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Contents

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.

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.
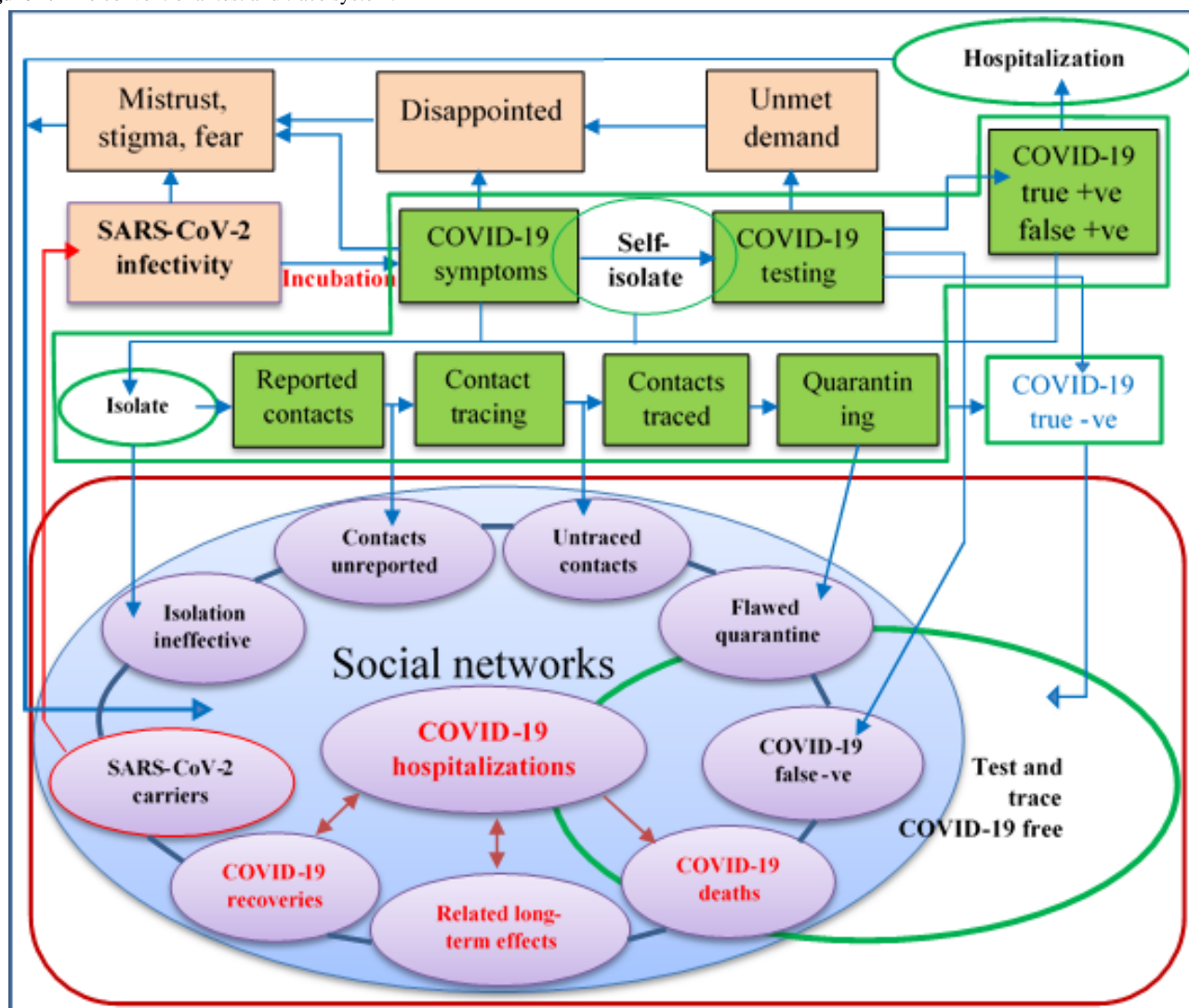
The "Infectivity Problem" of COVID-19

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.
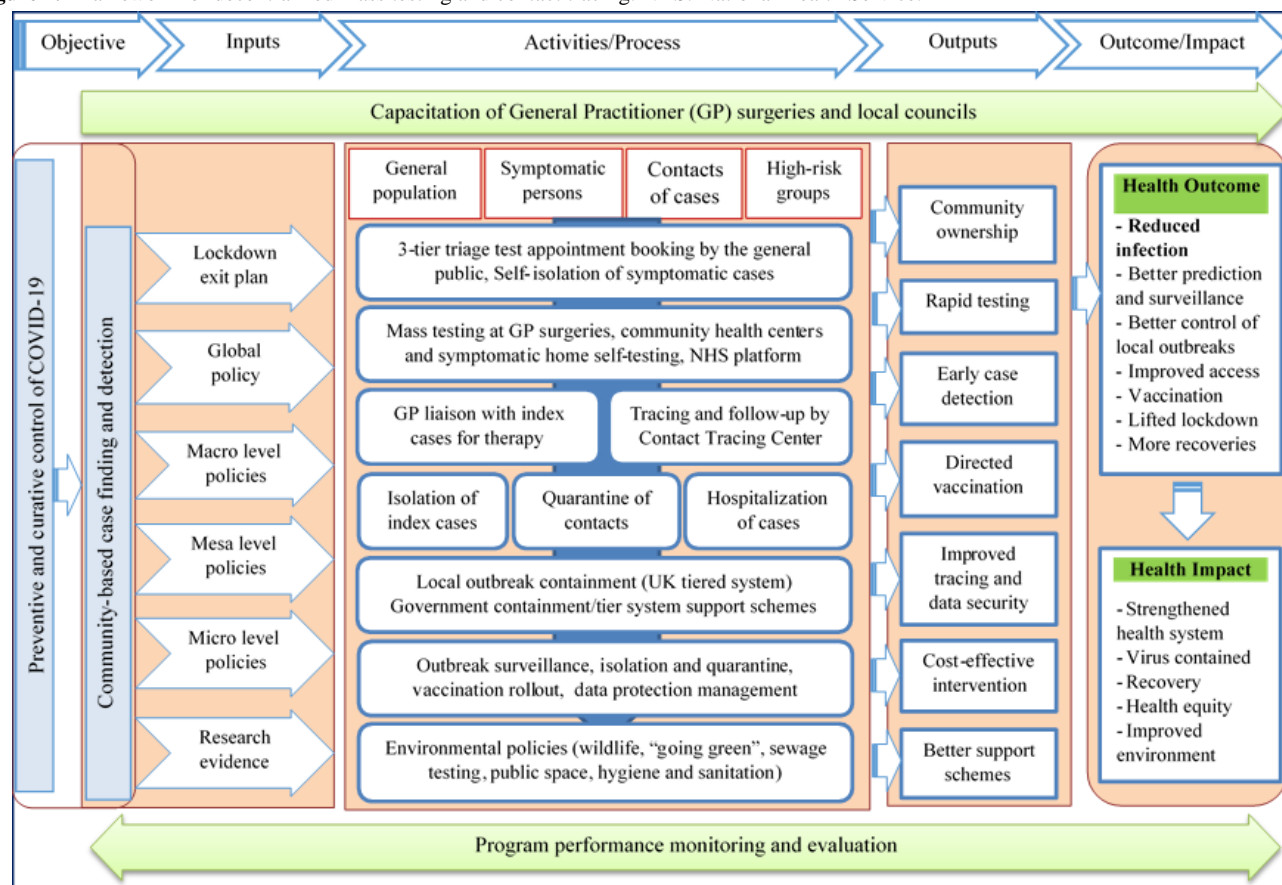
Results

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].

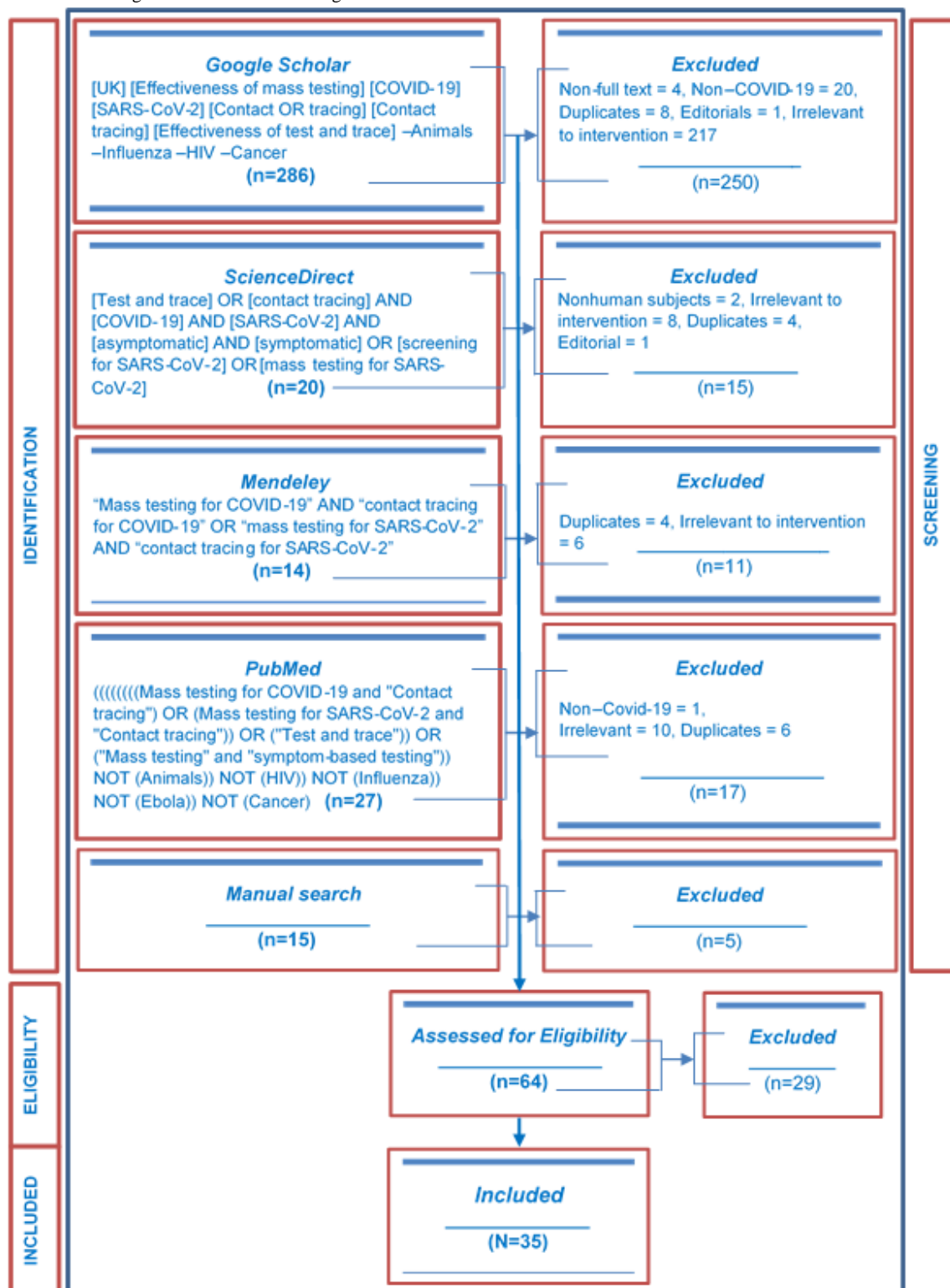**Figure 3.** Flowchart showing article counts at each stage as well as the number of included articles.

IDENTIFICATION

Google Scholar
[UK] [Effectiveness of mass testing] [COVID-19] [SARS-CoV-2] [Contact OR tracing] [Contact tracing] [Effectiveness of test and trace] –Animals –Influenza –HIV –Cancer
(n=286)

Excluded
Non-full text = 4, Non–COVID-19 = 20, Duplicates = 8, Editorials = 1, Irrelevant to intervention = 217
(n=250)

ScienceDirect
[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] **(n=20)**

Excluded
Nonhuman subjects = 2, Irrelevant to intervention = 8, Duplicates = 4, Editorial = 1
(n=15)

Mendeley
"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"
(n=14)

Excluded
Duplicates = 4, Irrelevant to intervention = 6
(n=11)

PubMed
(((((((((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) **(n=27)**

Excluded
Non–Covid-19 = 1, Irrelevant = 10, Duplicates = 6
(n=17)

Manual search
(n=15)

Excluded
(n=5)

SCREENING

ELIGIBILITY

Assessed for Eligibility
(n=64)

Excluded
(n=29)

INCLUDED

Included
(N=35)

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.
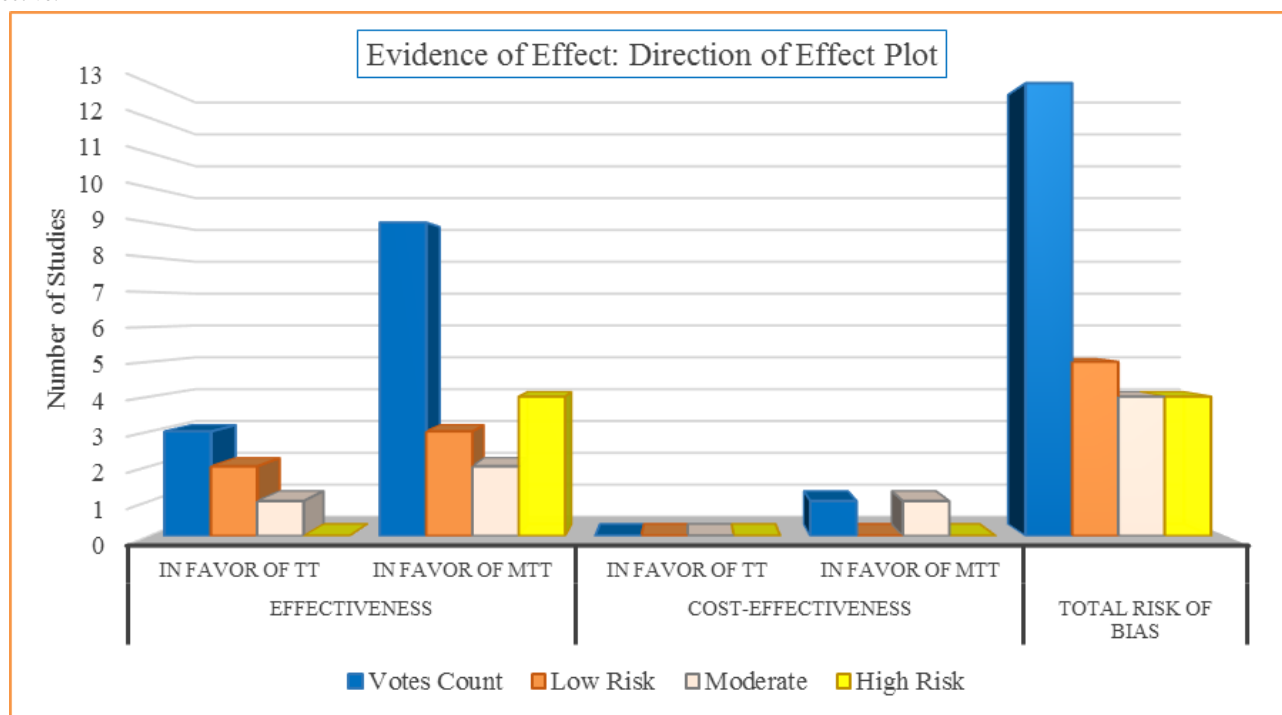
The results of 6 studies [44,47,52-54,56] were judged to be at low to moderate risk of bias. These studies were prioritized in concluding that the mass testing and contact tracing strategy was more effective in the suppression of community transmission of SARS-CoV-2 and the control of COVID-19 than conventional 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	Indirect-ness	Impreci-sion	Publication bias	TT[c], n	MTT[d], n	Direc-tion[e]	
Effectiveness										
Model	11	Serious	Serious	Serious	Serious	Unlikely	3	8	↑	Very low
Cross-section-al 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.
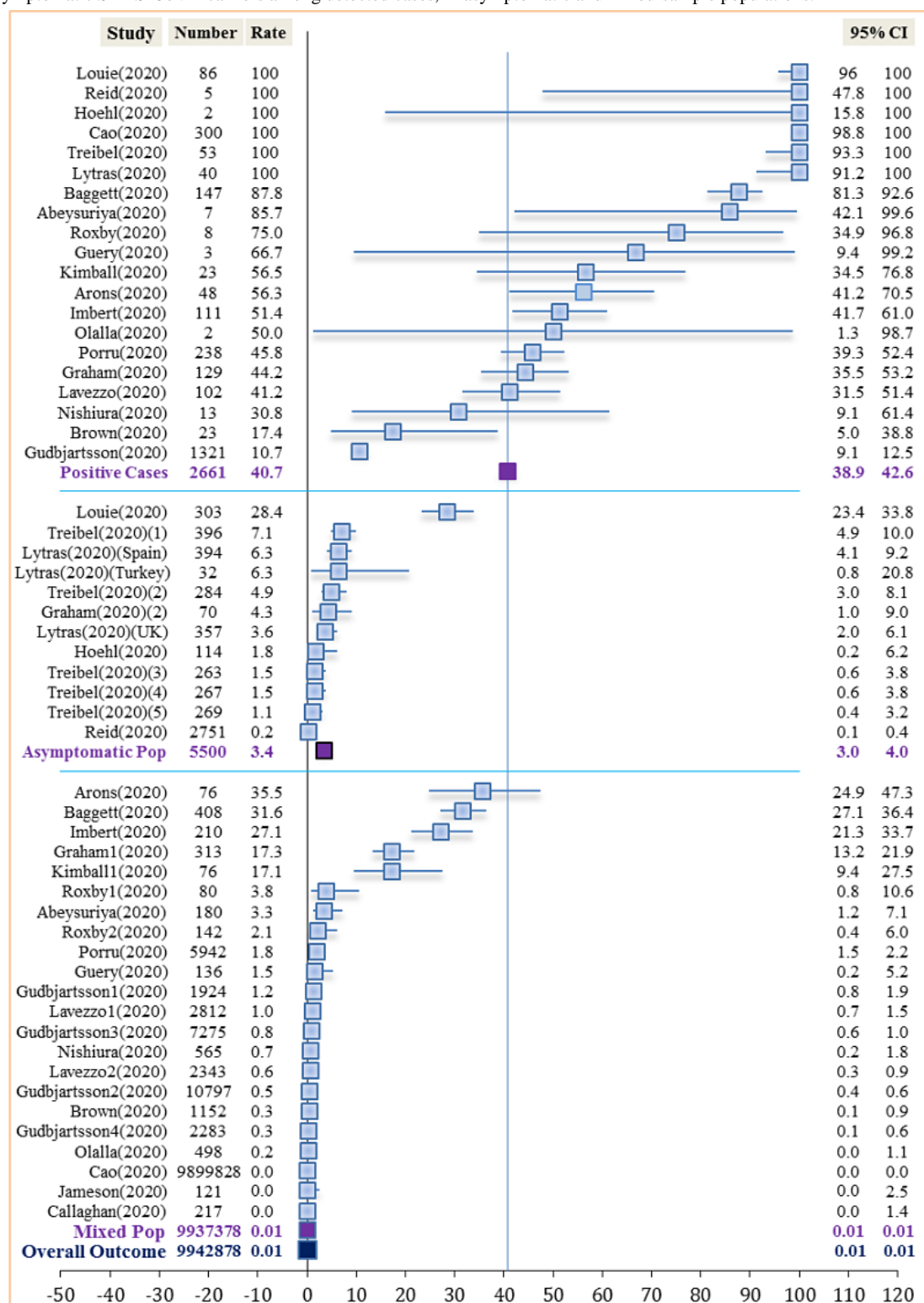
Outcome Among Stratified Positive Cases

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.
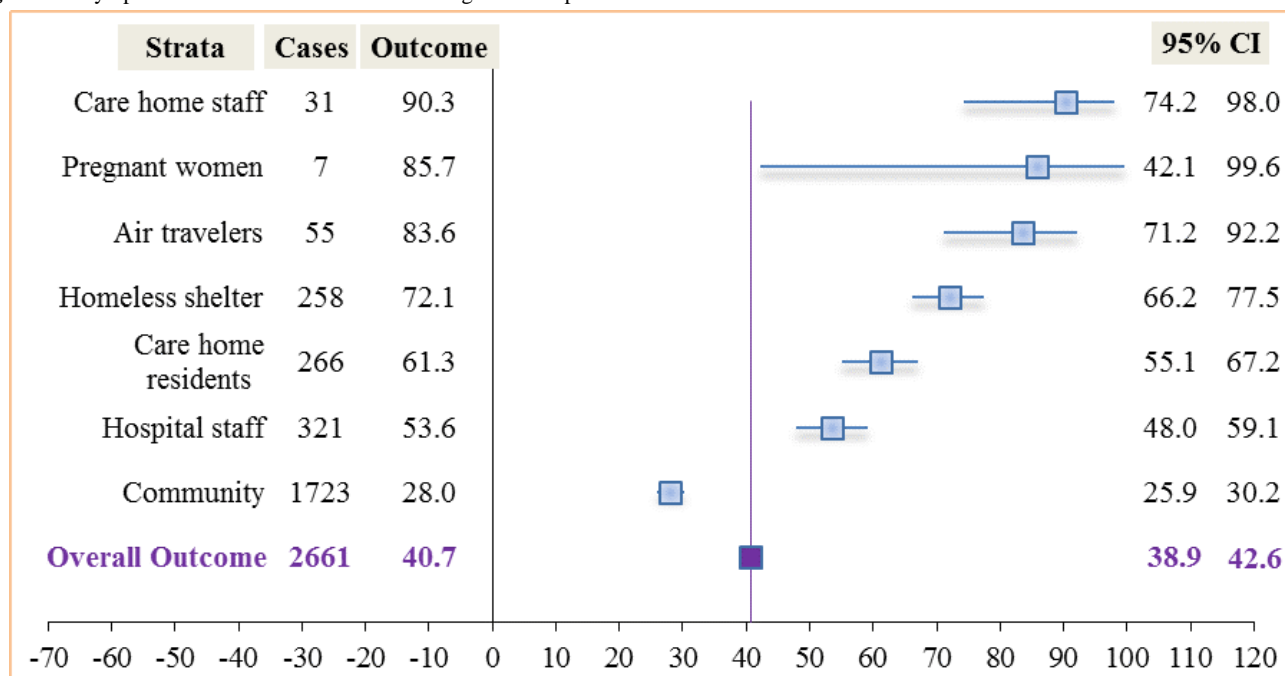
Outcome Among Stratified Sample Populations

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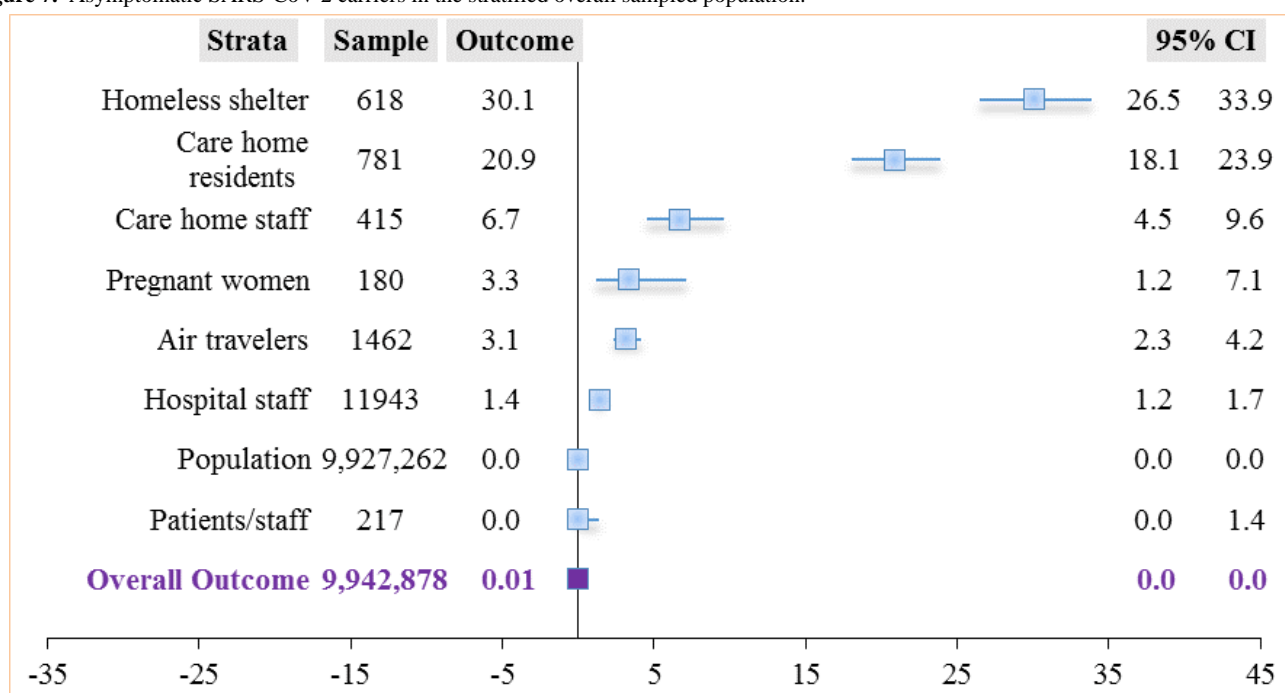
The prevalence among asymptomatic populations from 6 studies [59,62,66,68,74,75] was 3.4% (189/5500, 95% CI 3%-4%). The prevalence in a mixed population from 17 studies [57,58,60-65,67,69-73,76-78] averaged 0.009% (895/9,937,378, 95% CI 0.0%-0.0%) (Figure 5).

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.
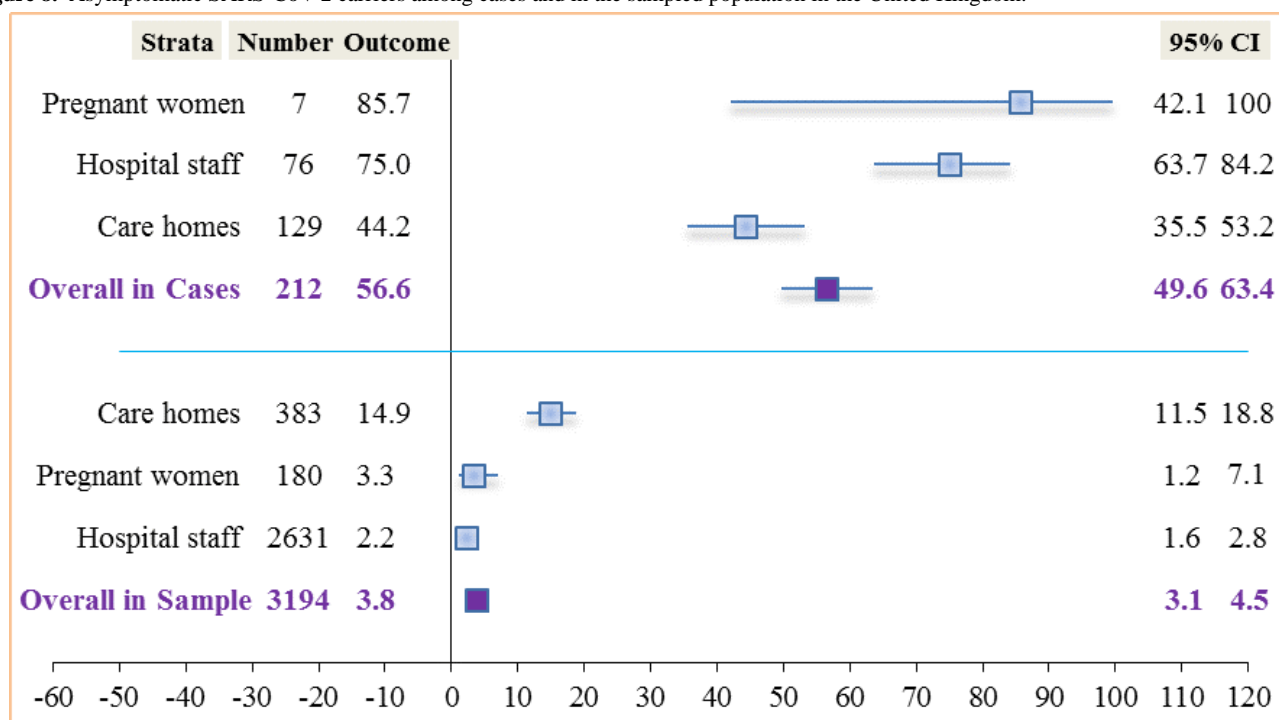
The overall prevalence of asymptomatic cases within the United Kingdom was found to be 3.8% (120/3194; 95% CI 3.1%-4.5%) with rates ranging from 2.2% (57/2631; 95% CI 1.6%-2.8%) among hospital staff to 14.9% (57/383; 95% CI 11.5%-18.8%) in care homes. Figure 8 demonstrates a higher overall rate among 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

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.

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.

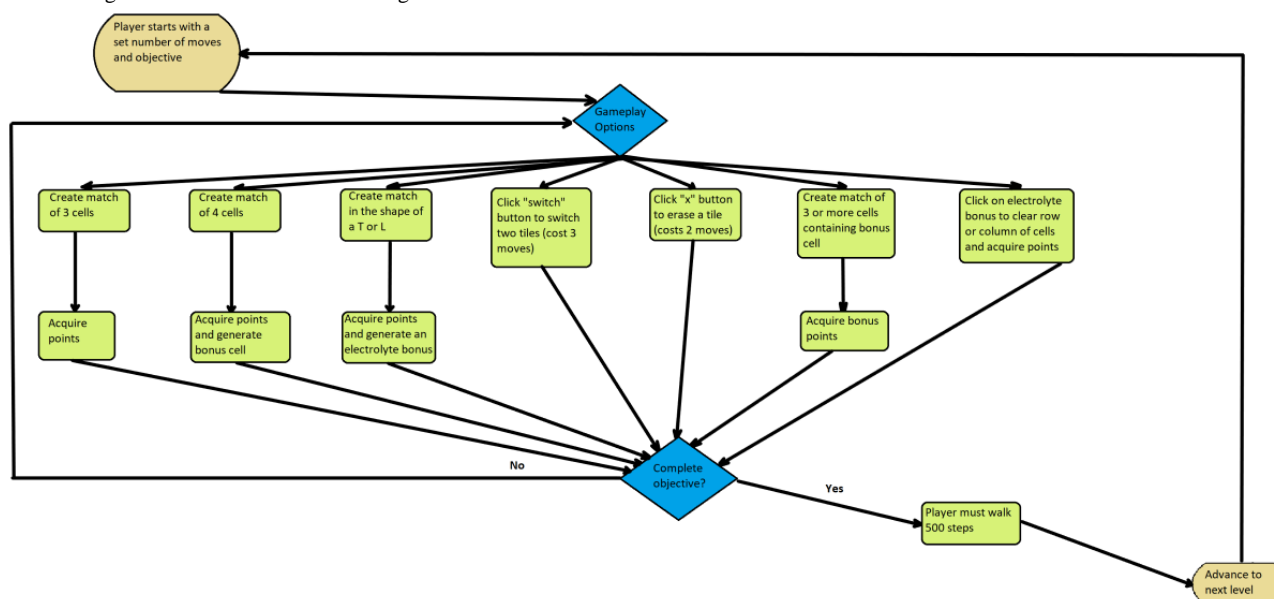**Figure 1.** The game's initial user interface design.
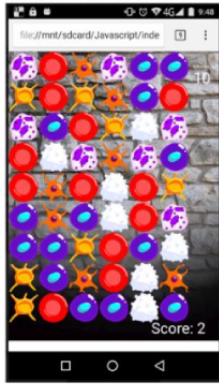
Figure 2. Prototype versions.

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

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

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.

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, $Pimm(t)$, by $R_t=R_0[1-Pimm(t)]$. 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 $\mu=0$ ($\sigma=3$). 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.

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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.
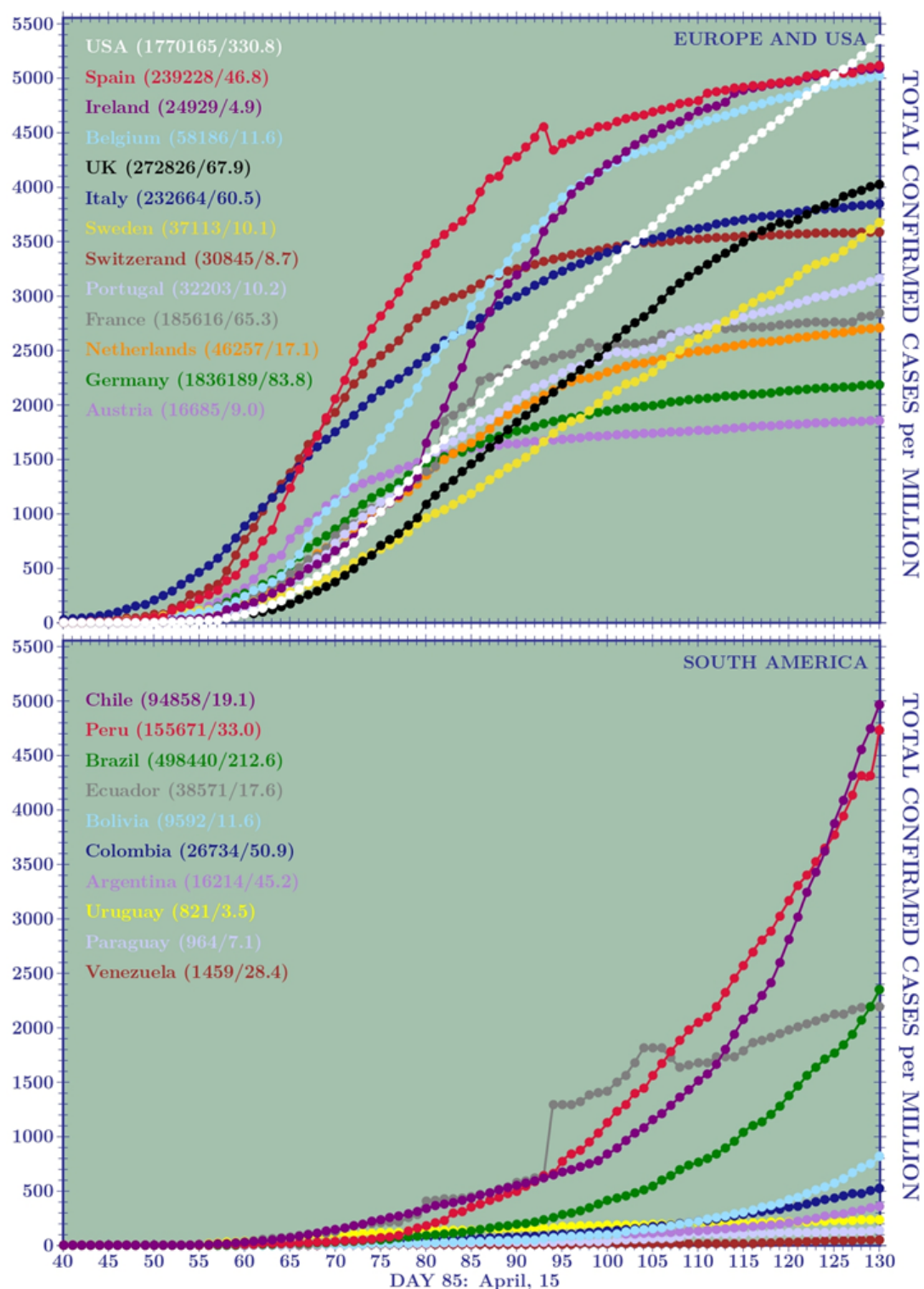
Figure 2. Curves of the total deaths per 1 million inhabitants (TDpM) for (A)12 European countries and the United States and (B) all South American countries, on day 130 (May 30, 2020). Among the 12 European countries analyzed, the higher TDpM numbers belong to Belgium, Spain, the United Kingdom, and 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.
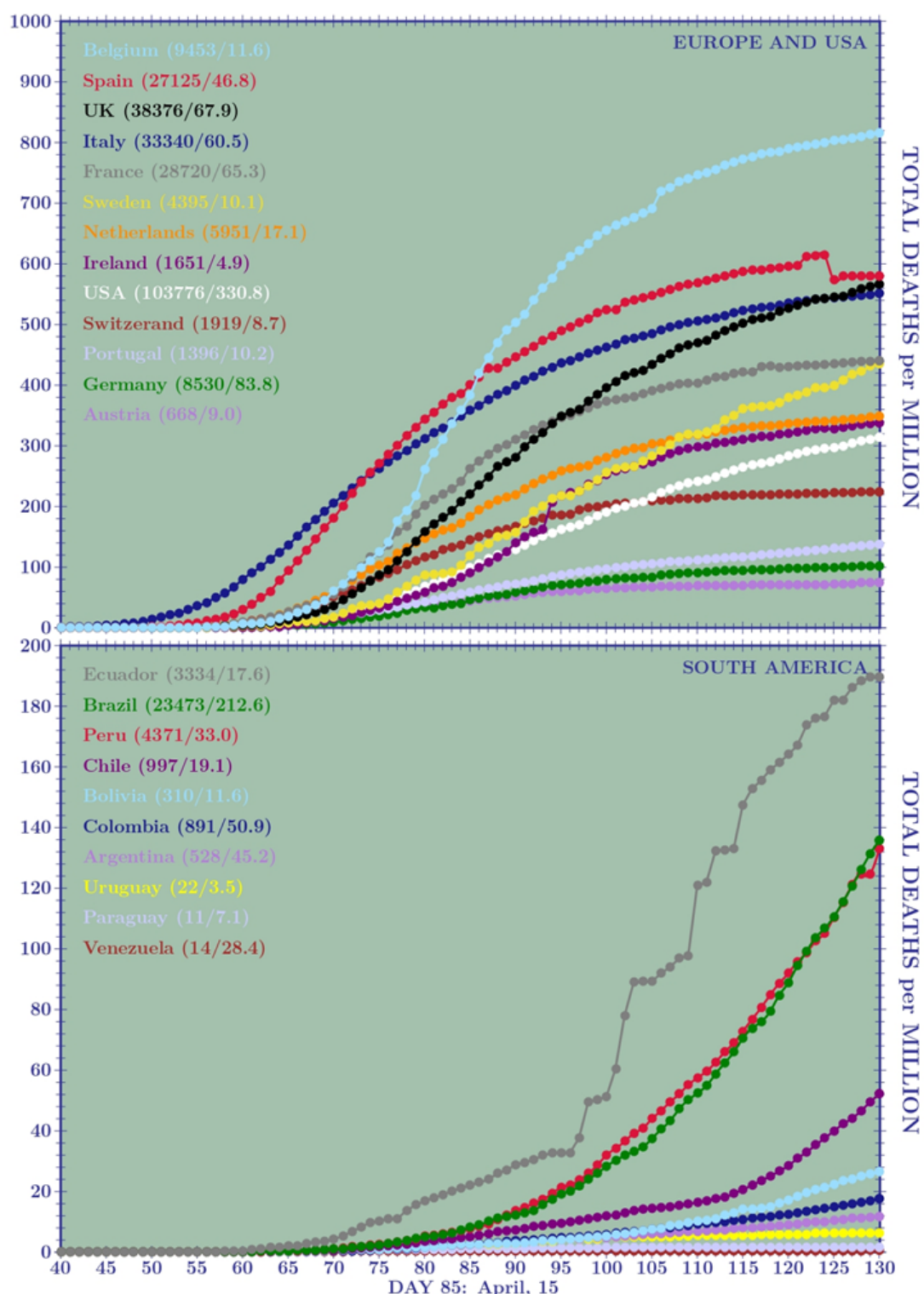
Weekly Transmission Rates

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 $(2.15/3.63) \times (200/1490) \approx 0.29/3.63$, 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.

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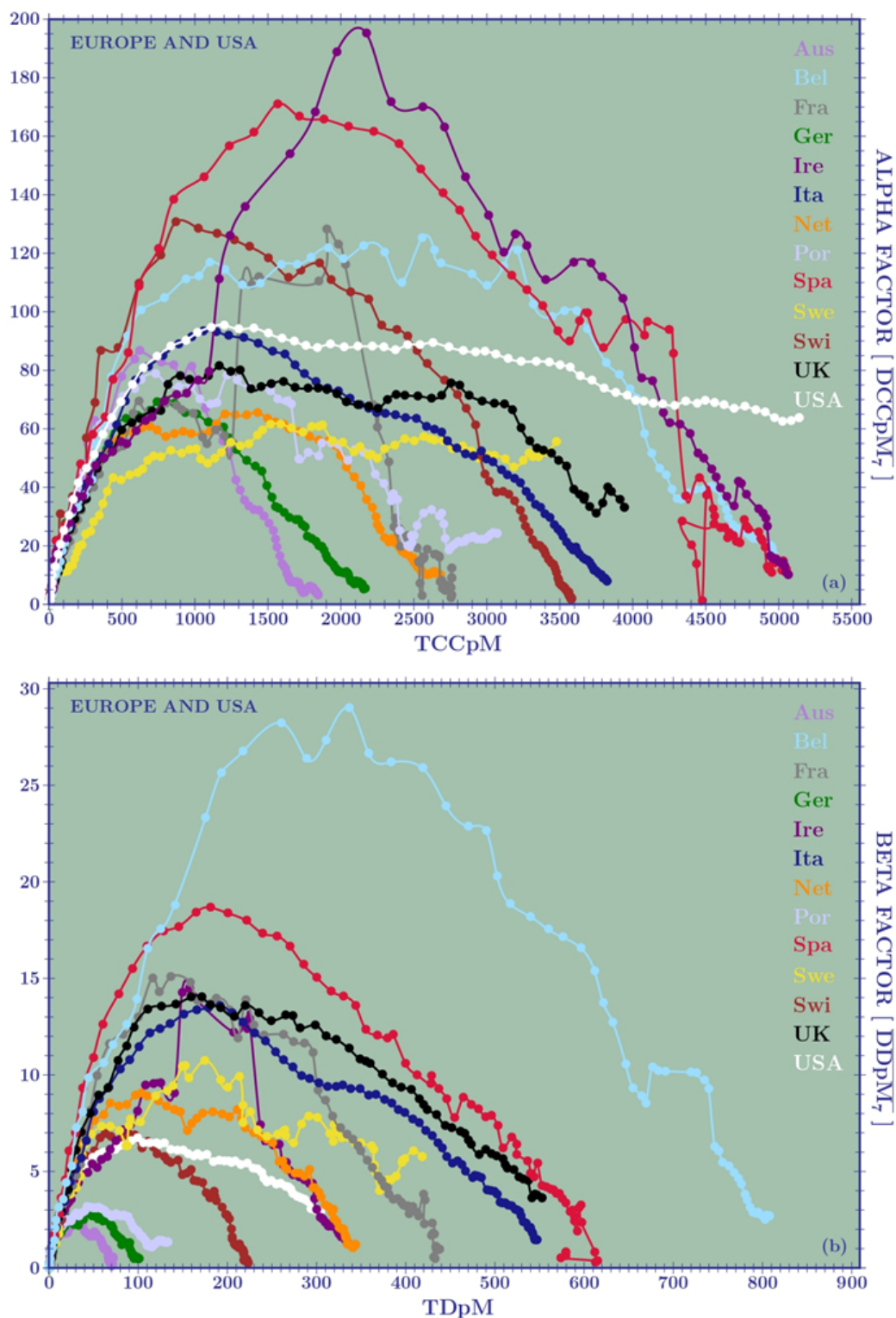
Figure 4. The weekly spreading rate at the beginning of the outbreak for 12 European countries, the United States, and Brazil. (A) Confirmed cases: Brazil, with an initial behavior similar to Sweden, shows a steep increase in its curve, overtaking most European countries and the United States. (B) Deaths: 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.
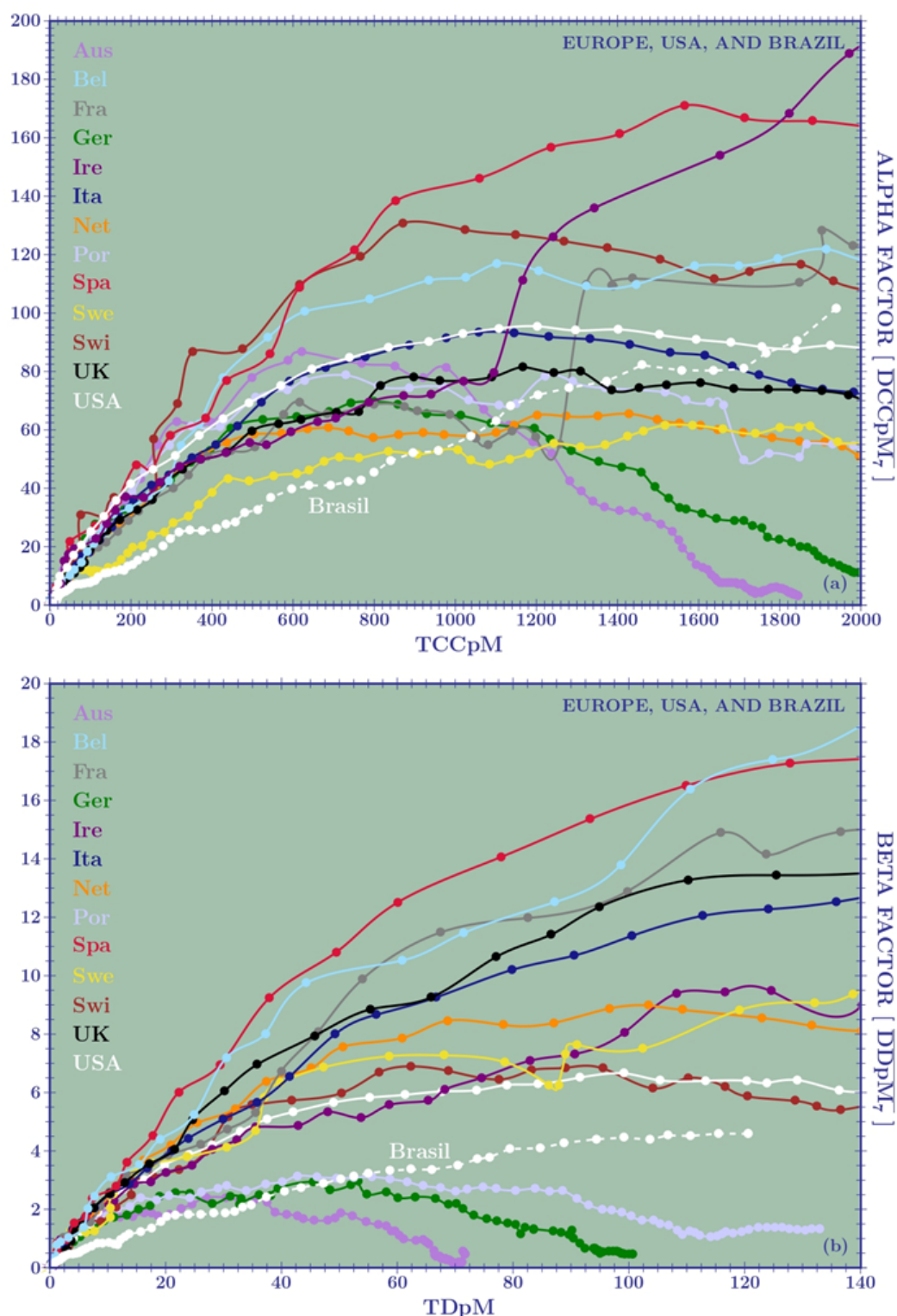
Next, we analyzed the weekly transmission rate for DDpM, the so-called β factor, which was done analogously to what has been done for the DCCpM. Table 5 takes Italy, Germany, the United States, and Brazil as illustrative examples.

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 (Δmean=μ_d–μ_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.
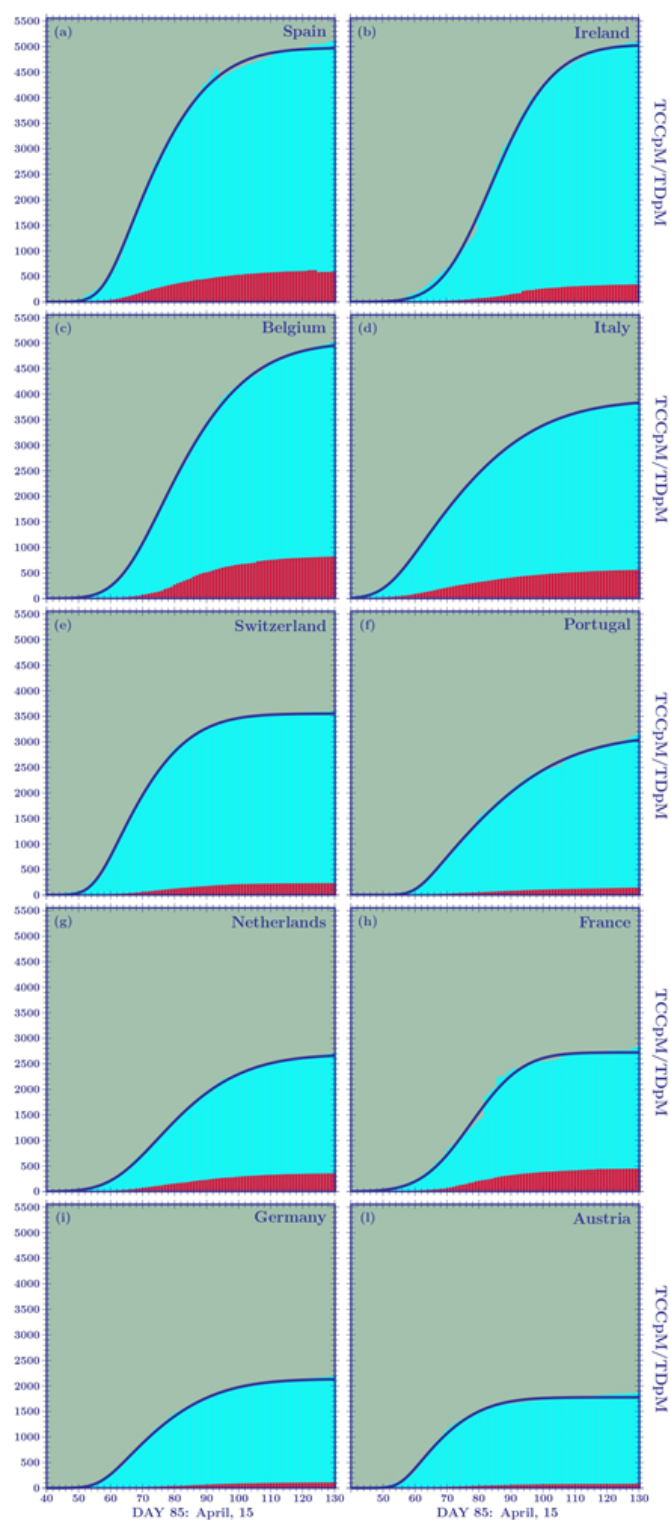
Figure 6. Skew-normal probability distribution functions corresponding to the cumulative distribution functions plotted in Figure 5. DCCpM: daily confirmed cases per million, DDpM: daily deaths per million.
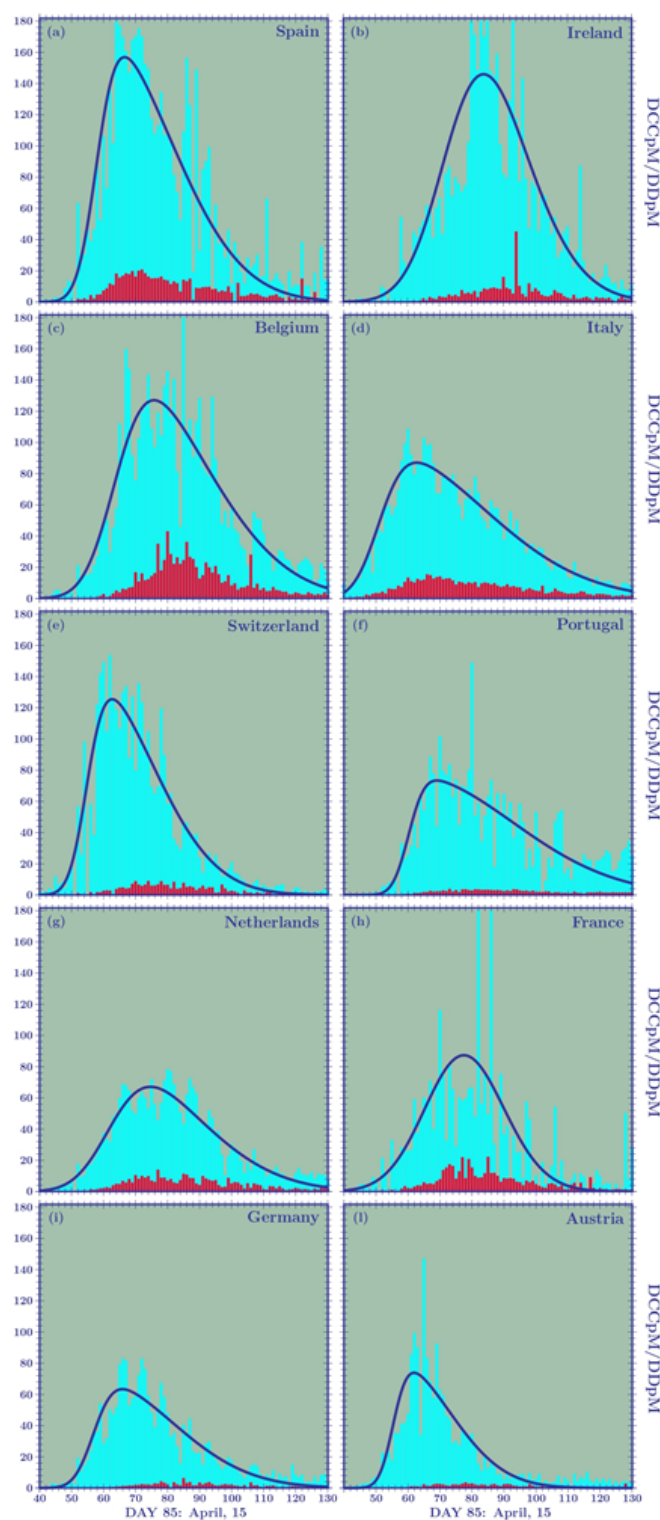
We observed that, among the distributions plotted in Figure 6, that of the Netherlands shows a smooth growth and a peak (comparable to that of Germany) and is lower than all the other distributions. The Netherlands attempted to adopt a different form of lockdown. In contrast to most other European countries, 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.
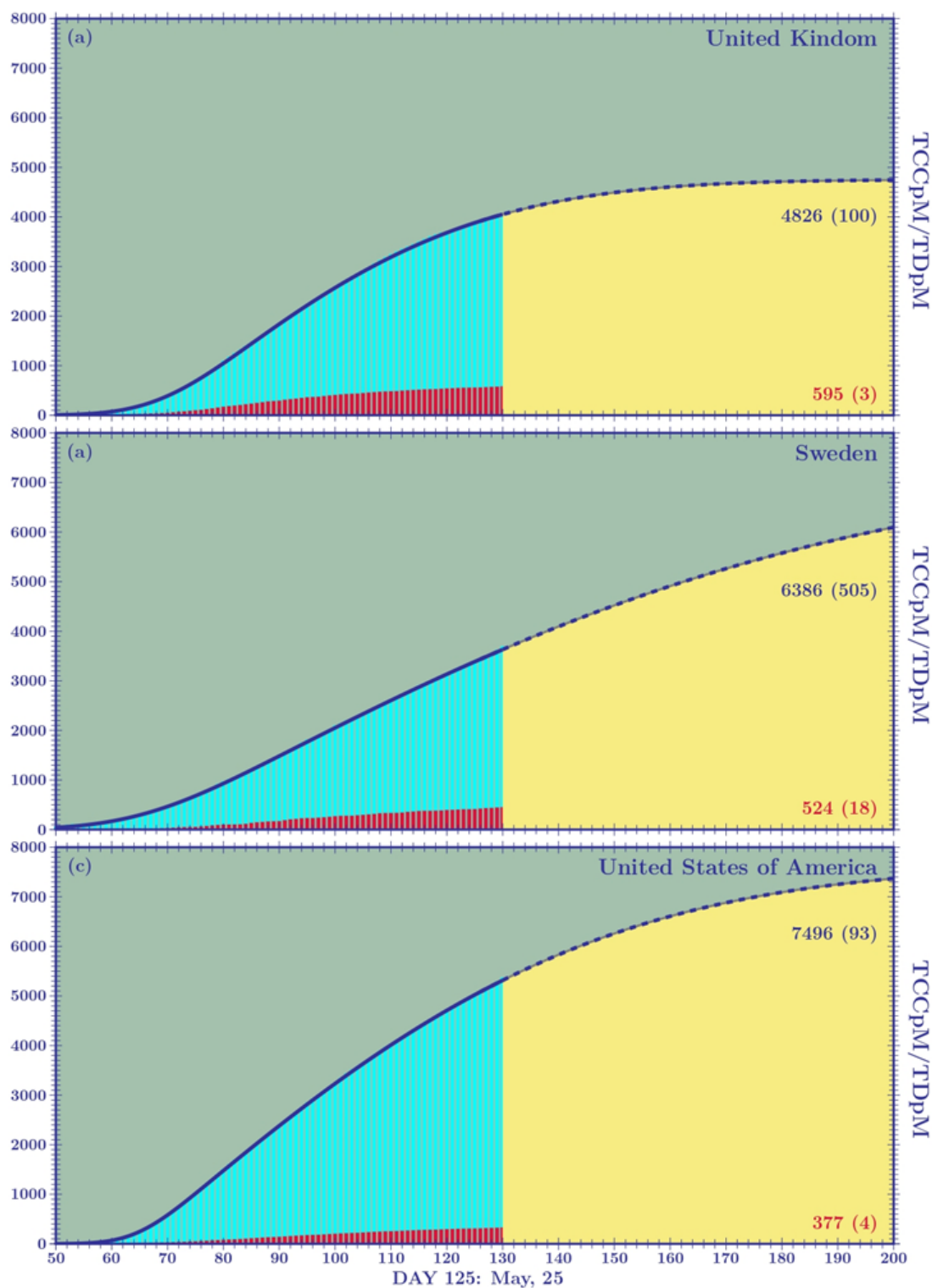
Figure 8. Skew-normal probability distribution functions corresponding to the cumulative distribution functions plotted in Figure 7. DCCpM: daily confirmed cases per million, DDpM: daily deaths per million.
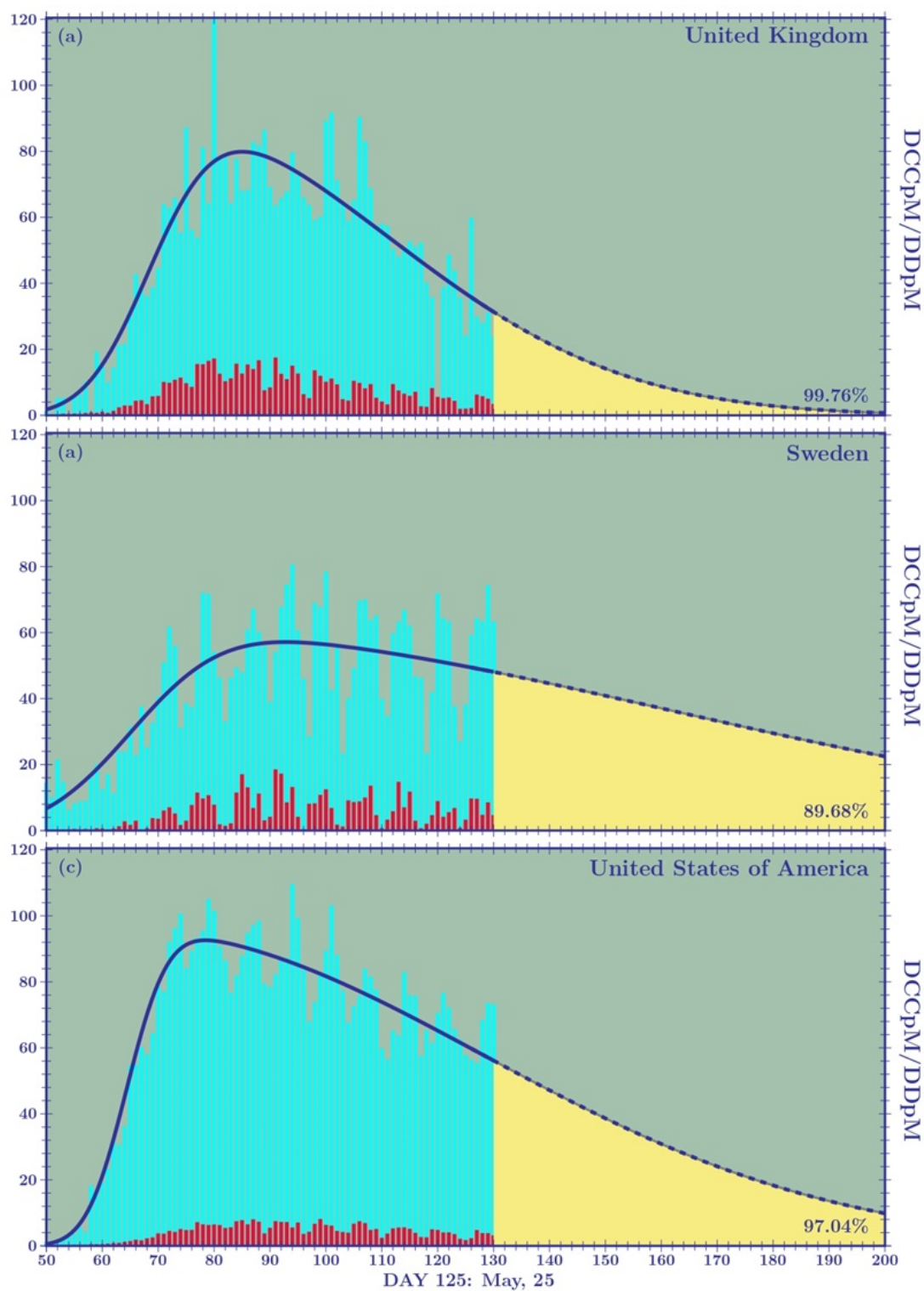
Table 8. The fitting parameters (center, standard deviation, and skewness) of the skew-normal distributions of the United Kingdom, Sweden, and the United States for total confirmed cases per million.

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.
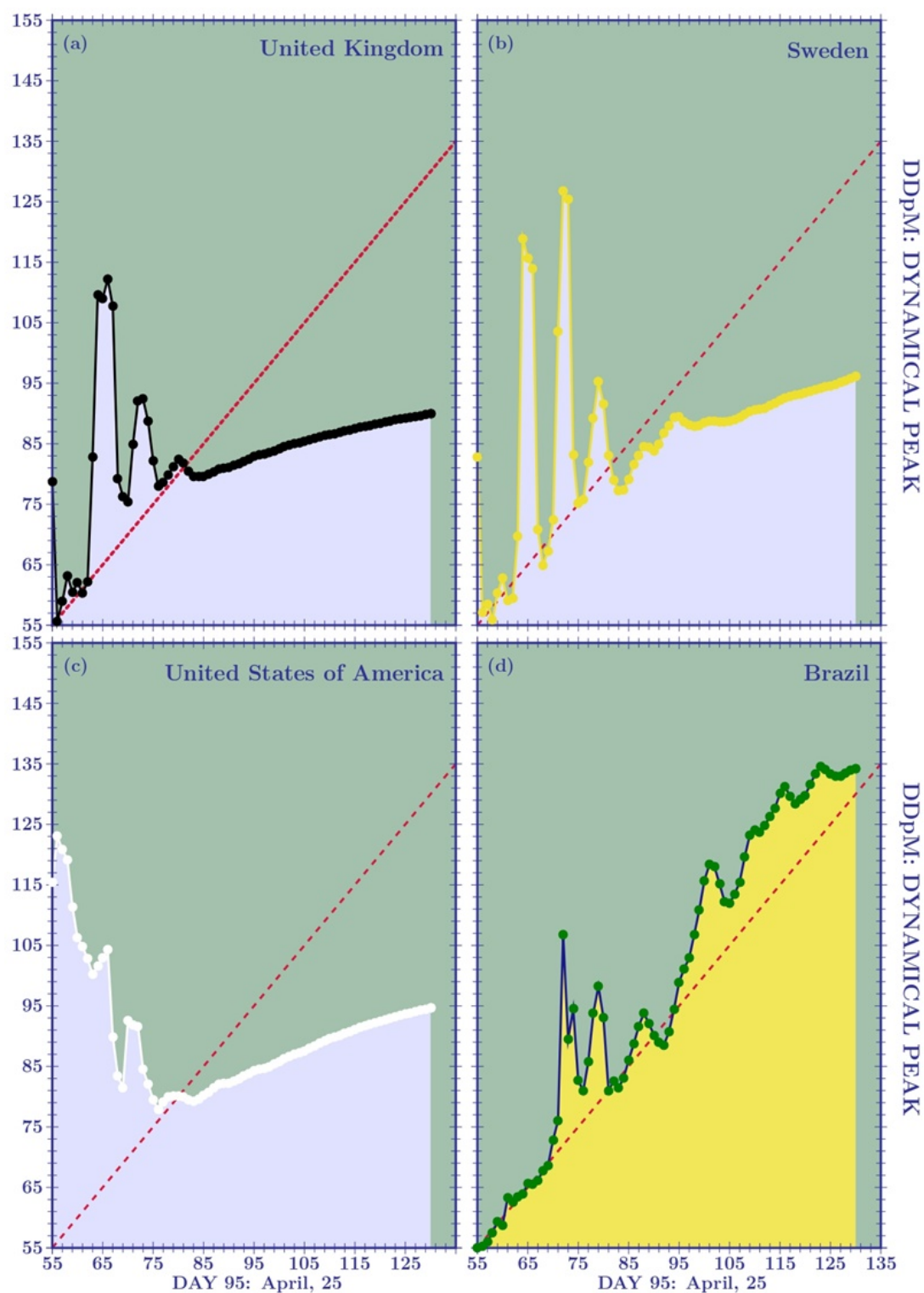
The dynamical analysis of Brazil's peak shows that the country is approaching its DDpM peak. To see when this will happen, let us consider the number of deaths on May 30 (day 130), that is, 28,834. If we go back to day 80 (April 10), we find 1057 deaths. Table 10 displays the number of deaths every 5 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.

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

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.

KEYWORDS

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 recommended 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).
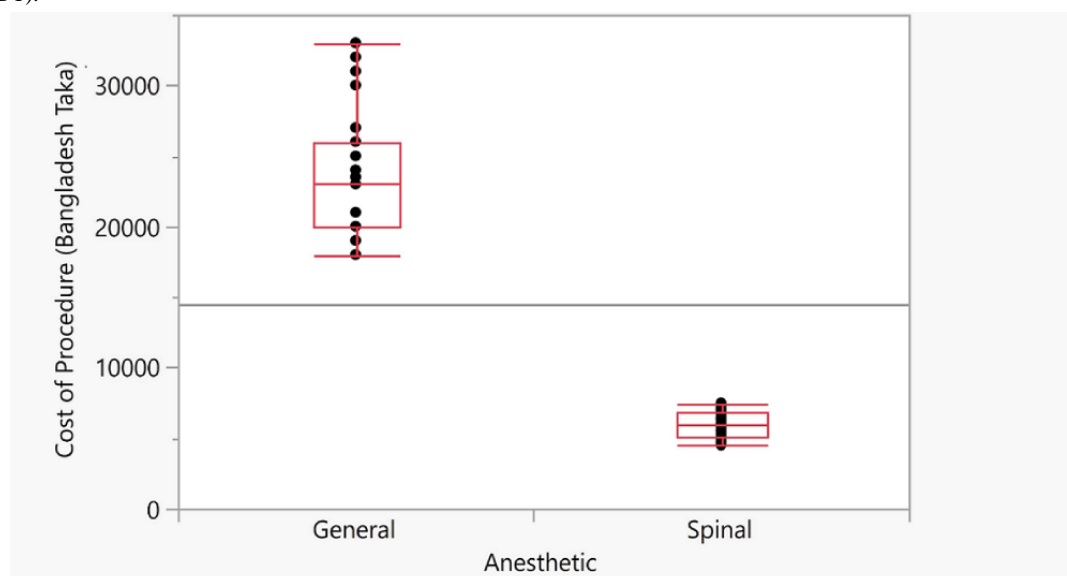
Figure 2. Multiple correspondence analysis plot from variables listed.
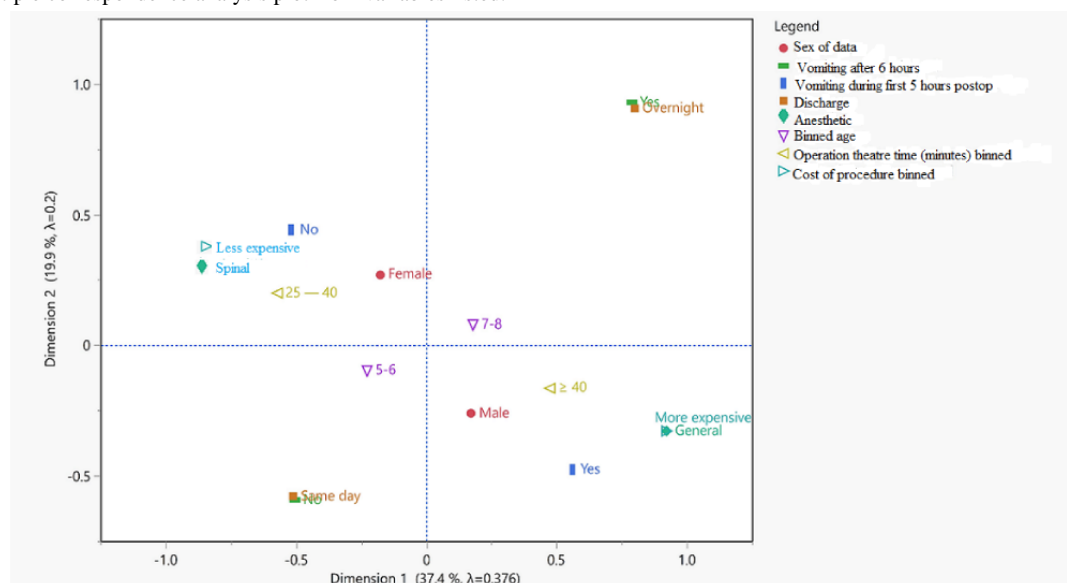
Discussion

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

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/

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.

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

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 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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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]

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

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Physical Activity and Health, Department of Behavioural Science and Health, University College London, London, United Kingdom

Related Articles:

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

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

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

Abstract

This is a peer review report.

(*JMIRx Med 2021;2(2):e28339*)   doi:10.2196/28339

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

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Department of Rehabilitation Sciences, The University of Texas Medical Branch, Galveston, TX, United States

Related Articles:

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]

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Abbreviations

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

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/

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

This is a peer-review report submitted for the paper "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

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]

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

This is a peer-review report submitted for the paper "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

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

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 of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series"

Anonymous

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

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

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

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]

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/

Abstract

These are author responses to peer review.

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

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]

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

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

Abstract

These are author responses to peer review.

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

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 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

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 of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series"

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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.

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. Anonymous. Peer Review of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series". JMIRx Med 2021 Apr;2(2):e29604 [FREE Full text] [doi: 10.2196/29604]
3. Aslanidis T. Peer Review of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series". JMIRx Med 2021 Apr;2(2):e29607 [FREE Full text] [doi: 10.2196/29607]
4. Anonymous. Peer Review of "Use of Spinal Anesthesia in Pediatric Laparoscopic Appendectomies: Case Series". JMIRx Med 2021 Apr;2(2):e29605 [FREE Full text] [doi: 10.2196/29605]
5. Peyton PJ, Wu CY. Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. Anesthesiology 2014 May;120(5):1137-1145 [FREE Full text] [doi: 10.1097/ALN.0000000000000122] [Medline: 24401771]

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