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Research paper

Attitudes, acceptance and hesitancy among the general population worldwide to receive the COVID-19 vaccines and their contributing factors: A systematic review

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ABSTRACT

Background: High rates of vaccination worldwide are required to establish a herd immunity and stop the current COVID-19 pandemic evolution. Vaccine hesitancy is a major barrier in achieving herd immunity across different populations. This study sought to conduct a systematic review of the current literature regarding attitudes and hesitancy to receiving COVID-19 vaccination worldwide.

Methods: A systematic literature search of PubMed and Web of Science was performed on July 5th, 2021, using developed keywords. Inclusion criteria required the study to (1) be conducted in English; (2) investigate attitudes, hesitancy, and/or barriers to COVID-19 vaccine acceptability among a given population; (3) utilize validated measurement techniques; (4) have the full text paper available and be peer-reviewed prior to final publication.

Findings: Following PRISMA guidelines, 209 studies were included. The Newcastle Ottawa (NOS) scale for cross-sectional studies was used to assess the quality of the studies.

Overall, vaccine acceptance rates ranged considerably between countries and between different time points, with Arabian countries showing the highest hesitancy rates compared with other parts of the world.

Interpretation: A variety of different factors contributed to increased hesitancy, including having negative perception of vaccine efficacy, safety, convenience, and price. Some of the consistent socio-demographic groups that were identified to be associated with increased hesitancy included: women, younger participants, and people who were less educated, had lower income, had no insurance, living in a rural area, and self-identified as a racial/ethnic minority.

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1. Introduction

Shortly after the coronavirus disease 2019 (COVID-19) outbreak was declared a pandemic across the world in early 2020, the World Health Organization (WHO) began the organization of a global campaign of prevention, early diagnosis, and medical treatment of the disease [1]. It was clear to medical scholars and leaders across the world that there was a strong call for developing a vaccine, as it was the only ultimate key that could completely resolve the COVID-19 pandemic [2]. In the months that followed, multiple vaccines were developed and tested in a variety of clinical trials across diverse populations, casting a new record timing of a breakthrough in the development of any vaccine so far. As of the first quarter of 2021, there

have been 85 vaccine candidates in the clinical phase and 184 in the pre-clinical phase [3]. On December 11, 2020, the U.S. Food and Drug Administration issued the first emergency use authorization (EUA) for a vaccine for the prevention of COVID-19 in individuals 16 years of age and older [4]. The EUA allowed the Pfizer-BioNTech COVID-19 vaccine to be distributed in the U.S as the first one in the world [5]. Within days, other countries followed and issued approval, while other vaccine candidates were arriving at the horizon. Of those reaching the fourth phase of clinical testing, four of them were licensed in a number of countries. Of these four, two use a mRNA vaccine platform (candidates developed by Moderna and National Institute of Allergy and Infectious Diseases and by BioNTech RNA Pharmaceuticals and Pfizer), one uses the novel chimpanzee adenovirus-vectored platform (developed by AstraZeneca and University of Oxford) and the fourth applied the inactivated virus (developed by Sinovac and Butantan Institute) [6–8]. However, shortly after the initiation of massive

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Research in context

Evidence before this study

Prior to conducting our systematic review, we searched PubMed and Web of Science without keyword or language restrictions to identify previous evidence in the form of a systematic review on our topic of interest. Prior to and during the conduction of this systematic review, we identified several other systematic reviews that have addressed the problem of vaccine hesitancy, some of them conducted before and some after the first vaccine candidate approval. The pace of publishing new studies that investigate the issue of hesitancy towards the COVID-19 vaccine across the world is very fast, and it is necessary to constantly update and summarize the available results. Given that hesitancy towards a vaccine is a subjective topic and constantly evolving with scientific updates, new evidence is needed to address the current barriers in receiving a COVID-19 vaccine upon its availability in the recent months.

Added value of this study

This review provides a thorough exploration of different factors that contribute to a COVID-19 vaccine hesitancy among the general population across different cultural and geographical contexts. Contrary to previously published systematic reviews that focused on willingness to vaccinate and vaccine acceptance rates solely, this review included other variables as well, such as parental hesitancy or willingness to participate in vaccine trials. We identified major themes that contribute to increased hesitancy, including concerns relating to vaccine efficacy, safety, side effects, convenience, price, beliefs that the vaccine is not necessary, that the testing for the vaccine was insufficient and that the pace of its development was too quick, as well as the financial motivation of the authorities/pharmaceutical companies. Several sociodemographic variables showed an association with increased hesitancy, providing evidence for identification of vulnerable populations.

Implications of all the available evidence

In order to adequately combat the current pandemic, herd immunity is necessary. Hence, a high rate of vaccinations among the entire population is essential in every country. The current presented evidence provides an opportunity to identify vulnerable populations that are prone to having low vaccination rates in the future. Consequently, this evidence helps direct policymaking and intervention measures to increase the rates of vaccination and increase the willingness of the people to receive a vaccine.

[13], the percentage of the population that must be vaccinated in order to reach herd immunity could be as high as 82.5% [13].

Vaccine hesitancy is not considered to be a new obstacle when discussing disease prevention since it was a major problem for the seasonal influenza and the 2009 H1N1 pandemic [14–16]. Emerging research in the literature in the past decade has suggested that vaccination hesitancy has been increasing in recent years across many populations, even among healthcare workers [17,18]. Olive et al. reported that a social movement of public health vaccine opposition has been growing in the United States and, among many other factors, has contributed to an increase in the percentage of the population in the US and Europe who refuse vaccination efforts in recent years [19,20]. Similarly, the uptake level of the seasonal influenza vaccine has also declined, while the measles outbreaks in recent years continue to demonstrate the importance of vaccine uptake among the population. Although the vaccine had succeeded in eliminating measles in the U.S., under- and non-vaccinated communities have contributed to its reappearance [21,22]. Vaccination hesitancy contributes to significantly decreased rates of vaccination among populations and resembles a great challenge to public health experts in terms of battling infectious diseases. In 2019, the WHO listed vaccine hesitancy as one of the top ten threats to global health. In the context of the COVID-19 pandemic, the threat of vaccination hesitancy became more relevant, as high rates of vaccination uptake are viewed as a necessary tool in combating the pandemic [23,24]. Given that it is very unlikely to mandate vaccination, especially in individualistic societies, it is necessary to understand the factors that contribute to the COVID-19 vaccine hesitancy in order to inform policy-makers and formulate direct intervention measures that will successfully handle the COVID-19 pandemic.

Vaccine hesitancy is considered to be a multi-factored phenomenon affected by an array of factors. This includes cognitive, psychologic, socio-demographic, political and cultural factors that contribute to it and differ across different populations [25]. In the context of the COVID-19 vaccine, the historic speed during which the vaccine was developed contributes to hesitancy among many populations. Upon these bases, this study sought to conduct a systematic review of the current literature regarding attitudes and hesitancy to receiving COVID-19 vaccination among the general population in a variety of geographical contexts. To the best of our knowledge, this is among the very first systematic reviews that investigates attitudes and hesitancy to the COVID-19 vaccination following its distribution in late 2020. Additionally, and compared to the reviews currently published in the literature, this systematic review has a wider scope and focuses on factors that contribute to both hesitancy and acceptance rates among a wider set of populations. Most importantly, this review will point out the barriers and concerns that are currently in place and that contribute to hesitancy among the general population, thereby providing valuable insights to policymakers. At the same time, it will also try to reveal the main factors that drive people's positive intentions towards vaccination. With increased availability of COVID-19 vaccinations across the world, there is a strong call to understand the roots of vaccine hesitancy and the drivers of vaccine acceptance to successfully combat the current pandemic.

2. Methods

A systematic literature search was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Multiple databases were searched, namely PubMed and Web of Science, on February 24th, 2021, using a set of developed keywords. Additionally, the peer review process required an update to the systematic search, which was performed concluding with the July 5th, 2021.

immunization, the real challenge was realized by many - will people be willing to receive a vaccine that has not been in use previously?

Vaccines represent the greatest protection in the context of public health, however, in order to be successful, the vaccination uptake level must be high [9]. Especially relevant in the context of the current COVID-19 pandemic, high vaccination coverage rates are necessary to enable indirect protection for the overall community, return society to the normal pattern of life, and reopen the global economy [10]. High vaccination rates are also crucial in achieving herd immunity in order to reduce the transmission of COVID-19 and create a decreased risk of infection among the general population and those most vulnerable to transmission [10–12]. However, the highly infectious nature of the COVID-19 disease presents a great challenge in achieving this goal. With a basic reproductive number as high as 5.7

2.1. Search strategy and selection criteria

Search keywords were developed by the authors in relevance to the research question. When relevant, Boolean operators were utilized to develop the most robust search in the databases chosen. The search keywords developed for this literature search are outlined in [Table 1](#). Search keywords were utilized to run searches on two databases, PubMed and Web of Science.

Retrieved articles were entered into Zotero reference manager software and duplicates were removed [26]. As illustrated in [Fig. 1](#), titles and abstracts of all search results were independently screened by two investigators (A.P. and Y.A.A.) for relevance. Upon exclusion of irrelevant articles, full-text articles were accessed and screened for eligibility. Studies were eligible if they: (1) were conducted in the English language; (2) investigated COVID-19 vaccine attitudes and hesitancy; (3) utilized validated measurement tools to measure hesitancy and attitudes; (4) had a full-text article publicly available; (5) were peer reviewed. Studies were excluded at this stage if they were: (1) not peer-reviewed; (2) written in a language that is not English; (3) did not have full-text available publicly. Additionally, when one study was reported in multiple publications, we selected the one that reported outcomes and more information that was relevant for our research question, or the one that was published in a more suitable format (for example a research letter vs. an original research article). Supplementary Table S1 in the supplementary section summarizes the inclusion and exclusion criteria of the studies screened during this systematic review.

2.2. Data extraction

A tabulated form was prepared for data extraction. Data extraction was performed by two reviewers (A.P. and G.F) using a pre-designed Excel sheet, and every disagreement was resolved by discussion with the third reviewer (Y.A.A.). The data reflecting surveyed participants' attitudes to receiving future COVID-19 vaccines were sought and the following measurements were included: the rate of vaccination acceptance/rejection, the rate of positive/negative attitude (expressed as the rate of positive/negative responses to a specific set of questions related to vaccine uptake), the rate of people willing to enroll themselves/their child in a COVID-19 vaccine trial, the rate of participants willing to pay for the future vaccine. Other relevant information regarding multiple dimensions were collected for each study, including: (1) the first author and year of publication; (2) geographical context (city and/or country); (3) study design; (4) population of interest; (5) data collection method; (6) demographic characteristics; (7) motivators toward vaccine acceptance and uptake; (8) barriers against vaccine acceptance and uptake. After summarizing all the data in the tabular form, it was possible to identify all eligible studies (those reporting some of the parameters related to the uptake of future COVID-19 vaccine) as well as identify those that did not fulfill the inclusion criteria.

Table 1
PubMed and web of science search strategy, highlighting keywords used when searching.

Journal Databases	Keyword Strategy
	Search Keywords
(1) Generic Topic of Interest	(vaccine [mh] OR vaccination [mh] OR immunization [mh] OR vaccin*[ti] OR immun* [ti]) AND (attitude [tiab] OR perception [tiab] OR receptivity [tiab] OR willingness [tiab])
(2) Disease focus: COVID-19	(COVID-19 [mh] OR 2019 novel coronavirus disease[tiab] OR COVID19[tiab] OR sarscov 2 infection[tiab] OR 2019 novel coronavirus infection[ti] OR 2019 ncov infection[tiab] OR 2019 ncov disease[tiab])

2.3. Data presentation

All extracted data of interest are presented in a tabular form according to the geographical context. Accordingly, the summaries of vaccine acceptance/hesitancy rates are presented in the textual format depending on the geographical context as well, followed by the main factors contributing to the observed results. Along with identifying the main reasons that drive people attitude towards vaccination, this data presentation provides an overview of the high/low vaccine acceptance regions.

2.4. Graphical presentation

Acceptance rates for countries where several surveys were conducted were calculated by dividing the total number of surveyed participants in all surveys by the total number of participants that stated they were willing to accept the future COVID-19 vaccine. The acceptance rates for the UK were derived by the studies that surveyed the UK and the English-speaking population. The results from the studies conducted in several individual states in the USA were not merged with the rest of the USA survey data and are not presented in the map. Additionally, surveys that included individual cities from countries were not merged with the country-level data and are presented only textually (not graphically), where relevant. Only the acceptance rates reflecting the willingness to vaccinate the participants themselves are presented graphically. The results from the surveys that assessed other parameters (willingness to pay for the vaccine, attitudes towards a COVID-19 vaccine, to enroll in a vaccine trial, to vaccinate their children, or to evaluate several hypothetical vaccines) were not included in the graphical presentation. The graphical presentation was generated in R software [27], by employing the package *rworldmap* [28].

2.5. Quality appraisal

The Newcastle-Ottawa scale (NOS) was used to assess the quality of the studies. Two reviewers (A.P. and Y.A.A.) independently assessed the risk of bias and any uncertainty was resolved by contacting the third independent reviewer (G.F). The quality assessment was performed only for studies of cross-sectional design and for original research articles, yielding a total of 180 studies for quality assessment purposes. Editorials, correspondences, research letters and studies that were not cross-sectional were not evaluated for quality and were only included for purposes of data synthesis. NOS was developed to assess the quality of nonrandomized studies with its design, content, and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results [29]. NOS has a total of 7 categories for scoring and uses a star system, categorized under three main themes: (1) Selection (4 sub-categories; maximum of 4 stars); (2) Comparability (1 sub-category; maximum of 2 stars); (3) Outcome (2 sub-categories; maximum of 3 stars). The sub-categories include representativeness of the sample, sample size, comparability between respondents and non-respondents, ascertainment of the exposure or awareness of COVID-19 outbreak and vaccine; comparability in the context of participant distribution and analyses; assessment of the outcome; and statistical tests assessment. A full list of adapted questions from the NOS is attached as a supplementary file.

2.6. Ethical approval

Ethical approval for this specific systematic review is not applicable since data utilized was collected from previously published research in the literature. All studies included in this review received ethical approval prior to data collection by their primary investigator.

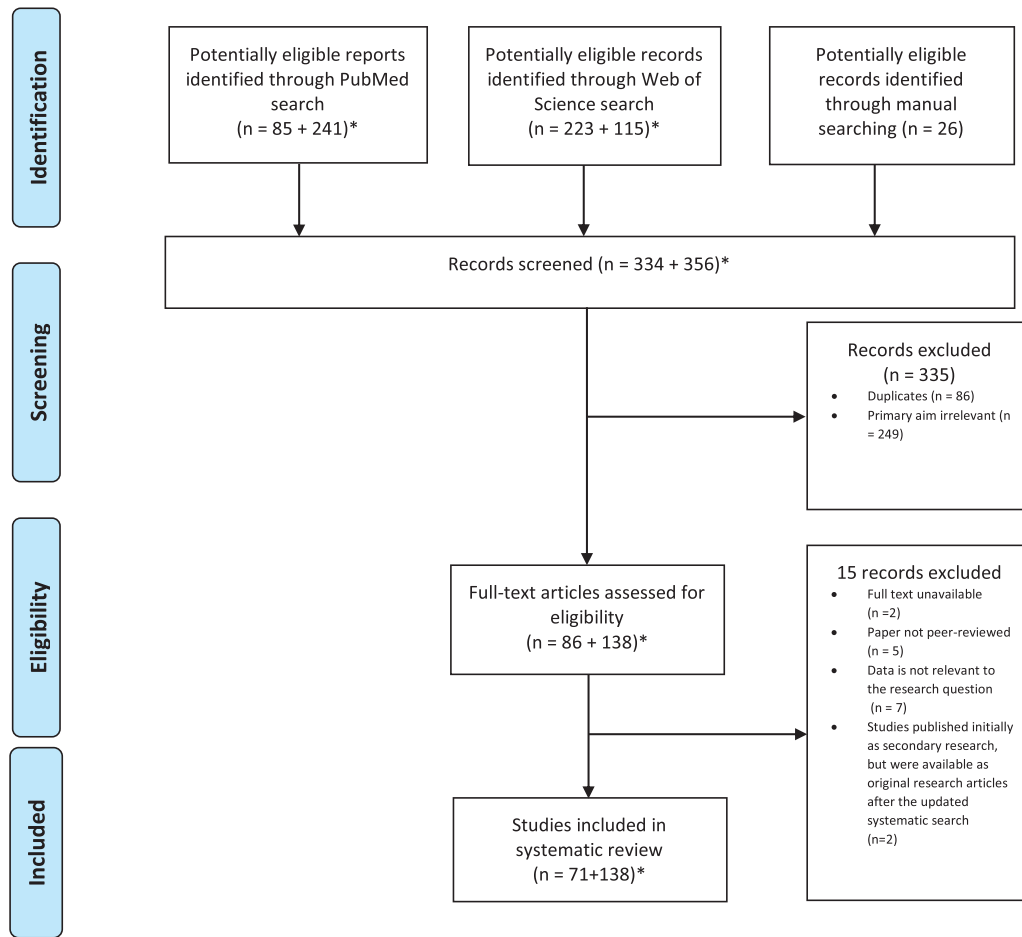


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) study selection flow diagram. *indicates numbers from both searches; former number refers to the initial systematic review conducted in February, the latter number refers to the update systematic review conducted in July.

2.7. Role of funders

This study was not sponsored nor funded.

3. Results

3.1. Search results

Upon conducting the systematic search, 85 studies were identified using PubMed and 223 studies using the Web of Science database, yielding a total of 308 studies. After removing the duplicates and locating an additional 26 studies by performing a manual search, a total of 288 articles were screened for title and abstract. After this step, 186 articles were removed due to their irrelevancy to the research question, 16 studies were excluded as they were either a review article, presented data not related to the research question, reported results regarding COVID-19 knowledge, or were about influenza vaccination acceptance. After performing the full text assessment, an additional 15 articles were excluded. Reasons for exclusion included the data not being relevant to the research question ($n = 7$) [30–36], unavailability of full-text ($n = 2$) [37,38], the paper not being peer-reviewed at the time of the search ($n = 4$) [39–42], and the studies were initially published as secondary research but were identified in the updated search as an original research article ($n = 2$). Thus, 71 studies from the first systematic search were included in the qualitative synthesis. However, after performing the updated search and removing duplicates, the number of additional and potentially relevant articles (from both PubMed and Web of Science database) was

356. Out of them, 218 were deemed to be either completely irrelevant to the research question, or reported no outcomes of interest, thus leaving a total of 138 studies to be included in the qualitative synthesis. Both the first and the updated search yielded a total of 209 studies to be included in this systematic review.

3.2. Study characteristics

Supplementary Table S2 presents study characteristics and primary study findings. The sample size of studies ($n = 73$) ranged from 103 to 36,220 participants. The 209 studies were conducted in five different continents, including Africa ($n = 17$), America ($n = 48$), Asia ($n = 78$), Australia ($n = 5$), and Europe ($n = 53$). Additionally, 8 studies were conducted in an international context (e.g., collecting data from a variety of countries). A total of 45 countries reported their vaccine acceptance rates, and these data are presented in Fig. 2.

3.3. Quality appraisal

Supplementary Table 3 (Table S3) presents the results of the study quality appraisal. All cross-sectional studies ($n = 194$) were assessed by the NOS protocol outlined in the Methods section. Overall, the majority of studies had a moderate quality, with an average of approximately 6 stars (range = 3–8 stars). There were 3 studies that received 3 stars, 9 studies with 4 stars, 26 studies with 5 stars, 94 studies with 6 stars, 40 studies with 7 stars, and 6 studies with 8 stars.

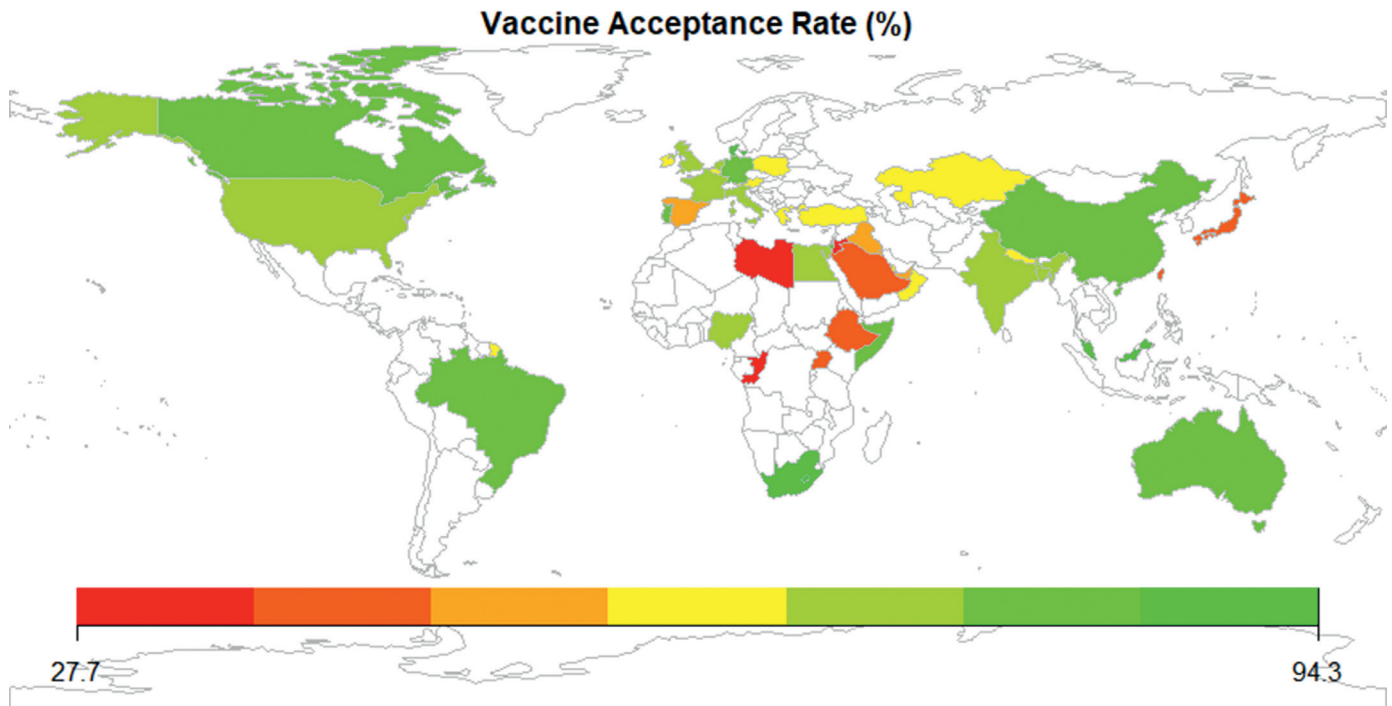


Fig. 2. Map reflecting vaccine acceptance rates worldwide.

3.4. Prevalence of hesitancy, motivators, and barriers by geographical context

Prevalence Rates Asia

A total of 78 studies were performed in Asia. The majority of articles report results from surveys conducted among Chinese people: China ($n = 16$), Mainland China ($n = 4$), and individual cities/provinces in China ($n = 7$). Nine surveys report data from Turkey, 6 from Saudi Arabia, 4 from Jordan, India, and Japan. Data obtained from 3 or less surveys are available for the following countries: Kazakhstan, Taiwan, Indonesia, Vietnam, Malaysia, Nepal, Bangladesh, Qatar, Kuwait, United Arab Emirates, Oman, Iraq, Israel and Lebanon, and 4 surveys included participants from several different countries.

Data from Chinese surveys indicate fairly stable vaccine acceptance rates across different time-points of 77% and above, with the exception of one survey conducted in February/March 2020 that included nurses (who reported an acceptance rate around 40%) [43]. A study that reports data obtained from pregnant women reports surprisingly high acceptance rates of 77.4% [44] while the same research group reports an even lower hesitancy among women of reproductive age (90.3%) [45]. Provinces in China, on the other hand, report variable results. In Mainland China, Shanghai and Shenzhen, people expressed high intention to vaccinate (with acceptance rates higher than 80%), while the proportion of affirmative population was considerably lower in Hong Kong [46], Wuxi [47] and Jiangsu province [48] (34.8%, 51.2% and 36.4%, respectively). It should be noted that the surveys were conducted in different time points, which might have imposed an effect on the final results.

Data from cross-sectional surveys conducted in Japan show a fluctuating trend in vaccine acceptance, and the surveys report a decrease followed by an increase in the rates during the following months. It is also evident from these data that the studies with smaller sample sizes report higher acceptance rates, compared with those that involved considerably more people.

Countries of South Asia report conflicting results. For example, results from a survey done in Nepal in April/May 2020 indicate very low hesitancy among the surveyed healthcare workers [49], while the one conducted in January/February 2021 observed quite the opposite, when almost one third of surveyed population expressed they would not to be willing to receive the vaccine [50]. On the other hand, neighboring India reports low hesitancy rates in January [51] and March [52] among the general population, as well as in medical students [42], while patients with rheumatic disease expressed lower intention to vaccinate compared with their control peers [53].

The countries of Middle East mostly report higher hesitancy rates compared with the other parts of Asia. The lowest acceptance rate of the general population was recorded in Lebanon (21.4%) [54], while the highest was reported by a survey conducted in Iraq (61.7%) [55]. One Saudi Arabian survey assessed the preferences of healthcare workers regarding the type of vaccine, and it found that out of all surveyed healthcare workers only 20% or 24% preferred to receive the AstraZeneca or the Pfizer vaccine, respectively, while much more declared themselves as "maybe" willing to receive them [56]. It should be noted that surveys that included healthcare professionals/workers report higher intention to receive the vaccine, compared with the general population, even in this region of the world. Furthermore, contrary to the survey conducted in China among pregnant women, a Turkish survey reported very low acceptance rates this population (37%) [57]. Another survey that included a specific population group (patients with rheumatoid disease) found a very low intention to vaccinate which was surprisingly similar to the rates reported by the control group reflecting the general population (29% and 35%, respectively) [58]. Despite the high rates of vaccine hesitancy in this part of world, individual cross-sectional data from three surveys conducted in Turkey indicate that it has declined from December 2020 to February 2021. Finally, large scale studies conducted among several Arab-speaking countries report high vaccine hesitancy rates among this population (up to 83% in January 2021) [59], while only one survey observed a fairly high vaccine acceptance rate (of 75%) among the population of Arab gulf countries in March 2020 [60].

Willingness to pay for the vaccine varied among the countries and depended on the price. The median prices people were willing to pay for the vaccine were as low as 7.08 USD in Bangladesh [61] up to 85.92 USD in Southern Vietnam [62]. Finally, the rates of parents' willingness to vaccinate their children varied from less than 50% [63] up to 76% [64], while the countries of the Middle East's similar willingness regarding their children's vaccination (from around one third in among Turkish general population [65] up to 75% among Turkish pediatricians [66]).

Americas

A total of 48 studies report the results from surveys performed on the American continent. Most studies ($n = 27$) surveyed the general USA population, with one of them including Canadians as well. Several studies focused on specific states, while 2 studies were performed in South America (specifically in Chile), and the rest were conducted in Colombia, Brazil and French Guiana.

The USA longitudinal data mainly report a decreasing trend in willingness to vaccinate over time [67,68]. Data from individual cross-sectional studies done in the general population in different time points, however, shows an inclining pattern—rising from 57.6% in April [69] to 69% in May [70] while surveys from July showed a decline in the rate of vaccine willingness (down to 59.9% [71], and in December down to 55%) [72]. The latest reference from a survey conducted during the period of active immunization process (April 2021) shows however a higher acceptance rate (of 75%) [73]. Specific populations, such as college students, reported high hesitancy [74] while another survey on people aged 14–24 years found that up to 75% of the participants would accept the future vaccine [75]. Adults (35–44 years old) representatives of social media users population, showed a surprisingly high intention to receive the vaccine with 81% of acceptance rate [76]. Data obtained from the older population report conflicting results—one survey that included elderly US adults (aged 65 and above) showed very low hesitancy towards vaccine (acceptance rate 91%) [77] while the same age group, characterized as Medicare beneficiaries showed a considerably lower acceptance rate (61%) [78].

Data from cross-sectional studies conducted in Canada points to the difference in vaccination intentions between age groups, where elderly participants showed to be more likely to accept the future vaccine [79]. Younger participants expressed lower willingness (acceptance rate 65%) [80], while the majority of surveyed healthcare workers replied affirmative towards vaccination (around 80%) [81].

The data from individual cross-sectional surveys across individual (or multiple) USA states report different rates of vaccine hesitancy/acceptance, however, they do differ in the time periods when they were conducted and the populations they surveyed. For example, two surveys conducted in New York state covering healthcare workers found lower willingness among this population in December [82] compared with the data collected in December 2020/January 2021 [83] when vaccination had already begun; however, it should be noted that the difference in sample size was considerable. The later study also observed an increase in willingness if the surveyed population had the option to consider vaccination in the future. Survey data also point to a difference between medical specialty students where higher hesitancy rates were observed among dental versus among medical students [84]. Detained people showed fairly low acceptance rates (around 45%) [85]. Patients with multiple sclerosis, on the other hand, showed a fairly high rate of intention to receive the vaccine (around 70%) [86]. Our systematic search identified one intervention study that suggests a willingness of people to be vaccinated after participating in an educational webinar. This was observed in a very vulnerable population of cancer patients and their caregivers [87].

The rates of acceptance among healthcare workers in South American countries were fairly high (from 77% and above in Colombia [88]

and 80.7% in Brazil [89]). Finally, studies assessing willingness to pay for the vaccine were conducted in Chile, and the reported acceptance rates were 83% and 90% [90,91]. On the other hand, it was estimated that the amount of willingness to pay by Brazilian consumers for a hypothetical SARS CoV-2 vaccine was US\$22.18 [89].

Australia, Africa, and Internationally

Five studies were conducted in Australia, where the number of surveyed participants ranged from 1313 [92] to 4362 [93] participants. The acceptance rates varied from 60% [94] to 85% [93]. One study measured the attitude of the participants towards a future vaccine against COVID-19, and 80% of them expressed a positive attitude [95]. This study concluded that women aged 70 years and above, those with a chronic disease, and those who held private health insurance were more likely to express a positive attitude.

Seventeen studies were conducted in Africa. The lowest vaccine acceptance rate was observed in Congo [96] (27.7%), while the highest was reported by a study conducted in South Africa (91% of healthcare workers would accept vaccination) [97]. Data from Nigeria from March to September 2020 show a positive, increasing trend in vaccine acceptance among this population. Studies from Uganda show that the willingness to participate in COVID-19 vaccine trials is considerably lower among the general population [98] compared with the healthcare professionals [99] (44.6% vs. 70.2%, respectively). Interestingly, two studies conducted during the same period of time (during the initiation of the immunization process in Uganda) showed considerably different rates of people's intention to receive the vaccine, with sufficiently lower rates observed in the population of medical students [100] 37.3%, compared with 70.1% observed among the general population. Studies conducted in Ethiopia during February [101] and February/March [102] report twice as large of a difference in vaccine acceptance rates among the general population (31.4% vs. 62.6%, respectively), while data obtained from specific parts of this country (North, Central, and South) are mainly in agreement (the acceptance rates are 45% on average).

Finally, eight articles reported results from surveys conducted in several countries in different continents, and 2 of them reported different results from the same study. The acceptance rates were 70% on average. Some authors observed that caregivers had a low willingness to enroll their children in a vaccine trial [103], while almost two-thirds of them would opt to vaccinate their children [104]. An international study involving dental students from 22 countries found that one fifth of them were hesitant, with 14% of them expressing rejection towards vaccination [105]. On the other hand, data obtained from healthcare workers from six Asian countries shows very low hesitancy among this population, with a high 95% acceptance rate [106]. Finally, a diverse study conducted among people from 42 African and Middle East countries found that up to one third of the participants did not have the intention to receive the vaccine [107].

Europe

A total of 53 studies assessed vaccine acceptance/hesitancy rates among European countries, namely: Italy ($n = 14$), Poland ($n = 8$), France ($n = 5$), Germany ($n = 5$), UK ($n = 3$), Greece ($n = 3$), England ($n = 2$), Denmark ($n = 2$), Belgium ($n = 2$), Portugal ($n = 2$), Ireland and UK ($n = 1$), Malta ($n = 1$), Lithuania (1), Austria ($n = 1$), Switzerland ($n = 1$), Spain ($n = 1$), and one article reported the results of a survey conducted in several countries (Denmark, France, Germany, Italy, Portugal, the Netherlands, and the UK). Studies from Portugal report low vaccine hesitancy rates among patients with multiple sclerosis [108], while a survey done on general population showed considerable willingness of people to receive the vaccine, however, more than half of the participants (55%) declared they would wait some time

before receiving it [109]. Two surveys on French healthcare workers indicated that a willingness to be vaccinated has declined over time from 77% in March/July 2,020,[110] to 53% in December2020/March 2021 [111]. The acceptance rates of the general population are around 77%, based on two surveys done in March/April 2020, while one study, which included a small sample of patients with inflammatory bowel disease, reported considerably lower intentions to be vaccinated (around 55%) [81]. A survey done in pregnant and breastfeeding women from Switzerland reports very low intention of this population to get vaccinated, with higher rates observed among the breastfeeding population (29.7% vs 38.6%) [112] Data obtained from German healthcare workers indicates a fairly higher acceptance rate in May/August 2,020 [113] compared to the data obtained during the initiation of vaccination (December 2020/January 2021) [114]. However, it should be noted that the first study had a significantly smaller sample size. Accordingly, a survey conducted in January 2021 reports that around 62% of German healthcare workers have already been vaccinated at least once, while additional 22% were planning to do so, which yielded a fairly low hesitancy rate among this surveyed population [115].

Longitudinal data from Denmark reveals a valuable insight around the thromboembolic episodes linked with Oxford-AstraZeneca COVID-19 vaccine, which reports sustained willingness of the general population to get vaccinated, however, there is a perception of lower safety of this vaccine compared with the Pfizer-BioNTechcandidate [116]. Data obtained from the Polish general public point to a low intention to receive the vaccine in June 2020 (37% responded affirmative) [117] while in March 2021 the rate of already vaccinated was 27% and 52% were planning to get vaccinated as well [118]. Other data from Polish surveys imply that the intention of healthcare workers to vaccinate is considerable (around 80%), ophthalmology residents reported somewhat lower (around 70%), while more than 90% of medical students expressed their intention to receive the vaccine once available. Interestingly, one Polish survey reports that their adult population expressed higher level of trust in vaccines that uses mRNA platform over other candidates [119].

Surveys from the UK show that the general population has become increasingly willing to get vaccinated from July to September/October 2020. Longitudinal study data from Italy observed that the willingness of adults to receive vaccination tended to increase during the lock-down phase, with hesitancy showing an increase after the re-opening [35] and indeed, the data obtained from cross-sectional studies at different time points confirmed a declining trend of vaccine acceptance among this population. Surveys conducted at specific Italian regions report conflicting results, from very high hesitancy observed in Naples (76%) [120], to a low one in Southern Italy (84.1%) [121]. A survey done on students as representatives of the younger population confirmed that the majority of them would accept vaccination [122] in both Naples and Southern Italy. Some specific populations that were also included in surveys included people experiencing homelessness, out of which two-thirds of them expressed willingness to vaccinate [123], while a high rate (74%) of willingness was also observed among celiac disease patients [124]. Finally, studies that assessed parents'/caregivers' willingness report that English participants were less willing to vaccinate their children (48.2%) compared with Italian participants [125], where more than 90% were willing to have their children take the recommended vaccine [126]. However, recent data obtained from Naples reports that a considerably lower portion of parents (less than 20%) would allow their children to be vaccinated [120].

3.5. Sociodemographic associations and reasons for hesitancy and acceptance

The participants' most common reasons for rejection were vaccine efficacy, safety, side effects, its convenience, and price. These

participants also hold the belief that the vaccine is not necessary, that natural exposure to infections gave the safest protection, that there has been insufficient testing of COVID-19 vaccines, that authorities are motivated by financial gain rather than the health of people, and had conspiracy beliefs and believed that COVID-19 has been exaggerated. In Australia, participants identified as willing to vaccinate reported exposing themselves to media coverage to a higher extent. Among those who were identified as vaccine-accepting, some of the identified reasons and perceptions they held regarding the future COVID-19 vaccine were: having trust in medical professionals and the government, expressing their worry about the outbreak, being more exposed to social media coverage, and showing a greater medical and scientific understanding of the virus, as well as higher compliancy with the proposed preventive measures of stopping the spread of COVID-19. They held the belief that vaccination was an effective, strong, and preventable tool for themselves and people around them, they had the desire to return to normal life and to protect themselves and children and others or perceived themselves as being in a high-risk group of severe COVID-19 consequences.

Identified socio-demographic categories of participants who were more likely to accept future COVID-19 vaccination included men, older people, those with higher income, those with higher education, doctors (compared with other healthcare professions), participants with private insurance, participants with prior vaccination history, and participants who were of White and Hispanic/Latinx ethnicity. On the other hand, groups that were identified as less willing to accept future vaccination included women, those with lower education, participants with less than a college degree, those without an influenza vaccination in the prior year, those without insurance, participants living in a rural area, those of Hispanic/Black ethnicity. Interestingly, the survey conducted among 19 studies found that women were slightly more likely to accept vaccination than men (in contrast with the majority of other surveys) [127]. In studies conducted in Asia, the association with age yielded inconsistent results. Furthermore, and in terms of religiosity or political affiliation, individuals reporting high levels of religiosity were associated with high rates of hesitancy in American studies. Being a conservative or indicating a republication political partnership or an independent one in America was associated with higher hesitancy. Similarly, in Europe, respondents who felt close to radical parties and those who did not feel close to any party and did not vote at the last presidential campaign were more vaccine-hesitant [128].

Studies that were conducted across different continents and that assessed the intention of caregivers towards vaccinating their children found that mothers and caregivers with children who are chronically ill were more hesitant towards vaccination. The groups of caregivers identified as more willing to vaccinate their children were fathers, people with children without a chronic disease, people with children who were regularly vaccinated, and people who had older children. The caregivers were mostly concerned with the novelty of the vaccine, while those who were affirmative towards vaccination were choosing this option to protect themselves and their children.

4. Discussion

This review explored the attitudes and hesitancy/acceptance associated with a COVID-19 vaccine among a variety of populations from a diverse set of geographical and cultural contexts. Overall, vaccine hesitancy rates ranged widely among different populations, across different countries and different time-points. Data from a single country could report variable results depending on the time when the survey was conducted, the surveyed population, and even depending on the geographical region/city that was surveyed. All these factors should be taken into account when translating these research data into specific policymaking interventions. A variety of themes contributing to high rates of hesitancy emerged, including

concerns relating to vaccine efficacy, safety, side effects, convenience, price, beliefs that the vaccine is not necessary, that the testing for the vaccine was insufficient and that the pace of its development was too quick, as well as the financial motivation of the authorities/pharmaceutical companies. Interestingly, in some studies, the willingness of people to be vaccinated has increased when they were offered to wait some more time until they receive the vaccine. The main barriers that contributed to vaccine hesitancy in the reviewed studies and were identified as the most frequent ones were the fear of the safety and side effects of the vaccine, its effectiveness, and the fast pace of the development, compared with other vaccines. On the other hand, themes that emerged contributing to positive attitudes toward the vaccine and/or high rates of vaccination uptake and were identified as the most frequent ones in the reviewed studies, included having higher trust in public health authorities and medical professionals, the participants' desire to return to normal life and to protect themselves and children and others and perceiving themselves as being in a high-risk group of severe COVID-19 consequences.

Upon the COVID-19 outbreak across the world, it quickly became evident to researchers and health professionals that the only tool to combat this disease may be to build herd immunity. Given its high infectiousness, a large percentage of the population must be immune to COVID-19 to establish herd immunity [129–131]. As such, vaccinations are essential in speeding up this process. Indeed, huge scientific leaps and breakthroughs were witnessed in the development of a vaccine in a timely manner. However, this contributed significantly to increased hesitancy for the vaccine among a variety of populations in different countries across the world. This was alarming to many scientists and medical professionals, as it is a possibility for vaccine hesitancy to become a limiting factor against the development of herd immunity worldwide [132]. However, and as exemplified by the results of this review, certain populations may be more vulnerable in the future for COVID-19 strictly due to low vaccination rates. Identifying the factors that interplay and result in high hesitancy rates among a population can allow formulating a directed intervention to increase their vaccination uptake rates.

Studies included in this review showed similar trends when identifying populations that are most vulnerable to being insufficiently vaccinated due to high hesitancy. Themes identified to contribute to high hesitancy were most prominently associated with certain socio-demographic variables. Such variables included income (e.g., being low-income population), age (e.g., younger patients were more hesitant, partially as they perceived being at lower risk compared to elders [69,74,79,80,96,149]), education (e.g., having a lower education degree [69,71,96,97,101,102,146,148,150,152]), area of residence (e.g., those in rural areas were more hesitant [69,101,149]), reported race and/or ethnicity (e.g., those who identified as minorities [38,69-71,75,77,78,103,149,151]). Interestingly, studies that included specific populations (such as patients with different health conditions) generally observed a lower intention to vaccinate among them compared with the general population. Although people with a chronic disease are at a higher risk of severe COVID-19 consequences, these data suggest that these groups need additional information about the impact of immunization and the coronavirus infection on their health status [58,108].

Those socio-demographic variables that were associated with low rates of vaccination uptake were consistent among a variety of geographical contexts and populations. Consequently, this review highlights the need to address such demographical variables and direct intervention measures and policymaking efforts. Targeting those variables could result in a decrease in the level of hesitancy among such vulnerable populations where rates of vaccination could be very limited, and hence promote herd immunity among them and improve COVID-19 related health outcomes.

Furthermore, given that the current vaccines on the market differ drastically by their mechanism(s) of action (e.g., mRNA-based

vaccines vs. genetically engineered pathogens), the different mechanism in which a vaccine work may have influenced people's opinion on it and hence hesitancy levels. Our systematic review does not address hesitancy differences specifically based on the differences in how current vaccines work, however, our systematic search did identify several studies that addressed people's preferences over different vaccine candidates [56,133]. Additionally, our systematic review identified the information regarding vaccine's safety and efficacy as the main barriers/motivators determining peoples' willingness to vaccinate, and although one Denmark survey observed a decrease in the perception of Astra Zeneca vaccine's safety (compared with the one produced by Pfizer BioNTech) after the thromboembolic events associated with this vaccine candidate, the rate of willingness to vaccinate [87] was sustained even after this published data [116]. Thus, these results suggest that the role of the type of vaccine candidate in hesitancy is actually a complex question and it should be addressed by future research to better inform policymaking.

The findings of this review, based on studies conducted across the globe, exemplify the urgent need for policymaking to address factor (s) that promote hesitancy towards vaccinations. Additionally, policies should continue focusing on positive themes that emerged encouraging high vaccine uptake. For instance, further emphasis should be placed on informing the public, especially the less educated populations and those based in rural settings, about the rigorous process of vaccine development and approval by the drug administration authority entities. One study included in the qualitative synthesis actually highlights the importance of such interventions after observing an increase in the willingness of cancer patients and their caregivers to vaccinate after attending an education webinar. A common theme that emerged contributing to high hesitancy rates was the belief that the speed in which the vaccine developed translated to it being less safe. This was also evident from several surveys where higher willingness was observed in the case where participants had the option to wait until receiving the vaccine. Among the scientific community, it is known that the rigorous nature of the approval process for any COVID-19 vaccine was not compromised on the expense of time [5]. Such understanding should be adequately passed to the public, mainly using health communications techniques on a variety of media platforms as well as by utilizing community leaders and influential characters within a given community. Furthermore, health communication must be employed to ensure individuals are aware of their perceived risk of the disease. Promoting vaccination uptake with a positive-sounded attitude regarding protecting oneself as well as the elderly and those most vulnerable may contribute to increased acceptance. This is particularly the case among younger populations, as they have been identified to be more hesitant in many studies in this review.

Moreover, the necessity of the vaccination to achieve herd immunity and return life to normal should be adequately stressed by policymakers and government entities. Many studies reported that participants who expressed hesitancy usually did not believe that the vaccine is necessary to combat the pandemic. Additionally, individuals in low-income settings [38,78,147], racial and/or ethnic minorities, and those with lower education were identified as more hesitant sub-populations. In the context of healthcare, it has been shown that minority populations, as well as those from low-income communities, express cultural strength and are more compliant to healthcare regulations when faced by a provider of their same cultural and/or community context [134]. Consequently, diversification and accessibility among all communities should be promoted by government entities across the world, including the provision of healthcare providers and workers of a given cultural context in identified vulnerable areas. Furthermore, the issue of mistrust with authorities has been shown to play a drastic role in guiding people's inclinations towards accepting a vaccine. More specifically, the internet and different forms of social media used in our world today have not only allowed

for rapid and ubiquitous sharing of information, but also of misinformation. While the availability of such information plays a role in mistrust development, other factors have also been identified. These include perceptions of knowledge and expertise, openness and honesty, and concern and care [135]. Additionally, the perceived trustworthiness of the messenger plays a major role in developing trust or not [135]. The latter factors are significant in countries where the public does not have a developed trust with the authorities. These factors, from a policy-making perspective, must be considered in order to address them and enhance public's trust in order to address vaccine hesitancy [136].

This review provides a high level of evidence by synthesizing the variety of research published in the literature regarding vaccine hesitancy and uptake. This study is meant to provide sheer evidence regarding the factors that contribute to decreased willingness of accepting the vaccine or increased hesitancy, to better direct intervention measures and policymaking. To date, very few studies have reviewed the evidence in the literature regarding the topic. However, this review provides the advantage of including the most recent studies published following the public distribution of the vaccines. Additionally, it covers a wider range of outcomes, inspects socio-demographic relationships with hesitancy and acceptance outcomes, includes only peer-reviewed articles as the source of information of high quality, and includes a wider scope of studies and populations. To establish herd immunity and combat the pandemic to normalize life again, intervention targeting vaccine hesitancy is required in a timely manner. Themes identified in this review from studies conducted all over the world should be a target of intervention to improve the health outcomes of vulnerable population and ease the world from the current state of a pandemic.

Albeit those strengths, it is important to note that this review is not without limitations. Firstly, the majority of studies included in this review were cross-sectional. Cross-sectional studies are usually unable to establish causation as they collect data at a given snapshot of time [137–139]. Given that vaccine development and knowledge is a rapidly evolving process around the world, results may change at a future date following a given study's data collection period. Partially, this may explain a minor inconsistency in the results of some studies reporting data from the same country and/or population. Furthermore, all studies utilized self-reported surveys as their main data collection method. Inherently, this approach is most suitable at the given time as such studies are measuring the subjective perception of individuals in a population. However, it is important to note that self-reported surveys have a number of limitations including social desirability bias and recall bias [140–142]. Moreover, the selected studies in this review are subject to volunteer bias, where participants who actively decide to participate in the research may systematically differ from the general population [143]. Furthermore, our systematic search did not capture the studies that specifically addressed the influence of social media on people's intention to vaccinate, such as the study conducted in the UK [144] and in the US [145]. However, it did identify one survey that included adults as representatives of social media users and found a surprisingly high vaccine acceptance rate among this population, which might not reflect the real picture related to this issue. Thus, future systematic reviews that will aim to address the problem of hesitancy associated with COVID-19 vaccine should take these studies into consideration as well when designing their search criteria. The graphical presentation reflecting vaccine acceptance rates worldwide failed to capture the heterogeneity in the intention of people to vaccinate in countries with diverse populations (such as the US). Thus, our review points to the need for future studies that should focus on collecting vaccine hesitancy/acceptance rates data from individual subdivisions from larger countries, in order to draw a more coherent and accurate conclusion regarding this issue.

Finally, it should be noted that the motivators and barriers for positive/negative vaccine uptake should represent a general framework for the future policy makers. Given that the countries included in the reviewed studies represent a diverse set of different governmental, healthcare, and social systems, the factors identified in this review should be adapted to the hesitant population defined by their socio-demographic variables.

This review sought to capture the current evidence in the literature regarding the factor(s) that contribute to vaccine hesitancy across a variety of populations in different cultural and geographical contexts. Given the exceptionally high burden of disease for COVID-19, urgent interventions and policies targeting the identified factors are necessary to decrease hesitancy for a COVID-19 vaccine. Targeting vaccine hesitancy is necessary to establish herd immunity worldwide and normalizing life with COVID-19.

Contributors

All authors contributed to revise work for important intellectual content, gave the final approval of the version to be published, and agreed on all aspects of the work, especially concerning its accuracy and integrity. Further specific activities have been distributed as follows: F.C. conceived the research hypothesis. F.C. and W.R. designed the study. A.P., YA-A. and G.F. performed the articles screening, the data extraction and quality assessment. Similarly, A.P., YAA and G.F. accessed the raw data. F.C. has shaped the manuscript with input from the entire team (written contributions of single paragraphs).

Data sharing statement

The authors declare that the data collected was gathered from publicly available databases and is available upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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