.35
120	18,859	1.26
125	23,473	1.24
130	28,834	1.23

[a]N/A: not applicable.

ρ Factor Analysis

Table 11 presents the ρ factor for the 10 European countries of Figures 5 and 6 by using the data in Table 1. A lower value implies a better rating.

Table 12 displays the ρ factor for countries that have adopted a smart testing strategy and reduced the number of deaths per 1 million inhabitants at the end of May 2020 [2].

Table 11. The ρ factor for 10 European countries.

Country	ρ factor
Switzerland	0.80
Ireland	0.86
The Netherlands	0.96
Germany	1.01
Portugal	1.07
Austria	1.08
France	1.16
Spain	1.69
Italy	2.35
Belgium	2.42

Table 12. The total deaths per 1 million inhabitants, total confirmed cases per million, tests per confirmed case, population size in millions, and ρ factor on May 31, 2020.

Country	Total deaths per million	Total confirmed cases per million	Tests per confirmed case	Population size in millions	ρ factor
Iceland	29	5295	33.8	0.34	0.19
South Africa	12	552	22.2	59.24	0.48
Norway	44	1558	29.1	5.42	0.82
Finland	58	1243	26.9	5.54	1.26
Czech Republic	30	866	47.8	10.71	1.66
South Korea	5	224	80.2	51.27	1.79
Australia	4	283	204.2	25.47	2.89

It is important to recall that the ρ factor considers not only the mortality rate but also the *immunization* rate. It is clear that with an indiscriminate and strict lockdown, a country will avoid deaths, but at the same time, it will have a very low immunization level when facing the second wave of the pandemic.

Table 12 is also useful for understanding why the TpC is important. For example, South Africa and South Korea have similar mortality rates: 12/552 and 5/224, respectively. However, South Korea's testing strategy led to a number of tests 4 times that of South Africa. Consequently, the number of infected people in South Africa is expected to be greater than that of South Korea probably by the same factor. This explains the final ratio of the ρ factor between South Africa and South Korea.

In the case of Italy, where a full national lockdown was imposed at the beginning of March, Table 13 presents metrics and the ρ factor associated with each of its regions.

Table 13. The total deaths per 1 million inhabitants, total confirmed cases per million, tests per confirmed case, population size in millions, and ρ factor for the regions of Italy on May 30, 2020.

Region/country	Total deaths per million	Total confirmed cases per million	Tests per confirmed case	Population size in millions	ρ factor
Piedmont	865	6857	10.3	4.46	1.30
Lombardy	1598	8823	8.4	10.06	1.52
Valle d'Aosta	1172	9697	12.7	0.12	1.53
Liguria	941	6226	10.9	1.55	1.65
Molise	71	1406	33.0	0.31	1.67
Emilia-Romagna	921	6224	11.6	4.46	1.72
Marche	645	4397	15.2	1.53	2.23
Trentino-Alto Adige	704	6565	21.6	1.07	2.32
Tuscany	278	2708	24.7	3.73	2.54
Umbria	86	1626	48.9	0.88	2.59
Abruzzo	308	2471	22.6	1.31	2.82
Apulia	124	1114	26.0	4.03	2.89
Lazio	124	1312	32.8	5.88	3.10
Veneto	390	3903	34.4	4.91	3.44
Sicily	55	688	43.3	5.00	3.46
Campania	71	827	41.3	5.80	3.55
Sardinia	79	827	41.7	1.64	3.98
Friuli-Venezia Giulia	273	2681	40.3	1.22	4.10
Basilicata	48	712	73.7	0.56	4.97
Calabria	50	594	59.9	1.95	5.04
Italy	551	3846	16.4	60.47	2.35

From these data, it is clear that regions such as Calabria (TCCpM=594, TpC=59.9), Sicily (TCCpM=688, TpC=43.3), Basilicata (TCCpM=712, TpC=73.7), Sardinia (TCCpM=827, TpC=41.7), and Campania (TCCpM=827, TpC=41.7) have a very low immunization rate; this should be considered when entering the second wave of the pandemic. The best factor, combining the mortality and immunization rates, belongs to Piedmont. The Italian data also show that a smart lockdown and an appropriate testing strategy should provide better results than an indiscriminate full lockdown.

Discussion

Principal Findings

In this final section, after studying the metrics associated with the COVID-19 outbreak, we recommend following these steps:

1. The weekly transmission rate of the DCCpM (DDpM) as countries reach the same number of TCCpM (TDpM) can be used to compare countries that are at different stages of the outbreak, which we refer to as the α (or β) factor;
2. Before reaching the peak, the dynamical (oscillatory) curve of the parameters to be fitted can be used to understand when such a curve crosses the critical line and tends to stabilize;
3. After reaching stabilization, asymmetrical distributions have to be introduced to model the DCCpM and DDpM curves (we used skew-normal distributions).

As shown in the previous sections, the timely massive testing strategy implemented by German authorities resulted in a substantial difference in the outcomes of Germany and Italy. Indeed, mitigation measures (such as physical distancing, contact tracing, restricting public gatherings, closing schools and universities) certainly become more effective when a country adopts a timely and massive testing strategy, thereby limiting transmission from asymptomatic cases and facilitating treatment for sick people before the disease worsens. The quantitative impact of a massive testing strategy has been studied by Gorji et al [28]. Clearly, if a country has not performed enough tests, a random smart testing strategy is required. By testing a much smaller number of randomly selected people per day, it is possible to obtain information on the local transmission rate [29].

The Brazilian mitigation measures are similar to that of the Netherlands, stricter than that of Sweden but certainly less severe than the Italian lockdown. On May 30, Brazil reached a TCCpM value of 2347 and a very low TpC number (1.9), suggesting a great number of hidden infected people. Nevertheless, the number of deaths (TDpM=126) still remain under control, and as shown in the *Results* section, the peak may possibly occur around June 10. For Brazil, the factor is 0.10. This means that, at the end of the first pandemic wave, Brazil will reach a great number of confirmed cases per million (with a consequently good level of population immunization) and a relatively low number of deaths. As shown for Italy, it is clear that a strict national mitigation approach is not the correct way to manage the pandemic. A smart local lockdown should be preferred to a national one, as in medieval times. In contrast to most other European countries where people were virtually housebound, the Brazilian, Dutch, and Swedish authorities adopted a different mitigation approach: conservative (but not medieval), moderate, and liberal, respectively. Italy and the Netherlands are closing their first pandemic wave with TDpM and TCCpM numbers of approximately 550 and 3800 for the former and 350 and 2800 for the latter. Sweden, if the predictions are correct, should close around 550 and 7500. The Dutch and Swedish approaches have yielded positive results in terms of deaths and confirmed cases per million compared to the European countries that adopted a strict lockdown (Belgium, Spain, the United Kingdom, and Italy), even though they were heavily criticized in the beginning for their mitigation measures and despite their less effective testing strategies.

Alarming predictions of the exponential growth rate of the pandemic led the local authorities of many countries to implement a strict lockdown. Nevertheless, the Swedish DCCpM curve does not confirm this fear, and it has a smooth increase with respect to the curves of the United Kingdom and the United States (Figure 7). Recently, Norwegian authorities have concluded that the virus was never spreading as quickly as predicted and that the effective reproduction rate had already dropped to a value around 1.1 before the implementation of most rigid mitigation measures [30]. This is also happening for Brazil (Figure 4A), where starting from day 80 (April 10) and reaching day 130 (May 30), we have, every 5 days, an increase of 1.30-1.45 in the total number of confirmed cases.

Need for a Massive Testing Strategy

Testing far more people means detecting more inhabitants with fewer or no symptoms. Increasing the number of known cases, but not the number of fatalities, we obviously decrease the fatality rate and obtain a more reliable number for the mortality rate of the pandemic. Nevertheless, this is not the main goal of a massive testing strategy. The strategy of early and widespread testing allows us to slow down the pandemic spread by isolating known cases while they are infectious and to deliver medical treatment in a timelier fashion, thereby saving lives. The possibility of an early diagnosis, before the health of a patient declines substantially, increases the chance of survival.

Long before recording its first case of COVID-19 in February, Germany, in mid-January, developed a test and posted the formula online, and laboratories across the country stockpiled test kits [31]. This permitted greater testing with respect to other European countries. The German and Austrian massive testing strategy, implemented during the early stage of the pandemic, made a great difference. Massive testing in the final stage is only useful for reducing the mortality rate on paper and not for saving a *substantial number of lives.*

At the beginning of its outbreak, Germany conducted 120 tests per confirmed case, far more than any other European country. Medical staff, who were at heightened risk of contracting and spreading the virus, were regularly tested. Donning adequate protection, physicians, nurses, and laboratory technicians took to the streets, conducting tests via the *corona taxi* and suggesting hospitalization even for patients with mild symptoms [31]. This was done at zero cost to the population (contrary, for example, to what happened during the first several weeks of the outbreak

in the United States), and this guaranteed broad-based testing. In most countries, including the United States and Brazil, testing was largely limited to the sickest patients. Testing and tracking was a successful strategy used by both South Korea and Germany.

Social distancing measures are important for flattening the pandemic curve and avoiding the collapse of national health care systems. Clear, detailed, and scientifically correct information is fundamental to reassure and calm citizens, but, as already mentioned, massive testing strategies make a noticeable difference in the fight against COVID-19.

An important consideration must be made about the absolute numbers often used in the media: they cannot be used when comparing different countries. For example, the absolute numbers of tests, on May 30, for Germany and Italy, are 3,824,621 and 3,952,971, respectively. At first glance, the small difference seems not to deserve a deep analysis of their strategy. However, as shown in this section, the massive testing strategy adopted by Germany in the early stage of the disease led to different results in terms of mortality rates, in favor of the German people.

Other absolute numbers often used to compare countries are total confirmed cases and total deaths. For example, in the COVID-19 world ranking on Worldometer [2] (which lists 215 countries), the absolute numbers for total confirmed cases and total deaths for Brazil on May 30 puts the country in position 2 for TCCpM (after the United States) and in position 4 for TDpM (after the United States, the United Kingdom, and Italy). To compare countries, we obviously have to normalize using their population; upon normalization, Brazil descends to position 39 for TCCpM and 22 for TDpM.

Conclusions

We conclude by noting that this paper only represents one of the many different ways of examining numerical data pertaining to the COVID-19 outbreak. Any scientific analysis should always be complemented by examining the local situation in terms of ICU beds, hospital capacity, and equipment. Researchers working with these data can certainly shed some light on the situation, but nurses and physicians struggle on a daily basis to help the population; they save lives, deserve protection, and all the necessary support.

Comparing the epidemic across various countries certainly is a difficult task. Mortality rates must always be traced back to the average age of the population, to the capacity of the health system, and to the strategies adopted by the authorities to manage the COVID-19 outbreak. The discussion and statistical analysis presented in this paper clearly show why Germany was so effective in pandemic management compared Italy. Massive testing strategies are a more appropriate way to control the pandemic. Skew-normal distributions allow us to obtain a more realistic prediction of the end of the pandemic in each country. The mortality rate has to be calculated by comparing the deaths in 2020 with those of 2019; this is the only effective way to understand the effect of COVID-19 on the mortality rate of a country and consequently to understand the real mortality rate associated with the disease and whether deaths were due to overloaded health care systems.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Illustration of normal and skew-normal distributions.
[PNG File , 435 KB - xmed_v2i2e21269_app1.png]

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Abbreviations

DCCpM: daily confirmed cases per million
DDpM: daily deaths per million
EF: effectiveness factor

ICU: intensive care unit
R_0: basic reproduction number
R_t: effective reproduction number
SARS: severe acute respiratory syndrome
TCCpM: total confirmed cases per million
TDpM: total deaths per million
TpC: tests per confirmed case
WHO: World Health Organization

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Viewpoint

Why We Are Losing the War Against COVID-19 on the Data Front and How to Reverse the Situation

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Abstract

With over 117 million COVID-19–positive cases declared and the death count approaching 3 million, we would expect that the highly digitalized health systems of high-income countries would have collected, processed, and analyzed large quantities of clinical data from patients with COVID-19. Those data should have served to answer important clinical questions such as: what are the risk factors for becoming infected? What are good clinical variables to predict prognosis? What kinds of patients are more likely to survive mechanical ventilation? Are there clinical subphenotypes of the disease? All these, and many more, are crucial questions to improve our clinical strategies against the epidemic and save as many lives as possible. One might assume that in the era of big data and machine learning, there would be an army of scientists crunching petabytes of clinical data to answer these questions. However, nothing could be further from the truth. Our health systems have proven to be completely unprepared to generate, in a timely manner, a flow of clinical data that could feed these analyses. Despite gigabytes of data being generated every day, the vast quantity is locked in secure hospital data servers and is not being made available for analysis. Routinely collected clinical data are, by and large, regarded as a tool to inform decisions about individual patients, and not as a key resource to answer clinical questions through statistical analysis. The initiatives to extract COVID-19 clinical data are often promoted by private groups of individuals and not by health systems, and are uncoordinated and inefficient. The consequence is that we have more clinical data on COVID-19 than on any other epidemic in history, but we have failed to analyze this information quickly

enough to make a difference. In this viewpoint, we expose this situation and suggest concrete ideas that health systems could implement to dynamically analyze their routine clinical data, becoming learning health systems and reversing the current situation.

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KEYWORDS

COVID-19; learning health systems

The Problem

Many countries reacted late to the spread of the COVID-19 pandemic, although once they realized the seriousness of the situation, they took strong measures. The best-known measures relate to restrictions on population movement; other important implementations include increasing the capacity of health systems and the mobilization of the military to aid in this health emergency. Using a martial simile, it appears that governments have prepared their "health" armies and their populations for the war against the virus.

An additional necessity is a good intelligence service to fight the war. This requires a system to collect data on the enemy and a group of analysts who can extract relevant information. Most current information systems pertaining to the pandemic focus on counting numbers of individuals tested, infected, hospitalized with serious conditions, recovered, and deceased. Data have also been collected to understand public behaviors [1], some of which was planned for [2]. These kinds of data can serve to estimate epidemiological curves and predict how the pandemic might evolve (if everything continues as it has been so far), but they provide very limited insight into how frontline doctors can fight the virus.

Epidemiological data often combine a limited number of variables for substratification of cases; these data categorize continuous variables for reporting purposes and often lack detailed information on variables collected during hospital care. Epidemiological curves do not allow us to answer clinical questions such as what the most relevant risk factors are for becoming infected, having symptoms, becoming seriously ill, or dying. They also do not allow us to study which treatments work better and what patient characteristics can influence the success or failure of the treatments. These are the questions that we need to answer to improve patient care and to rationalize the use of resources when health systems are at the limit of their capacities. These questions have not been answered satisfactorily. On March 24, 2020, a senior intensive care unit physician working in a big hospital in Madrid told the lead author that, "We learn things about the disease as we go along every day." Two weeks later, on April 9, 2020, a colleague working at a hospital affiliated with University College London Hospitals said, "…is a new disease with a pathology and clinical course that none of us know about." In between these two statements, thousands of patients have died or recovered from SARS-CoV-2 infection in Spain, the United Kingdom, and many other countries. It seems we hardly learned anything from those patients since months later we continue to ask the same clinical questions: what are the determinants for bad prognosis? How do we best treat patients?

What Do We Need to Solve the Problem?

To answer clinical questions, we need clinical data from individual patients. We need a database where the anonymous clinical information of hospitalized patients with COVID-19 can be stored, curated, and made accessible to researchers. The structure of the data set does not have to be very complex since, for each patient, the disease involves basically a single hospital episode that does not usually last more than 4-5 weeks. The database would be continually fed with each hospital discharge. Statistical models to answer each clinical question can be programmed and automatically updated as more data come in. In this way, we would have a continuous information system growing with the epidemic and generating knowledge in real time that could be fed back to the frontline doctors treating patients. Therefore, the health system to fight the epidemic would have two subsystems working together: a care subsystem to treat patients and a knowledge subsystem to learn about the disease. This is what the literature has described as a learning health system [3,4].

Although it would be ideal to link up with the patient's medical history in specialized and primary care, this may not be necessary to answer the most pressing clinical questions about prognosis and the best therapeutic strategies. Initially, each health system (country/nation/region) would implement its own database including as many hospitals as possible although sharing information between countries would be advantageous. In addition, because the epidemic develops asynchronously in different countries, what we can learn from the data in one country can help to improve patient treatment in other countries.

What Is Being Done?

There are many private initiatives to create registries of patients with COVID-19 that include clinical data, some supported by professional societies [5-14]. Although understandable and praiseworthy, these initiatives are generally burdened with problems:

1. Often these registries are disconnected from the electronic health records of hospitals and require extra effort from health care professionals to input the data. This has long been known to be a major barrier to usage [15]. These professionals are likely to be heavily overloaded with work, and many of them simply refuse to fill out another form.
2. Since some of these registries are for patients with a specific disease (eg, atopic dermatitis) and they try to collect very detailed patient data, entry forms can be lengthy and detailed.

3. Since some of these data sets recruit only specific kinds of patients, their analysis will only apply to certain subpopulations.
4. Contribution to these data sets is voluntary, and the speed at which they grow depends on many factors, such as how many professionals they have managed to reach and persuade to collaborate, how many patients with the specific selection criteria are available, and how easy they are to feed. For example, as of April 11, 2020, the LEOSS (Lean European Open Survey on SARS-CoV-2 infected patients) [8] reported having 642 collaborators involved from 165 centers, but only 770 patients enrolled. However, the Intensive Care National Audit & Research Centre [6], a long-standing registry, reported having captured 2621 COVID-19 admissions to the intensive care unit by April 4, 2020.
5. Many of these registries have been designed to collect data that will be analyzed when the epidemic is over, and the research questions behind them are not always connected to the needs of health providers at the front line. Many of these analyses will not be timely enough to confront the current epidemic, and it is unclear whether they will be useful to deal with the next one. One cannot blame clinicians treating patients if they do not put much interest in filling these forms that will not result in immediate tangible benefits to their patients. Those who do the work need to see the benefits to be motivated to participate [16-18].

Some governments and health institutions have implemented important initiatives to share individual patient clinical data on COVID-19. For example, the Mexican government, following a policy of open data, has been sharing clinical data on all COVID-19 cases since April 13, 2020, with a daily update of the entire data set [19]. The Health Insurance Review & Assessment Service of South Korea also intended to make anonymized clinical data pertaining to patients with COVID-19 available [20]. One of the most comprehensive initiatives is the OpenSAFELY project [21] in the United Kingdom, which created a new secure analytics platform for electronic health records in the National Health Service (NHS) to deliver urgent results during the global COVID-19 emergency. This platform includes not only patients with COVID-19 but almost any patient registered in participating primary care practices (more than 24 million patients' full pseudonymized primary care NHS records, with more to follow). Their complete analytic software is open for security review, scientific review, and reuse.

Although all these initiatives are laudable and valuable for facilitating important research to be undertaken and even breakthroughs to be made in the fight against the pandemic, none of them are learning systems that are integrated within health care systems. They have not been designed within the health care system to answer specific health care questions. In our view, a health learning system would work best when integrated with the care services through a constant feedback loop to respond as quickly as possible to the most pressing clinical questions as mentioned above [22]. The OpenSAFELY platform is aiming to comply with this model although it was not actually created within the NHS as an integral part of it but by academics in universities who saw the potential of making these data available to researchers outside the NHS who were eager to help in the fight against the pandemic.

What Can Be Done?

The health systems should plan the collection, availability, analysis, and reporting of clinical data in a timely manner that can effectively influence the response to the epidemic. That is, they should strive to become learning health systems during the epidemic. We offer some suggestions to achieve this.

1. Design

There should be protocols to ensure that at least a minimum set of relevant clinical variables are collected using the same criteria and procedures across all units of a health system. Failure to regulate and standardize clinical data collection might lead to the development of several independent data sets that are not easy to link to one another. Interoperability solutions are vital [23]. It is not our purpose here to propose a specific set of variables for the COVID-19 pandemic; we believe this should be agreed upon by appointed expert panels, but below we point out some important considerations that should be addressed when designing the database.

Scope

The database should be designed in such a way that it can be implemented in most health units expected to collect the data. In general, the more heterogeneous the data collectors, the simpler the database will need to be to maximize the possibility of collecting comparable data across units. For example, if a supranational organization such as the World Health Organization (WHO) were to suggest a data structure, it is advisable to keep the specifications as simple as possible to be applicable to most countries, bearing in mind the diversity of health systems and resources available. In contrast, a country with a highly digitalized and homogeneous health system can specify a more complex data structure. The advantages of the WHO approach would be to potentially collect a much larger data set covering diverse populations in different countries, while a country-specific model could collect less but more detailed data. A combination of the two approaches might be possible with the WHO producing a data structure with different layers of complexity starting from a top, simpler level collecting the most basic data to answer the most pressing questions down to levels of highly complex data. Each health system could then try to achieve as many levels as possible depending on their capabilities.

Objectives

It is important to design the data collection process with a specific research question(s) in mind to determine how and what data should be collected. For example, to answer the question "what risk factors affect the probability of infection?" we might want to collect information on the patient's circumstances (social, family, and work) before and around the infection time, but to answer the question "what conditions determine poor progression after hospital admission?" it might be enough to collect clinical information at hospital admission. A question about treatment effectiveness will require health services to

collect detailed information on treatments and all potential confounding factors. In general, the more questions we want to answer, the more data we need to capture and the more complex the system will be.

Costs

Obtaining each piece of information bears a cost. Sometimes this is minimal (eg, when information is collected routinely in the health system and easily retrievable) or it can require specialized resources and personnel who might not be available. Costly and complex information is more likely to not be properly collected in a system already under stress. Information partially and poorly collected is a potential source of bias if included in the analysis, and it might be therefore better to ignore it altogether. Hence, the costs and benefits of the information must be carefully balanced to reduce waste of resources, time, and the potential for bias.

Benefits

The benefit of variables is their potential contribution to answer one or more of the research questions. This does not mean that we can only include in the database variables that we know in advance to have some explanatory power for the outcomes that we want to study; in fact, we will not know this until we analyze the data after collection. However, there must be some reasonable expectations that the variable has an explanatory role or is a potential confounder that we need to adjust for in the analysis. The potential benefits must outweigh the costs of collecting and processing the information. Collecting variables with a priori limited expected explanatory power just in case someone finds a good use for them in the future is not a wise strategy when answers need to be found quickly. Apart from the extra cost of collection and processing, more statistical models might need to be run to confirm whether those variables are indeed irrelevant. This can unnecessarily increase the chances of finding false-positive associations that might divert efforts and attention from exploring the important causal associations [24].

In summary, a combined panel of experts with knowledge of the specific disease, epidemiology, health information systems, and statistics should design a database structure to answer a specific set of questions, considering the cost/benefit balance of the information to be collected, bearing in mind who is going to collect the data, and possibly proposing several layers of data collection from a minimum, simpler-to-collect set of variables to more complex data structures for highly digitalized systems.

2. Plan

A good plan will fail if the means to execute it are not made available. Technology can facilitate the collection of data. Where good electronic health records exist, relevant clinical data can be extracted from them. The particular implementation will depend on the characteristics of each health system and the data to be collected as defined in the *Design* section. For example, if a health system is highly informatized and most of the required data are already collected in electronic health records routinely, then perhaps only a database operator is needed to extract the relevant data. If the health system's information is mainly on paper, a team of dedicated researchers with a sufficient medical background will need to be recruited to extract the data and input the information into an electronic format. We cannot specify here what kind of professionals need to be hired or reinforced in each health system, but we can provide some points that should be considered to define needs:

- Consider the level of medical/epidemiological knowledge needed for the personnel involved in data extraction;
- Consider the technical difficulties of data extraction, storage, and curation, as well as knowledge of information technology and informatics needed to do this;
- Consider the complexity of the statistical analyses to be done with the data.

The golden rule is that these processes should not burden and distract care providers from their main job—treating the patients. Similar to how extra teams of doctors and nurses were brought in to care for patients on the frontline, and mathematical modelers were recruited to predict the progression of the epidemic, experts in medical informatics and data analysis should also be recruited to help analyze the clinical data on a nearly daily basis.

3. Integrate

Protocols permitting the two subsystems, care provision and data analysis, to work in synchrony need to be established [22]. The care system will provide data and the relevant questions, and the analysis system will run statistical and computer models to try to answer those questions. The findings will then be fed back to the care system, which can revise its strategy in light of new evidence. In the initial stages of the epidemic, clinical questions can be formulated, and the analysis team can design Bayesian models using existing prior clinical and biological knowledge. Once data start accumulating, the Bayesian models will be updated, and they can be used for decision making.

The kind of study designs that can be implemented in a learning health system can vary from simple case reports to randomized clinical trials, and one can potentially do several designs in parallel [25]. For example, a cohort analysis can be set up to look at risk factors at the diagnosis point for disease progression, so that patients can be triaged more efficiently at overloaded hospital admission departments. At the same time, if clinicians had clinical equipoise of treatment options for a subgroup of patients, a registry-based randomized clinical trial could be set up to decide the best treatment options in a timely manner [26-28]. In large health systems that cover most of the population, cases can be captured rather quickly if the learning system is implemented and coordinated across sites (hence the need for regulating and standardizing the methods).

4. Enforce

Data collection should not be regarded as an optional task in an epidemic as it is a necessary resource to learn how to fight the epidemic more effectively, to guarantee the right of the patient to the best possible care, and to reduce the number of deaths. The term "enforcement" might have negative connotations when related to health care research where we expect that participation of both researchers and patients should always be voluntary. However, a pandemic is an exceptional situation where the health (and possibly survival) of the population is at serious

risk, and the public good must be balanced against individual rights. This is indeed the case when restrictions such as quarantines or curfews are imposed during pandemics. Enforcement is much more likely to work if care professionals and patients are willing to collaborate. Early engagement through appropriate communication with health professionals and the public is explained below.

5. Engage Health Professionals

Collaboration as early as possible with clinical users is key to ensure these systems are usable and useful and to encourage adoption [3,18,23]. Cooperation of clinical users is not only key to ensuring good data quality; they also have to produce relevant clinical questions and incorporate the new knowledge generated into their practice. For care providers to spend time and energy engaging with the system, they must see it as an investment that will benefit their work and their patients rather than another administrative burden. It is crucial that they are involved in the design of the system to ensure that the system meets their needs and to facilitate trust in the system.

6. Inform the Population

Plans need to be made to address concerns around patient privacy and confidentiality [23], including appropriate legislative frameworks for emergency situations. In particular, ethical issues around data usage for research, by people inside and outside the system, need to be tackled from the beginning. In a setting of an infectious epidemic, it might be impossible to obtain informed consent from every single patient for their data to be used for research purposes. There are also procedures by which a priori one presumes consent of a patient who is unable to provide it in a critical situation, and later this consent is confirmed when the patient recovers or through relatives, and the data can be pulled out of the study if consent is revoked. These procedures have been implemented successfully in randomized clinical trials of emergency treatments [29].

On the other hand, these data are urgently needed to learn as quickly as possible about the disease, to stop the epidemic, and to save lives. The right to confidentiality should be balanced against urgency to control the epidemic. Data for research should be anonymized as much as possible. Ideally, an anonymized data set would have the ethical approval to be freely used for research in such a way that individual researchers would not have to seek approval separately for each project that uses the same data.

7. Share

Data should be made available to external researchers, and administrative burden should be reduced. Often, research projects in traditional settings have to go through tedious administrative procedures, seeking approval from different committees on different aspects such as ethics, technical quality, economic viability, chances of success, etc. This can delay data acquisition, analysis, and generation of results by weeks or months that might cost thousands of lives during an epidemic. Within a learning health system that sets up its own analysis teams, which are well coordinated with clinical teams, as specified in the *Plan* section, most of these requirements should be removed, so that the analysis can be done efficiently in real time in house. However, the system should also consider opening its data (anonymized as required) to external researchers. The health system could then benefit from the brain power of thousands of teams that might be able to tackle many problems simultaneously from different angles. For example, in the current COVID-19 epidemic, there have been thousands of highly qualified researchers literally locked at home, willing to help, and eager to analyze clinical data. Health systems might not have the capacity and resources to recruit, incorporate, and coordinate all these groups into their internal structure, but they might benefit from their ideas and skills if they provided them with data and research questions. This could render benefits to the health system, the scientific community, and society as a whole. However, to allow these groups to provide answers quickly, administrative procedures should be simplified as much as possible. For example, if adequately anonymized data sets are created and approved for external research by an ethics committee of the health system, they can be made freely accessible and readily usable to external researchers without having each of them apply and wait for ethics approval.

In the current COVID-19 epidemic, most of the registries mentioned above have tried to implement this model. However, to make the data accessible, they still require the potential researcher to present a project that has to be evaluated by an expert committee before the data can be released. The consequence of this policy is to produce a bottleneck of project approvals that delays necessary research. Paradoxically, the more relevant the data of the registry and the larger the potential research community, the bigger the bottleneck is likely to be (unless more resources are put into place to manage requests). Is not always clear what the purpose of this step is. New ethical approval should not be necessary if the data are correctly anonymized and ethically approved already. Often the argument is to act as a gatekeeper against potential “bad science” practices. However, the gate keeping can be done a posteriori by the scientific community by looking at the outputs of the research, as it is normally done for peer-reviewed publication or preprints. This will not delay the finding of potentially important results. It would certainly be encouraged to avoid publication bias by making all research available even if results are not positive or conclusive, but this can be solved through setting up a registry of protocols (similar to, for example, ClinicalTrials.gov [30]) that does not create a bottleneck neck and delay research.

8. Revise and Update

A health learning system is not a one-off exercise in design. It should be a life system constantly adapting itself to a changing environment [22], especially during epidemics where the situation is expected to change rapidly. There should be a permanent committee made up of clinicians, epidemiologists, health care system experts, medical informatic experts, and statisticians, who will supervise (daily if needed) the functioning of the system and steer the necessary changes. The committee should check, on a long-term basis, if:

- The system is doing what it was designed to do, that is, collect the right data, perform the planned analysis, and answer the questions that were asked);

- The outcomes from the learning system are having an impact on health care decisions and outcomes (ie, assess whether there is a connection between the two systems);
- Any new questions need to be answered as the epidemic evolves. If yes, determine how the learning system should be adapted to address them.

Conclusions

This paper is a reflection on the lack of a strategy involving learning health systems, which is proving to be a critical shortcoming of the current health care systems' ability to fight the pandemic. It is also a proposal of points that need to be considered for implementation and integration, such as learning systems within the health care system. Different countries may need to apply different strategies to organize and implement a system to collect, analyze, and disseminate results and relevant information in a timely fashion. Those strategies will depend on health governance, and, in particular, on how health systems are structured around a unique legal and administrative body.

However, as a scientific community, we need to change the way we think about clinical data and clinical research in epidemics. Clinical data should be valued not only as an information source for the patient who has generated it but also as the main resource for learning about the disease and saving the next patient. Clinical research should not be considered an academic activity to be done once the epidemic is over; it should be viewed as the main way of learning from clinical data and be completed as close as possible in time during clinical practice while the epidemic is ongoing and with the fastest possible feedback between the two activities (care and research).

Perhaps the most compelling evidence that we are doing things wrong is the actual macro figures of the COVID-19 epidemic. As of today, with over 117 million confirmed cases around the world and deaths approximating the 3-million mark, we are still asking many of the clinical questions that we were asking in the beginning. We hope that this piece acts as a wake-up call on this issue.

Conflicts of Interest

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Abbreviations

LEOSS: Lean European Open Survey on SARS-CoV-2 infected patients
NHS: National Health Service
WHO: World Health Organization

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Viewpoint

COVID-19 and Cybersecurity: Finally, an Opportunity to Disrupt?

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Abstract

COVID-19 has challenged cybersecurity to meet the ultimate need of guaranteeing the privacy and security of human beings. Although personal and sensitive health data are needed to better understand, detect, and control the disease, many related cybersecurity challenges and vulnerabilities require further analysis and proper discussion. The aims of this viewpoint are to explore the consequences of COVID-19 on cybersecurity and health care as well as to foster awareness regarding the need for a change in paradigm on how cybersecurity is approached. Education and information technology literacy are important when they are suitably provided; however, they are certainly not a complete solution. Disruption needs to occur at the core of human-device interactions. Building trust, providing novel means to interact with technology (eg, digital humans), and supporting people—the most important cybersecurity asset—are only some of the recommendations for a more human and resilient approach to cybersecurity, during or after the pandemic.

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KEYWORDS

COVID-19; cybersecurity; challenges and disruption; data protection; privacy; health data

Introduction

The COVID-19 pandemic has created many difficult challenges and required many decisions to be made to quickly adapt to the situation on a daily basis. However, COVID-19 has serious consequences related to cybersecurity and the human right to privacy, security, and even physical integrity. Many of these consequences are directly related to the treatment of the disease, such as sharing of personal and sensitive data for research and treatment or contact tracing of patients; meanwhile, other consequences can be indirectly linked with the pandemic but are equally dangerous. These consequences include the continued treatment of other diseases while patients are confined to their homes and the increased vulnerabilities and risks of physical and web-based security when people rely on the internet for most of their daily activities (eg, working from home, homeschooling, shopping on the web, home banking, contact with friends and family, exercising, and entertaining).

Within the literature, it is recommended that data analyses should be performed in accordance with the law and with respect for privacy, which can increase public trust and adherence [1,2]. The need for transparency is even greater when personal and sensitive data are used for contact tracing using smartphone technology. Contact tracing apps are powerful tools that can help limit disease transmission during a pandemic, enforce quarantine rules, notify users of risk zones, or warn infected people [3]. However, contact tracing apps present significant privacy concerns because they collect personal data, such as location, which can also be used to perform a high degree of surveillance and harm individuals' privacy [4]. An adequate balance between anonymity and data quality and integrity, with adequate transparency by certified authorities, is required.

Although many other diseases or conditions may require constant support and treatment, the COVID-19 pandemic has also exacerbated emergencies that may not be promptly addressed, such as chronic, oncological, or mental health conditions [1,5]. Health care professionals must opt for alternative (possibly less secure) means to support their patients, such as teleconsultation, email, and social networks [6].

These cybersecurity issues are just the beginning. In the first part of this viewpoint (COVID-19, Cybersecurity, Privacy, Security, and Safety), the authors identify and discuss cybersecurity challenges and consequences that COVID-19 has brought to the surface that need urgent attention. This part is based on our published work [7]. In the second part (Required Changes in Cybersecurity), recommendations for novel approaches to address the identified issues are advanced to foster a change in the current cybersecurity paradigm. This section comprises the authors' original recommendations and are specific to this viewpoint.

COVID-19, Cybersecurity, Privacy, Security, and Safety

The authors have categorized the identified cybersecurity issues as direct and indirect consequences of COVID-19, as presented in Figure 1.

Figure 1. Direct and indirect consequences of COVID-19 for cybersecurity as identified by the authors.

Direct Consequences of COVID-19

Data Sharing

The most pressing challenges related to contact tracing focus on the balance between sharing and maintaining the privacy of personal data, which is crucial but difficult to achieve [3,4]. Contact tracing apps should not be made available without proper risk assessment and data integrity verification [8]. If data are anonymized, integrity is more difficult to guarantee because anonymized data are more susceptible to undetected interference; thus, these data are not useful and trustable for the proposed health care goal. Data integrity can only be achieved by forfeiting some degree of privacy, ideally to a trusted entity.

The lack of information technology and cybersecurity literacy can also make it more difficult for most individuals to adequately install and use contract tracing apps, while the apps themselves may integrate technical security vulnerabilities and risks [9]. For instance, the most commonly used protocol in tracing apps is Bluetooth, which has known and intrinsic vulnerabilities, such as a lack of boundary control. Bluetooth signals can traverse walls and cars, and individuals who receive the signals may not be actually in contact with an infected person. The balance between frequent false positive or negative results may need adjustment according to the evolution of the pandemic, as it may be safer to obtain more false positives than false negatives, especially if the virus is very contagious [10].

Finally, even if these contact tracing apps gain wide adherence and use, questions arise. What is the effective return or benefit for individual or public health? How can this return or benefit be measured in relation to the loss of privacy? Now is the right time to answer these questions.

Fraud and Theft

There has been a great increase in false messages associated with the COVID-19 pandemic [11]. These messages feed on the spread of misinformation, "fake news," fear, isolation, and lack of awareness to turn the confined population into a vulnerable target for those types of attacks [12] and persuade victims to give away money, personal data, and credentials (eg, phishing, ransomware, false fundraising campaigns) [13]. Further, when people are isolated, they tend to buy more products on the web; therefore, attackers can take advantage of fraudulent product delivery messages. It should be noted that security data breaches performed during this time will not only be exploited now but will have an extremely wide impact in the future, as this exploitation will continue for a long time after the pandemic has subsided.

In drastic times such as the COVID-19 pandemic, other serious issues may arise. International espionage and sabotage can become more common. Recent examples are the lack of proper management of vaccination procedures as well as the reliance on large multinational companies to fairly distribute and sell the vaccines [14,15]. The provision of preventive means and appropriate public policies to detect and avoid these issues is essential to protect people's lives.

Vulnerable Systems

Most health care systems are underbudgeted, use obsolete technology, and are noninteroperable, and they often lack the latest patches and adequate configurations [16,17]. The COVID-19 pandemic has cleared the way for attackers to better exploit these vulnerabilities. The stress placed on these systems is very high; additionally, there is a risk of shortage of equipment due to the high number of hospitalized patients at one time. European Union countries are required to comply with the General Data Protection Regulation (GDPR) to protect personal data. Unfortunately, this is still not common practice, and organizations attempt to address the situation with few or no resources and, most importantly, with no expert knowledge [18].

Indirect Consequences of COVID-19

Managing Other Non–COVID-19–Related Diseases and Emergencies

Although the COVID-19 pandemic is a serious situation worldwide, with the looming threat of collapse of health care systems, it is not possible to put the treatment of other diseases on hold. Patients with chronic, oncological, mental health, obstetrical, and other health care conditions must be treated. Teleconsultation and web-based medical advice are available [19,20], but at what price for patients' privacy? The security systems in most home infrastructures are not prepared to adequately control and protect personal and sensitive data.

Increased Risks to Physical Security and Integrity

One serious consequence of the COVID-19 pandemic is the isolation of a large part of the world's population. Fifty years ago, when information was only communicated through the mail and landline telephone companies, cybersecurity was not an issue. Currently, however, almost all daily activities have become virtual. Still, in an ideal world where all home infrastructures are secured and people take the necessary precautions to protect their data and physical integrity, cybersecurity will still be an issue. This is due to the complex relationships between humans and technology. Some common examples are listed below:

- Risky behaviors may arise, as simultaneously assessing every interaction and message from different contexts, 24 hours per day 7 days per week, can create stress and lead people to make poor and unsafe decisions.
- Different contexts (eg, personal, professional, familiar, educational) can easily lead to confusion and mistakes.
- Different populations are affected differently (eg, older people, minority groups, children, and adolescents). Words such as cyberbullying, fake profiles, impersonation, trolling and *Zoombombing* (disrupting Zoom conferences) may come to mind [21]. Home infrastructures are not prepared from a security standpoint, and adults working from home are burdened and distracted, leaving younger people more vulnerable.
- People are engaging in frequent telephone or video calls, and they may often forget to consider the environment they are in and who may be listening. From balconies and gardens, or even through doors or walls, information can slip out more frequently than we may think. Espionage and theft can and often do occur undetected [22].
- Unlocked sessions or devices and microphones or cameras connected at unwanted times can share more personal information than they should.

Required Changes in Cybersecurity

During the pandemic, the world has been experiencing one wave of COVID-19 after another; still, governments, companies, and the public are all focused on returning to their "normal" prepandemic routines. However, in cybersecurity (as in other areas), "normal" involves low budgets, lack of awareness and education, lack of proper infrastructures, and inability to adapt to different uses by various people and in various contexts. "Normal" also means that privacy and security are still among the greatest challenges in human-computer interactions [23].

Change is crucial, and the COVID-19 pandemic has stressed this even more; however, this change is difficult to achieve. Hence, like a small pebble in a large pond, the authors wish to use this viewpoint to disrupt existing ideas and paradigms and promote other perspectives for discussion in cybersecurity as well as its associated technologies and procedures.

Cybersecurity literacy and education are essential, even more so during pandemic times. One way to achieve these goals is generating scientific research, such as this viewpoint, to raise awareness, provide recommendations, and try new or improved

solutions. However, the current times demand web-based, easy, fast, accurate, and objective but personalized and meaningful information and education that is adapted to the situation and context and to the target population [24]. Due to the unpredictable nature of human behavior and actions, humans are an important element and the main enablers of the level of cybersecurity that each system can and will have [24].

However, education is not sufficient. People have thrived for thousands of years by successfully using tools, and not because they are experts or have complete knowledge about every tool or activity [25]. Why should their relations with technology be much different? Several factors may come into play in human-device relations (eg, security, usability, design, efficiency, demographics, previous interactions); however, even when these factors are addressed, adequate and secure use of technology may still not be possible. There is a pervasive line that permeates all these relations and factors that is known as *trust*. Although this can be a *feared* (subjective) subject in computer science, trust can be established on the web because technology has a social presence to which people respond [26]. However, research fails to capture the reasons why end users choose to trust or distrust systems [27] and what factors contribute to trust [28]. A solid formalization of computational trust, to explain how relationships develop through interactions across a range of web-based contexts, would provide enhanced web-based security [29]. Researchers and developers should be brave enough to consider trust development within technology design by providing features that support end users in evaluating the trustworthiness of the technology, helping to promote proper use of technology, and minimizing the frequency of security incidents [30].

By addressing the previous issue, much more can be understood in terms of personality traits, tendency to trust, and propensity toward manipulation and victimization in human-device relations. This will certainly enable the implementation of more adequate strategies to address one of the most critical unsolved problems in cybersecurity—social engineering.

Further, advancements in trust in human-device relations can open the way to more confident use of innovative solutions such as high-fidelity digital humans [31]. These advancements can work to promote *second life* or augmented reality contexts and to improve privacy, for instance, of children and adolescents, with their many interactions using videoconferencing tools (eg, homeschooling, exercise, music lessons).

Some of the discussed ideas can take longer to study and implement; however, while this is being done, the authors suggest the use of anonymous “digital twins” to easily and quickly test interactions between users and technology. Mockup interfaces complemented with anonymous surveys available on the web can be quickly developed to test the security, privacy, and usability of a technology by a large sample of people with a wide range of experiences, characteristics, and behaviors.

Limitations of this viewpoint are its space constraints and the fact that it is based on an original paper published in conference proceedings. Because of this, a more technical and detailed discussion about the introduced subjects is not possible.

Conclusion

This viewpoint has highlighted the many cybersecurity challenges associated with COVID-19; however, none of the identified challenges are new but have clearly been exacerbated by the pandemic. Therefore, the problems existed before the pandemic, and still no adequate solutions are available. Change and disruption needs to occur at the core of human-device interactions and relations, with a focus on trust and on how humans have thrived with each other over thousands of years, even in threatening situations.

We should take this opportunity to face those challenges before they pile on top of the pandemic toll. In extreme situations, it is normal that exceptions need to be made to prioritize specific parts of society or infrastructures. However, this needs to be accomplished in a transparent and controlled way so that after the exceptional situation subsides, people can easily take back their fundamental right to privacy [32], the loss of which has affected so many lives in the past. We must also claim the right of trust in technology, with more appropriate and improved cybersecurity, for a safer and healthier human population.

Conflicts of Interest

None declared.

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Abbreviations

GDPR: General Data Protection Regulation

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Original Paper

Mobile App–Reported Use of Traditional Medicine for Maintenance of Health in India During the COVID-19 Pandemic: Cross-sectional Questionnaire Study

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Abstract

Background: India follows a pluralistic system for strategic and focused health care delivery in which traditional systems of medicine such as Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy (AYUSH) coexist with contemporary medicine, and this system functions under the Ministry of AYUSH (MoA). The MoA developed a mobile app, called AYUSH Sanjivani, to document the trends of the use of AYUSH-based traditional and holistic measures by the public across India. Analysis of the data generated through this app can help monitor the extent of the use of AYUSH measures for maintenance of health during the COVID-19 pandemic and aid effective health promotion and communication efforts focused on targeted health care delivery during the pandemic.

Objective: The purpose of the study was to determine the extent of use of AYUSH measures by the public in India for maintenance of health during the COVID-19 pandemic as reported through the AYUSH Sanjivani mobile app.

Methods: Cross-sectional analysis of the data generated through the Ayush Sanjivani app from May 4 to July 31, 2020, was performed to study the pattern and extent of the use of AYUSH-based measures by the Indian population. The responses of the respondents in terms of demographic profile, use pattern, and benefits obtained; the association between the use of AYUSH-based measures and symptomatic status; and the association between the duration of use of AYUSH-based measures and the outcome of COVID-19 testing were evaluated based on bivariate and multivariate logistic regression analysis.

Results: Data from 723,459 respondents were used for the analysis, among whom 616,295 (85.2%) reported that they had been using AYUSH measures for maintenance of health during the COVID-19 pandemic. Among these 616,295 users, 553,801 (89.8%)

either strongly or moderately agreed to have benefitted from AYUSH measures. Ayurveda and homeopathic measures and interventions were the most preferred by the respondents across India. Among the 359,785 AYUSH users who described their overall improvement in general health, 144,927 (40.3%) rated it as good, 30,848 (8.6%) as moderate, and 133,046 (40.3%) as slight. Respondents who had been using AYUSH measures for less than 30 days were more likely to be COVID-19–positive among those who were tested (odds ratio 1.52, 95% CI 1.44-1.60). The odds of nonusers of AYUSH measures being symptomatic if they tested positive were greater than those of AYUSH users (odds ratio 4.01, 95% CI 3.61-4.59).

Conclusions: The findings of this cross-sectional analysis assert that a large proportion of the representative population practiced AYUSH measures across different geographic locations of the country during the COVID-19 pandemic and benefitted considerably in terms of general well-being, with a possible impact on their quality of life and specific domains of health.

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KEYWORDS

AYUSH Sanjivani app; COVID-19; traditional medicine; Ayurveda; Siddha; Unani; homeopathy

Introduction

Coronaviruses, a large family of single-stranded RNA viruses, can infect animals and humans, causing respiratory, gastrointestinal, hepatic, and neurologic diseases [1]. To date, 6 human coronaviruses (HCoVs) have been identified, including the alpha coronaviruses HCoVs-NL63 and HCoVs-229E and the beta coronaviruses HCoVs-OC43, HCoVs-HKU1, and severe acute respiratory syndrome coronavirus (SARS-CoV) [2]. New coronaviruses appear to emerge periodically in humans owing to the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of their genomes, and the increase of human-animal interface activities [3]. The first case of COVID-19 in India was reported on January 31, 2020 [4]. The World Health Organization observed that with appropriate integration, traditional medicine would be a significant option to balance curative services with preventive care, which can help address the unique health challenges of the 21st century [5].

Clinical evidence from a study on the effects of Chinese traditional medicine in the treatment of SARS-CoV-2 demonstrated significant results, and the study proposed that herbal medicine has a beneficial effect in the treatment and prevention of epidemic diseases [6]. A Cochrane systematic review in this area reported that herbal medicine combined with western medicine may improve symptoms and quality of life in SARS-CoV patients [7]. The National Health Commission in China has declared the use of herbal medicine combined with contemporary medicine as a treatment for COVID-19 and has issued many guidelines on herbal medicine–related therapy [8]. The acronym AYUSH stands for Ayurveda, yoga and naturopathy, Unani, Siddha, and homeopathy; these indigenous systems of medicine are practiced in India under the Ministry of AYUSH (MoA). Considering the present scenario and penetration of the AYUSH system into the mainstream health care system in India for preventive and curative purposes, the MoA released an advisory to the public for maintenance of general health and well-being during the COVID-19 pandemic on March 6, 2020 [9]. Although India is a country that follows a pluralistic approach to health care, data regarding the use of traditional systems of medicine or health-seeking trends of people are not available in the public domain. There are reports in the press regarding the use of AYUSH prophylactic measures for COVID-19 [10] as well as for lifestyle and other diseases; however, the extent of their use and the outcomes and benefits obtained are not known. Health care delivery, as well as research in times of natural disasters and epidemics or pandemics, is challenging [11]. The concept of infodemiology has evolved significantly with the ever-increasing penetration of the internet in society and is being efficiently being used to nowcast epidemics, quantify the different trends in epidemics, and document and synthesize data on the use of health care services and other public health–related issues [12,13].

The government of India has taken the initiative to use and integrate the preventive, curative, and rehabilitative potential of AYUSH systems of medicine to strengthen the health care delivery system, and the AYUSH Sanjivani app was developed through a consultative process among experts in the field of AYUSH and information technology (IT) by the MoA to record the patterns and trends of the use of preventive measures adopted by the public to enhance immunity and maintain health during the COVID-19 pandemic. The AYUSH Sanjivani app was intended to motivate and persuade users to achieve a status of healthy well-being while thwarting the tendency of the masses to use untested and unproven remedies or over-the-counter or self-prescription measures, especially when faced with the threat of the pandemic and the physical, physiological, social and economic ramifications of the containment measures required of the public.

Through recent initiatives in smart devices, mobile apps have become a convenient, easy-to-use, and less time-consuming method to generate data from the public. Self-reported health status and health care service use are indispensable indicators to assess the performance and attitude of any health system in the absence of recorded health administration data [14]. An app-based survey has advantages such as wider population access, better response rates, lower cost, ease of analysis, ease of use for participants, assurance of user anonymity and preferences, greater flexibility, and faster data synthesis compared to traditional epidemiological and surveillance methods. Various previous research studies in the field of mobile-based health apps and the adoption of information technology have identified individual preferences and motivations to use these apps based on socioeconomic characteristics, demographics, access to health care facilities,

perceptions about the usefulness of the apps, and the effect of existing or perceived disease conditions [15-18].

Hence, a cross-sectional analysis of the data generated from the app was performed to determine use trends of AYUSH measures by the public during the COVID-19 pandemic.

The primary objective of the cross-sectional analysis was to determine the extent of use of AYUSH advocacies and measures by the public for maintenance of health during the COVID-19 pandemic, as reported through the AYUSH Sanjivani mobile app.

Secondary objectives were to compare the self-reported incidence of COVID-19 and symptomatic status of the respondents affected with COVID-19 among the users of AYUSH measures as compared to nonusers and to determine the pattern of use of AYUSH measures by users across India. Perceived change in general well-being in terms of appetite, bowel habits, sleep, stamina, and mental well-being among users of AYUSH measures, the relationship between the duration of the use of AYUSH measures and the incidence of COVID-19, and the relationship between the symptomatic status of COVID-19–positive respondents among users and nonusers of AYUSH-based measures were also included as secondary objectives.

Methods

Study Design

This is a cross-sectional analysis of data generated through the AYUSH Sanjivani mobile app. The MoA launched the AYUSH Sanjivani app to generate data on the acceptance and use of AYUSH advocacies and measures by the population and its possible impact on the maintenance of health during the COVID-19 pandemic. The content of the app is a self-reporting questionnaire intended for the public to report their preferences, patterns, and trends of use of the measures circulated through the AYUSH advisory released by the MoA for maintenance of health during the pandemic. Self-perceived impact on improvement in general health and the benefits of using AYUSH measures during the COVID-19 pandemic by the respondents were also recorded in the app. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines when reporting the findings [19].

Informed Consent and Ethical Consideration

The study was approved by the Central Ethics Committee of Central Council for Research in Ayurvedic Sciences, Ministry of AYUSH, India (1-12/2020-CARICD/Tech/CEC). Upon downloading the app, before voluntary consent was obtained, the user was informed that the information they entered would only be used for research purposes and that their anonymity and confidentiality would be maintained. The users were also informed that by choosing to provide information in this app, they were making a valuable contribution to public health research in the country. It was made explicitly clear that by participating in the survey, users were voluntarily giving their consent to use the data for research purposes.

Study Setting

The app was released through the Google Play store in May 2020 and was available for download across India. The data generated from respondents across all States and Union Territories of India during the period from May 4 to July 31, 2020, were used for the analysis.

Participants

All the residents of India who possessed a smartphone, tablet, or other such device and who were willing to download the app and voluntarily provide the requisite information to the questionnaire in either English or Hindi were eligible to participate in the study. The primary respondents were health seekers of AYUSH or their families, who preferred AYUSH systems for preventive or curative purposes; health seekers who sought consultation at the outpatient department of a national institution, research council, college, hospital, or primary or secondary health care facility across the country; and members of the public who were motivated to use AYUSH measures for maintenance of health during the COVID-19 pandemic. These beneficiaries were sensitized to the AYUSH measures through interaction with health professionals.

Data Sources and Data Collection Methods

The AYUSH Sanjivani app was conceived to motivate and persuade the public to achieve a state of general well-being during the COVID-19 pandemic while documenting the patterns and trends of the use of AYUSH systems in India. The app was also announced and promoted through social media platforms such as the Twitter accounts, Instagram, and Facebook pages of MoA, AYUSH institutions, and hospitals, as well as AYUSH professionals and students, which enabled a wider reach among the general public. The AYUSH Sanjivani app was available for the Android and iOS (Apple) platforms and was made available through the App Store and Google Play store, and the questionnaire was drafted in a simple, easily comprehensible manner, initially launched in English and later rolled out in Hindi according to the World Health Organization guidance for translation and adaptation of instruments [20]. The app started with a COVID-19 guide for users that elaborated the importance of AYUSH for health, the need for self-care, and general and AYUSH measures to practice to improve immunity and maintain health. The Welcome screen of the app is shown in Multimedia Appendix 1.

The app contains three modules to report the desired data (Multimedia Appendix 2). The first module comprises a questionnaire for capturing the trends of use of AYUSH measures among the public across different geolocations. The second module is intended to capture the use trends of AYUSH measures by physicians. The third module aims to garner the cumulative data of health seekers and beneficiaries who were advised to use AYUSH preventive measures by their physicians. This paper focuses on the data collected through the first module of the app, which pertains to use trends of AYUSH preventive measures self-reported by the public. The questionnaire in the app was finalized by collaborative discussions with experts, followed by iterative refining, and included multiple choice questions, modified Likert scales, and yes/no questions. There

were no open-ended questions. The questions were drafted in a simple, easy-to-understand format in English and Hindi so that they were comprehensible to people with basic education and knowledge of how to use smartphones.

The questionnaire was subdivided into three different layers. The first layer captured basic sociodemographic characteristics, such as gender, and the geographical location of the respondents. A question on whether they were using AYUSH measures (advised by the MoA or State governments, or other AYUSH measures) or not using any AYUSH measures was also included to classify the respondents into two categories (users or nonusers of AYUSH measures). Those who responded that they are using or have used AYUSH measures during this pandemic were asked three additional questions. The first question was related to the duration of use of AYUSH measures, and the second question captured the opinions of the respondents on whether the practice of AYUSH measures had benefitted them. The third question was intended to capture the possible reasons for finding AYUSH beneficial, reported as per the respondent's experiences.

The second layer of the app contained another four questions, which could be answered by all respondents irrespective of whether they were using AYUSH measures. The questions were intended to capture the information such as the respondent's occupation, presence or absence of any pre-existing disease, the risk of contracting COVID-19 ("at risk" was categorized as being in quarantine, a health care worker treating COVID-19 patients at hospitals or in communities, a general public official implementing lockdown, or a primary contact of a COVID-19–positive patient). The COVID-19 test status was elicited through a separate question in which the respondent was required to select any of the options of tested positive and asymptomatic, tested positive and symptomatic, tested negative, and never tested. The respondents were required to furnish data related to their COVID-19 status if they underwent testing either on their own or on medical advice.

The third layer of the app was accessible to only those respondents who were using AYUSH measures, and the questions included in it pertained to the use trends of measures advised under various AYUSH systems. This layer contained another set of six questions, namely duration of intake of AYUSH measures, the regularity of intake, self-perceived improvement in parameters of well-being (appetite, bowel habits, sleep, stamina, and mental well-being) or no improvement after use of AYUSH, and the onset of any influenza-like-illness symptoms. The respondent's self-perceived impact on their general health was also captured (see the detailed questionnaire in Multimedia Appendix 3).

Outcome Measures

The primary outcome was to measure the extent of use of AYUSH measures by the respondents who reported they used or did not use AYUSH measures during the COVID-19 pandemic. Further, the patterns and extent of use were assessed as distributions across sociodemographic characteristics such as geographical location, gender, urban or rural location, and occupation.

Secondary outcomes were to compare the incidence of COVID-19 among the respondents who did or did not use AYUSH measures, the pattern of use in terms of duration, regularity, use trends across different AYUSH systems, and the extent of benefits received assessed through a 5-point Likert scale ranging from strongly agree to strongly disagree. The reasons for finding AYUSH prophylactic measures beneficial in terms of responses were categorized as an overall feeling of good health, reducing the severity of symptoms while having COVID-19, or improvement in other minor ailments; these were also evaluated as a secondary outcome. Another secondary outcome was the overall improvement in the general health of the respondents based on the responses ranging from "no change" to "excellent improvement." The change in parameters of well-being categorized as "improved or no change" elicited individually for all the parameters was also a secondary outcome. The association between the symptomatic status of respondents affected by COVID-19 and use or nonuse of AYUSH measures was evaluated. The association between the duration of use of AYUSH measures and incidence of COVID-19 was also evaluated as a secondary outcome.

Bias

The app was promoted across social media platforms and through AYUSH institutions across the country for wider reach among all geographic and socioeconomic strata. However, the data are not representative of the population, as the respondents were restricted to people who are smartphone users and are more active on the web as well as those who already follow the MoA and other AYUSH-related pages on social media platforms. Moreover, the proportion of nonusers was much smaller compared to that of users; hence, the findings may have limited generalizability. The possibility of information bias could also not be completely ruled out, as the information provided in the app was retrospectively obtained, such as frequency of use, regularity of use, type of medicines used with the duration of use, etc.

Study Size

Data from 723,459 respondents collected from May 4 to July 31, 2020, through the AYUSH Sanjivani mobile app was used for this cross-sectional analysis.

Statistical Analysis

The qualitative data received through the app were imported into Excel (Microsoft Corporation), where they were numerically coded. Numerical codes were assigned to all the options for each question in the questionnaire. This coded Excel file was then imported into STATA 16.1 (StataCorp LLC) and used for statistical analysis. Descriptive statistics for categorical data were reported using frequencies and percentages. Comparisons among users and nonusers of AYUSH measures were performed using the chi-square test in terms of respondents being tested or not for COVID-19, the outcome of COVID-19 testing, the symptomatic status of the COVID-19–positive respondents, the risk status of the respondents, and the presence or absence of comorbid conditions. Logistic regression analysis was performed to compute the crude odds ratio by measuring the association between the duration of use of AYUSH-based

measures and the outcome of COVID-19 testing (positive or negative). The association between the use of AYUSH-based measures and the symptomatic or asymptomatic status of COVID-19–positive respondents was also evaluated. Adjusted odds ratios considering the risk status and presence of comorbidities as confounders were also computed. A *P* value of <.05 was considered significant.

Results

Sociodemographic Profile of the Respondents

Data from 723,459 participants who downloaded the app and furnished the required information were available for analysis. The majority of the respondents (616,295/723,459, 85.2%) reported having been using AYUSH measures for maintenance of health during the pandemic. Among the 616,295 respondents who were AYUSH users, 493,766 (80.1%) were male, and 467,047 (75.8%) lived in rural areas. Data for occupation was available for 359,745 users, of which the majority were self-employed (123,274, 34.3%); 83,281 (23.2%) were students, and 67,230 (18.7%) were unemployed (Table 1).

Table 1. Demographic and basic characteristics of the respondents.

Characteristics	n (%)
Used AYUSH[a] measures during the COVID-19 pandemic (N=723,459)[b]	
Yes	616,295 (85.2)
No	107,164 (14.8)
Gender (n=616,295)[c]	
Male	493,766 (80.1)
Female	122,188 (19.8)
Did not wish to disclose	341 (0.1)
Location (n=616,295)[c]	
Urban	148,888 (24.2)
Rural	467,407 (75.8)
Occupation (n=359,745)[d]	
Student	83,281 (23.2)
Regular or salaried worker	33,989 (9.4)
Casual worker	30,092 (8.4)
Self-employed	123,274 (34.3)
Unemployed	67,230 (18.7)
Any other	21,879 (6.1)

[a]AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy.

[b]Distribution of total respondents.

[c]Distribution of respondents who were users of AYUSH-based measures.

[d]Distribution of users who responded to this question.

Among the 616,295 AYUSH users, the maximum participants were from Uttar Pradesh (158,053, 25.6%), followed by Maharashtra (86,328, 14.01%); Madhya Pradesh (57,894, 9.39%); Gujarat (46,815, 7.59%); and Chhattisgarh (44,461, 7.21%). A small proportion of the respondents were from the states of Rajasthan, Odisha, Haryana, Bihar, Karnataka, and West Bengal. The smallest number of respondents were from the states of Meghalaya and Manipur and the union territories of Ladakh and Lakshadweep (Multimedia Appendix 4).

Use Trends Among Different Streams During the COVID-19 Pandemic

The number of respondents who reported using Ayurveda measures was 90,357/433,560 (21.0%), Homeopathy was used by 47,639/433,560 (11.0%), while a small proportion reported the use of Unani and Siddha Interventions. It is intriguing to note that 291,251/433,560 (67.0%) of the users reported having been using yoga, pranayama, meditation, or the use of home remedies such as spices in cooking, drinking warm water, steam inhalation, and other such practices for maintenance of health (Multimedia Appendix 5).

The use of warm water in routine life for drinking purposes was reported as the most commonly adopted measure, followed by the practice of yoga or pranayama as a choice for the maintenance of health and well-being. Among homeopathy medicines, Arsenicum Album 30C was the intervention of choice, while *Samshamani Vati* and AYUSH-64 were the most

popular among the Ayurveda interventions. *Kaba Sura Kudineer*, a decoction used in the Siddha system, and the Unani interventions of *Behidana*, *Unnab*, and *Sapistan* decoction were reported as the most commonly used, albeit by only a small proportion of users. *Agastya Hareetaki* (an Ayurvedic intervention); use of *Anu Taila*, coconut oil, or sesame oil for nasal instillation, or oil pulling with coconut or sesame oil; use of *Chyavanprasha*; turmeric milk; and herbal tea were the other frequently used interventions in the Ayurveda stream. *Bryonia alba*, *Rhus toxicodendron*, *Belladonna*, *Gelsemium*, and *Eupatorium perfoliatum* were the other commonly used homeopathic interventions. *Nilavembu Kudineer* decoction and *Adathodai Manapagu* were some other popular Siddha interventions (Multimedia Appendix 6).

Benefits Obtained by the Public Through the Use of AYUSH Measures

Among the 616,295 respondents who used AYUSH measures, 231,552 (37.5%) reported using them for more than 30 days, while 231,735 (37.6%) reported having used them for less than 15 days. A considerable proportion of respondents either strongly agreed (420,395/616,295, 68.2%) or moderately agreed (133,406/616,295, 21.6%) that the use of AYUSH measures had benefitted them. AYUSH measures were considered beneficial by 487466/616,295 (79.1%) of the respondents, as these measures gave them an overall feeling of good health. Most of the respondents (227,952/616,295, 63.6%) reported improvement in parameters of well-being in terms of their perception of change in appetite, bowel movements, sleep, stamina, and mental well-being. Improvement in appetite was reported by 20,618/359,785 respondents (5.7%), while improvement in bowel habits was reported by 42,017/359,785 respondents (11.7%). Moreover, improvement in more than one parameter was reported by 98,352/359,785 respondents (27.3%). Overall improvement in general health was rated as excellent by 30,848 of 359,785 respondents (8.6%), while 144,927 (40.3%) reported good improvement and 133,046 (36.9%) reported slight improvement (Table 2).

Table 2. Trends of use and benefits obtained by respondents who were users of AYUSH measures (n=616,295).

Characteristic	Value, n (%)
Duration of use of AYUSH[a] measures	
Less than 15 days	231,735 (37.6)
15-30 days	153,008 (24.8)
More than 30 days	231,552 (37.6)
Opinion on whether the AYUSH prophylactic measures have benefitted them during the COVID-19 pandemic (n=616,295)	
Strongly agree	420,395 (68.2)
Moderately agree	133,406 (21.6)
Moderately disagree	11,309 (1.8)
Strongly disagree	17,496 (2.8)
Neutral/can't say	33,689 (5.5)
Reason for finding AYUSH prophylactic measures beneficial (n=616,295)	
Overall feeling of good health	487,466 (79.1)
Helped prevent COVID-19 (respondent's perception)	50,721 (8.2)
Reduced symptoms while having COVID-19	31,057 (5.0)
Helped improve minor ailment other than COVID-19	47,051 (7.6)
Improved parameters of well-being (n=359,785)	
Appetite	20,618 (5.7)
Bowel movements	42,017 (11.7)
Sleep	13,559 (3.8)
Stamina	26,397 (7.3)
Mental well-being	27,009 (7.5)
Improvement in more than one of the above parameters	98,352 (27.3)
No change	131,833 (36.6)
Overall improvement in general health (n=359,785)	
Excellent improvement	30,848 (8.6)
Good improvement	144,927 (40.23)
Slight improvement	133,046 (36.9)
No change	18,240 (5.1)
Unknown	32,724 (9.01)

[a]AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy.

Data on Pre-existing Diseases, Symptoms, and Risk Status Among the Respondents

Data on pre-existing diseases (comorbidities) were furnished by 408,089 respondents, of whom 380,731 (93.3%) reported the absence of any pre-existing disease. Hypertension was the most common pre-existing disease (comorbidity), reported by 11,941/408,089 respondents (2.9%), followed by diabetes mellitus, heart disease, and asthma. The presence of more than one pre-existing disease was reported by 9266/408,089 respondents (2.3%) (Table 3).

Table 3. Comparison of COVID-19 test status, incidence, and symptomatic status among users and nonusers of AYUSH measures. Percentages are calculated based on the total for each column.

Characteristics	Total, n (%)	Respondents who were users of AYUSH[a] measures, n (%)	Respondents who were nonusers of AYUSH measures, n (%)	*P* value[b]
COVID-19 test status (n=408,089)				.67
Tested	27,661 (6.8)	24,368 (6.8)	3293 (6.8)	
Not tested	380,428 (93.2)	335,469 (93.2)	44,959 (93.2)	
Total	408,089 (100)	359,837 (100)	48,252 (100)	
COVID-19 test result (n=27,661)				<.001
Positive	13,320 (48.2)	12,002 (49.3)	1318 (40.0)	
Negative	14,341 (51.8)	12,366 (50.7)	1975 (60.0)	
Total	27,661 (100)	24,368 (100)	3293 (100)	
Symptomatic status of COVID-19 positive respondents (n=13,320)				<.001
Asymptomatic	8545 (64.2)	8100 (67.6)	445 (33.8)	
Symptomatic	4775 (35.8)	3902 (32.5)	873 (66.2)	
Total	13,320 (100)	12,002 (100)	1318 (100)	
Risk category (n=408,089)				<.001
In risk category	19,757 (4.8)	16,583 (4.6)	3174 (6.6)	
Not in risk category	388,332 (95.2)	343,254 (95.4)	45,078 (93.4)	
Total	408,089 (100)	359,837 (100)	48,252 (100)	
Comorbid conditions (n=408,089)				<.001
Hypertension	11,941 (2.9)	10,638 (3.0)	1303 (2.7)	
Asthma	1089 (0.3)	413 (0.1)	676 (1.4)	
Diabetes mellitus	2772 (0.7)	2284 (0.6)	488 (1.0)	
Heart disease	1230 (0.3)	992 (0.3)	238 (0.5)	
Kidney disease	671 (0.2)	490 (0.1)	181 (0.4)	
Cancer	389 (0.1)	234 (0.1)	155 (0.3)	
Presence of multiple comorbid conditions	9266 (2.3)	8033 (2.2)	1233 (2.5)	
None	380,731 (93.3)	336,753 (93.6)	43,978 (91.2)	

[a]AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy.

[b]Compared using chi-square tests.

COVID-19 Status Among Respondents

Among 408,089 participants, only 27,661 (6.8%) underwent testing for COVID-19. Out of the 27,661 respondents who underwent testing, 13,320 (48.2%) tested positive for COVID-19, among whom 8545 (64.2%) reported themselves to be asymptomatic.

Duration of Use of AYUSH and Symptom Status of COVID-19–Positive Respondents

Among the 12,002 respondents who tested positive for COVID-19 and used AYUSH measures, 8101 (67.5%) reported their duration of use of AYUSH measures as less than 30 days, and the others reported a longer duration of use. Among the 12,002 COVID-19–positive respondents using AYUSH measures, 8100 (67.5%) were asymptomatic.

Association Between Duration of Use of AYUSH Measures and Incidence of COVID-19

The results of the logistic regression analysis depict that the odds ratio (OR) of testing positive for COVID-19 is 1.52 (95% CI 1.44-1.60, *P*<.001) for respondents who were using AYUSH measures for less than 30 days compared to those who were using these measures for more than 30 days. The adjusted OR considering the effects of confounders, namely the presence of comorbidities and the respondent being in a risk category, is 0.90 (95% CI 0.85-0.95, *P*<.001) (Table 4).

Table 4. Logistic regression analysis to identify the association between the duration of use of AYUSH-based measures and the outcome of COVID-19 testing.

Variable	COVID-19–positive (n=12,002)	COVID-19–negative (n=12,366)
Duration of use of AYUSH[a]-based measures[b,c]		
More than 30 days	3901 (32.5)	5221 (42.2)
Less than 30 days	8101 (67.5)	7145 (57.8)
Comorbidities		
Absent	5679 (47.3)	10131 (81.9)
Present	6323 (52.7)	2235 (18.1)
Risk category		
Not in a risk category	4866 (40.5)	10203 (82.5)
In a risk category	7136 (59.5)	2163 (17.5)

[a]AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy.

[b]Crude odds ratio (95% CI) 1.52 (1.44-1.60). The crude odds ratio was computed through univariate logistic regression analysis by taking the outcome of the COVID-19 test (positive or negative) as the dependent variable and the duration of use of AYUSH measures as the independent variable.

[c]Adjusted odds ratio (95% CI) 0.90 (0.85-0.95). The adjusted odds ratio was computed through multivariate analysis adjusted for the presence of comorbidities and risk category as confounders.

Association Between the Use of AYUSH Measures and Symptomatic Status of COVID-19 Respondents

The results of the logistic regression analysis revealed that the OR of being symptomatic was 4.01 (95% CI 3.61-4.59) for nonusers of AYUSH measures compared to users. The adjusted OR considering the effects of confounders, namely the presence of comorbidities and respondents being in a risk category, is 3.48 (95% CI 3.06-3.95) (Table 5).

Table 5. Logistic regression analysis to identify the association between use of AYUSH-based measures and symptomatic status of respondents who tested positive for COVID-19.

Variable	Symptomatic COVID-19–positive participants (n=4775)	Asymptomatic COVID-19–positive participants (n=8545)
Used AYUSH[a]-based measures[b,c]		
Yes	3902 (81.7)	8100 (94.8)
No	873 (18.3)	445 (5.2)
Comorbidities		
Absent	1576 (33.0)	4499 (52.6)
Present	3199 (67.0)	4046 (47.4)
Risk category		
Not in a risk category	785 (16.7)	4345 (50.8)
In a risk category	3900 (83.3)	4200 (49.2)

[a]AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, Sowa Rigpa, and homoeopathy.

[b] Crude odds ratio (95% CI) 4.01 (3.61-4.59). The crude odds ratio was computed through univariate logistic regression analysis by taking the symptomatic status of COVID-19–positive respondents as the dependent variable and use of AYUSH-based measures as an independent variable without adjusting for confounders.

[c]Adjusted odds ratio (95% CI) 3.48 (3.06-3.95). The adjusted odds ratio was computed through multivariate analysis adjusted for the presence of comorbidities and risk category as confounders.

Discussion

Principal Findings

A representative population of 723,459 people from different geolocations across the country downloaded the AYUSH Sanjivani app and reported the perceptions and practices they had adopted in the wake of the COVID-19 pandemic that significantly altered their lifestyle. A majority of the respondents used AYUSH measures for maintenance of health and prevention of disease, and most of them reported having benefitted from the use of various interventions and practices. A positive association between the prolonged practice of AYUSH measures and symptomatic status could be observed in the respondents who were infected with COVID-19.

In this study, the maximum representation was of AYUSH users, and it is expected that the willingness to use an app specifically

targeting AYUSH users will be greater among health seekers who are familiar with these systems of medicine. Findings from a previous study revealed that even in a developing country such as India, 32% of the patients attending a medical care facility in urban settings used the internet, and 75% of them sought medical information through the internet; this would support the substantial amount of data generated through this app [21]. In a national representative cross-sectional survey conducted in 2014 in India, it was observed that 6.9% of all patients sought AYUSH services for different ailments in a recall period of 2 weeks, without a great differential between urban and rural regions [22]. This targets the reported use of AYUSH care services for disease management, which is expected to be lower compared to the use of the AYUSH system for preventive care.

Maximum reporting was observed from the states of Uttar Pradesh, Maharashtra, and Madhya Pradesh, which can be attributed to the high population density in these states. The decision to seek health care is not only contingent upon the experience of illness but also depends on various social, economic, and demographic factors [22]; it was observed that approximately three quarters of the total respondents were from rural areas, and most of them were users of AYUSH measures. This can be attributed to the tendency of people in rural areas to adhere more to tradition compared to the urban population. This is consistent with a study based on the World Health Organization Study on Global Ageing and Adult Health (WHO-SAGE) survey, which suggests that individuals living in rural areas are more likely to report the use of traditional healers [23]. In this study, it was observed that in the setting of India, being female was associated with a lower likelihood of users downloading mobile apps and furnishing their personal information and preferences, despite evidence from recent studies that does not suggest differential internet use between males and females [17]. Students and self-employed workers accounted for the majority of respondents as well as of users of AYUSH measures, which underlines the findings of earlier studies that predict that the younger population, literate people, and full-time workers are more likely to use health apps and be motivated to use health-related advice [24].

The majority of respondents reported having benefitted from using AYUSH measures; they rated the degree of improvement as mild, good, or excellent, and attributed this improvement to their perceived experience of overall well-being. The self-reported public experience of improvement in parameters of well-being, such as sleep, appetite, stamina, mental well-being, and sleep, is a good indicator for integrating AYUSH measures for well-being into the daily routine. Preliminary evidence on the impact of COVID-19 on the public reveals significant health-related anxiety, generalized anxiety, psychological stress, and sleep disorders, and government-implemented lockdowns inculcated many habits, such as decreased physical activity and exercise and increased snacking, with deleterious effects on vulnerable populations and especially on those with pre-existing comorbidities [25,26].

The improvements perceived in the level of well-being and the general aspects of health measured in terms of individual satisfaction with appetite, sleep, stamina, mental wellness, and bowel habits indicate a positive role for the use of traditional AYUSH interventions and practices in maintaining holistic health and preventing long-lasting adverse health outcomes.

Ayurveda and homeopathy were the systems of medicine that were preferred by the majority of the respondents; this can be attributed to the maximum number of hospitals and health care providers in India under these two AYUSH systems. Arsenicum Album 30C, *Samshamani Vati*, and Ayush-64, which were deployed as frontline prophylactic interventions, were the most used interventions by the public to maintain health. Arsenicum Album 30C is a homeopathic intervention that is used for respiratory ailments; meanwhile, the other two interventions are Ayurvedic formulations (*Samshamani Vati* and Ayush-64), which are prescribed for the clinical management of pyrexia, influenza-like illness, cough, and dyspnea [27].

The practices that the public engaged in include the practice of yoga, pranayama, and meditation along with common home remedies such as using spices in cooking, drinking turmeric milk, drinking warm water, and steam inhalation. The practice of engaging the mind and body through meditation, pranayama, and yoga has attracted significant attention and has been extensively studied for its possible beneficial effects on physical and mental health outcomes [28]. A growing body of evidence suggests that the elements of physical postures, breathing, and meditation can improve physical well-being, including balance, range of motion, blood pressure, pain, fatigue, and general health, which could be correlated with the benefits reported by the AYUSH users [29].

The proportion of participants who underwent laboratory testing for COVID-19 among AYUSH users and nonusers could not be compared to arrive at meaningful outcomes, as the majority of the respondents were using AYUSH measures, and those not using it were few in number. A longer duration of use of AYUSH measures is more likely to produce better protection when compared with use for less than 15 days, as it was observed that the likelihood of being COVID-19–positive was lower in respondents who were using the AYUSH measures for more than 30 days. In AYUSH systems, the use of diet or medicine is targeted at producing an ideal state of homeostasis, which would reflect the inherent strength of the body in immunopotentiation and prevention of diseases. Clinical studies demonstrating *Rasayana* activity (medicines or practices with rejuvenating potential) in healthy individuals reflect better outcomes when administered for 60 days or more, which implies that compliance with AYUSH measures would ideally require a longer duration to act in the macrochannels and microchannels of circulation to bring about optimal health; this underlines the pattern seen in this analysis, where the odds of being COVID-19–positive or symptomatic for respondents who tested positive are greater in respondents who have used the preventive measures for a lesser duration [30]. Moreover, a good proportion of the respondents who used AYUSH measures used home remedies, yoga, pranayama, meditation, and other practices without resorting to the use of any AYUSH medications with specific prophylactic potential.

The qualitative appraisal of the analyzed data reflects that a considerable majority of the respondents benefitted from the

use of AYUSH measures, which were either traditional formulations with centuries of use in the maintenance of health or home remedies and are an integral part of Indian culture and cuisine. Due to the long history of use of many herbal remedies and the experiences that have passed from generation to generation, people are relying on herbal remedies and some simple home remedies for common diseases that are used across India irrespective of sociocultural, religious, and geographical differences [31]. The use of AYUSH measures is likely to evoke a positive response to the psychological and physical well-being of the respondents [32].

Limitations and Strengths of the Study

Because this is a cross-sectional analysis of the data generated from a mobile app, the documented data are a representation of smartphone users only. A limitation of the study is the inability to capture generalizable data reflecting true health-seeking trends, as only people with access to smartphones and good internet connectivity responded to the questionnaire. Because the representation of nonusers of AYUSH measures was minimal, statistical comparison among users and nonusers of AYUSH measures could not be performed. Although AYUSH measures are generally practiced in many states for both curative as well as preventive aspects, representation from some of these states was meager; hence, a true representation of users or nonusers of AYUSH measures could not be captured. The incidence of COVID-19 among the respondents was self-reported, and it is difficult to determine the relationship between the use of AYUSH measures, duration of use, and incidence of disease or symptomatic status among the general public.

Finally, this is the first study to document how time-tested indigenous systems of medicine are being used by the public during a pandemic of unprecedented spread, morbidity, and mortality. The large amount of data obtained is the greatest benefit of this analysis, as it would sweep outliers that may misrepresent the data and has enabled us to provide a realistic picture of the characteristic attributes and patterns of the population. This analysis offers a starting point for future researchers to initiate more interventional studies based on the use trends demonstrated in this study.

Conclusion

The findings of the cross-sectional analysis assert that a good proportion of the representative population has practiced AYUSH advocacy across different geolocations of the country during the COVID-19 pandemic. Although anecdotally, people report that traditional systems of holistic healing are good for the maintenance of health and well-being, our study findings also support that use of AYUSH measures provided better health, improved parameters of well-being, and even helped prevent other illnesses. This pattern suggests possibilities of exploring the role of AYUSH care, considering its acceptance, accessibility, and possible benefits, in the area of pluralistic health care.

To improve the use of a pluralistic health care delivery system, it is imperative to understand the acceptability, use trends, and possible impact on the quality of life and specific domains of health among the public. The response obtained in this study points to a possible functional integration and cross-hybridization of the merits of different systems to effectively generate a positive outcome on integrated health care delivery targeting universal health coverage. To assess the multiple levels of impact of AYUSH preventive measures on health, future studies need to apply diverse disciplines and methods, including intervention studies, longitudinal cohort studies, as well as qualitative observations to examine the nature of the benefits offered by these measures.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Welcome screen of the app.
[PDF File (Adobe PDF File), 208 KB - xmed_v2i2e25703_app1.pdf]

Multimedia Appendix 2

Modules and layers of the app.
[PDF File (Adobe PDF File), 289 KB - xmed_v2i2e25703_app2.pdf]

Multimedia Appendix 3
Detailed questionnaire.
[PDF File (Adobe PDF File), 440 KB - xmed_v2i2e25703_app3.pdf]

Multimedia Appendix 4
Statewise distribution of the respondents.
[PDF File (Adobe PDF File), 177 KB - xmed_v2i2e25703_app4.pdf]

Multimedia Appendix 5
Distribution of respondents as per their choice of AYUSH streams for prevention.
[PDF File (Adobe PDF File), 41 KB - xmed_v2i2e25703_app5.pdf]

Multimedia Appendix 6
Distribution of the respondents as per the choice of AYUSH interventions and the duration of use.
[PDF File (Adobe PDF File), 193 KB - xmed_v2i2e25703_app6.pdf]

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Abbreviations

AYUSH: Ayurveda, yoga and naturopathy, Unani, Siddha, and homeopathy
HCoV: human coronavirus
IT: information technology
MoA: Ministry of AYUSH
SARS-CoV: severe acute respiratory syndrome coronavirus
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WHO-SAGE: World Health Organization Study on Global Ageing and Adult Health

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