Covid-19 Pandemic and its Impact on Vaccine Hesitancy: Is it a Big Elephant in the Room?

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Received: 16 April 2024

Accepted: 10 June 2024

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DOI 10.5001/omj.2024.103

Abstract

Vaccination is one of the most effective public health initiatives in human history at considerably lowering the prevalence of infectious diseases. To ensure the success of vaccination programs, numerous measures should be conducted, including effective leadership, funding, distribution management, and addressing vaccine hesitancy. The delay in accepting or declining vaccinations despite the availability of immunization services is known as vaccine hesitancy. Anti-vaccine sentiment has always been seen, but recently, its reflection on society has become more evident during the Covid-19 pandemic period. A number of factors contribute to vaccine reluctance, such as personal views or worries about the efficacy and safety of vaccines. One major problem in the success of the Covid-19 immunization program is indeed vaccine reluctance. Anti-vaccine activists have gained momentum to spread rumors, propaganda, and conspiracy theories during the Covid-19 pandemic. Thus, the Covid-19 pandemic may have a significant impact on vaccine hesitancy, which influences the general acceptance of other available vaccines. This literature review will discuss vaccine hesitancy and its trend during and after the Covid-19 pandemic. We particularly mention the reasons for Covid-19 vaccine refusal and what can be done to address vaccine hesitancy in the future.

Keywords: Anti-Vaccine; Covid-19 Vaccine; Hesitancy; Pandemic; Vaccine.

Introduction

Coronavirus disease 2019 (Covid-19) become the most devastating public health issue in recent years. From January 1, 2020, until December 31, 2021, a total of 5,940,000 deaths due to Covid-19 were reported globally.[1] Besides wearing masks, social distancing, and other preventive strategies, the Covid-19 vaccines have become one of the preventive measures for SARS-CoV-2 infection.[2] The availability of the Covid-19 vaccines helps to curb the pandemic. The Covid-19 vaccines, including Oxford-AstraZeneca, Moderna, Janssen, and Pfizer-BioNTech vaccines, have approximately more than 80% effectiveness in preventing SARS-CoV-2 infections within 12 to 42 days post-vaccination, even though the level of effectiveness declined by 112 days following vaccination.[3] However, booster vaccines could recover the effectiveness of Covid-19 vaccines during 0-3 months after the booster shot.[4] Moreover, a systematic review found that the Covid-19 vaccine is cost-effective in overcoming the pandemic.[5] In spite of the benefits of Covid-19 vaccine, hesitancy in receiving the vaccine have become a concern due to misinformation.[6]

Many efforts should be made to succeed in vaccination programs, for instance, efficient leadership, vaccination workforce, service delivery, financing, distribution, and addressing vaccine hesitancy.[7] From those measures, vaccine hesitancy has become a prominent issue because of its difficulty to tackle. A qualitative study from Germany revealed that people did not accept the Covid-19 vaccine because of its rapid development and emergency approval. They worried that the vaccine research and development were not well conducted.[8]

Similarly, research in the Philippines found that people were doubtful if the vaccine development was only in months since it usually needs a very long-term period.[9]

This literature review will discuss vaccine hesitancy during the Covid-19 pandemic and its impact during the Covid-19 vaccination era. Following the Covid-19 era, vaccine hesitancy appears to be on the rise due to widespread misinformation and conspiracy theories about vaccines that emerged during the pandemic. We particularly mention the reasons for Covid-19 vaccine refusal and what can be done to address vaccine hesitancy. Healthcare workers need to be thoroughly trained in addressing vaccine hesitancy to prevent decreased vaccination coverage in the general population.

Definition and determinants of vaccine hesitancy

According to the Strategic Advisory Group of Experts on Immunization (SAGE) Working Group in 2014, vaccine hesitancy is defined as "delay in acceptance or refusal of vaccines despite availability of vaccination services".[10] Even people or parents who vaccinate themselves or their children also could be hesitant in deciding for vaccination. For instance, they are still afraid of the adverse events of vaccines after making those decisions.[11] Many aspects impact vaccine hesitancy, such as confidence, complacency, convenience, and confidence, which are called "the vaccine hesitancy models". Confidence issues include the vaccine's safety and effectiveness. Complacency is influenced by whether the immunization program is successful or not. While convenience is affected by the accessibility and affordability of the vaccines.[10]

In addition, according to the working group determinants of vaccine hesitancy matrix, there are three categories which may influence vaccine hesitancy. They are (1) contextual, (2) individual and group influences, as well as (3) vaccine- or vaccination-specific influences. Contextual influence is related to socio-cultural issues. Individuals and groups influence knowledge and attitudes toward health. Vaccine- or vaccination-specific issues influences cover all about vaccines, for instance, risk and benefit, schedule, and costs.[10] As an example of the third determinant, there was anxiety among the public regarding thimerosal in the measles, mumps, and rubella (MMR) vaccine as the cause of autism in the 1990s. Consequently, in 1999, the United States Public Health Services and the American Academy of Pediatrics (AAP) recommended to remove thimerosal in childhood vaccines although there was no evidence that thimerosal caused autism.[12] Accordingly, a recent study from Saudi Arabia reported that concerns about side effects are the most frequent reasons or barriers to receiving shingles vaccines.[13]

In some countries or regions, vaccine coverage was associated with religion or other personal beliefs. During the past two decades in the Netherlands, there were epidemics of measles, mumps, rubella, and poliomyelitis in the Bible belt area where Orthodox Protestants reside. They did not receive vaccines due to religious concerns.[14] There is also the Bible belt area in Canada, where a mumps outbreak occurred in February-October 2008.[15] In Pakistan, there is a conspiracy theory that polio vaccination is an effort of Israel and the United States (US) to eradicate the Muslim community.[16] During the year 2003, religious Muslim leaders in northern Nigeria banned polio vaccination among children since they believed that the vaccine could lead to cancer and infertility, as well as could spread human immunodeficiency virus (HIV).[17]

Various religious-based concerns are also associated with vaccine hesitancy. Research among Muslim communities and leaders in Guinea showed that fasting during Ramadan becomes the reason for vaccine hesitancy since anything is banned from entering the body during fasting. Moreover, they did not want the adverse events to break the fast.[18] There is a difference in intention for vaccination between religions since a study in Israel found that Jewish mothers tend to allow their children to get the human papillomavirus (HPV) vaccines than Muslim mothers.[19] Among 15 countries in Sub-Saharan Africa, nine countries had lower coverage of childhood immunization in Muslim families than Christian families. This situation could be associated with higher health literacy in those societies.[20] In Indonesia, parents rejected immunization since they believed the vaccine is *haram* or not allowed by Islam. The pig-related substance in vaccines makes vaccines haram, as Islamic law forbids Muslims to consume pork.[21] Religious and community leaders in Yogyakarta, Indonesia argued that *halal* certification or permission from Islamic law was needed for acceptance of rotavirus vaccine.[22] To address this issue, an example effort from a vaccine manufacturer in Indonesia, Bio Farma, has produced halal vaccines. Thus, it could be distributed to other Muslim countries. However, producing halal vaccines is not easy because most of the vaccine components are from non-Muslim countries, which do not really comprehend about halal terminology.[23]

Prevalence and reasons of vaccine hesitancy against Covid-19 vaccines

Vaccine hesitancy has a notable impact on the Covid-19 pandemic. Vaccine hesitancy and loose public health interventions lead to an increment of mortality about 7.6 times.[24] A regression model by Dhalaria *et al.* revealed that an increase in percentage of vaccine hesitancy could decrease about 30% of vaccine coverage in India.[25]

During the period of 2021, a study about vaccine hesitancy towards Covid-19 vaccines in 23 countries reported that vaccine hesitancy declined globally from 28.5% in June 2020 to 24.8% in June 2021. Yet, Russia, Nigeria, and Poland still had high levels of vaccine hesitancy, about 48.4%, 43%, and 40.7% respectively.[26] In line with this report, widespread vaccination programs in the US and approval of Covid-19 vaccines from regulatory authorities decreased vaccine hesitancy in all demographic categories from October 2020 until March 2021, particularly among those who are Black and Hispanic. Previously, these two groups had low Covid-19 vaccination acceptance rates.[27] Not only among the general population, a number of 3,295 healthcare workers in 23 countries also experienced vaccine hesitancy, with physicians having the lowest hesitancy level.[28] The side effects and safety of vaccines became common reasons for vaccine hesitancy among healthcare providers.[29] The occurrence of adverse events could be different among various vaccine types.[30] Hence, this issue must be addressed strategically to target all populations.

Studies about Covid-19 vaccine hesitancy have been conducted in many countries. A cross-sectional survey from China in March 2020 showed that among 1,879 participants who accepted vaccines, 47.8% delayed getting them until they confirmed that the vaccines were safe.[31] During September-October 2020, an online survey in the UK using the Oxford Covid-19 vaccine hesitancy scale described that among 5,114 adults, 11.7% had a strong hesitancy. The factors contributing to vaccine hesitancy include the side effects and the speed (accelerated) development of Covid-19 vaccines during the pandemic crisis.[32] Meanwhile, during the second wave of Covid-19 in Indonesia in 2021, a cross-sectional study from Malang (East Java) found that 60.2% of 3,014 adult participants had hesitancy towards Covid-19 vaccines. The major reasons were also the vaccine development speed and side effects.[33] A systematic review of observational studies in Nigeria elucidated that the acceptance rate of Covid-19 vaccines was below 60% due to concerns about vaccine safety and efficacy as well as socio-demographic factors.[34]

Socio-demographic factors, for instance low education level, were associated with more hesitancy.[35] Women were more hesitant because they worried about side effects, safety towards breastfeeding and pregnancy, and the effect on fertility.[36,37] Government mistrust was also related to reluctance to receive the Covid-19 vaccine in Nigeria.[38]

Furthermore, according to a study in Nigeria, some people argued that Covid-19 is a biological weapon to decline the population by having microchips inside the vaccine. Also, vaccines could alter human DNA and cause danger to the human body. Meanwhile, others believed that Covid-19 happened because God was angry, and it is a sign of the end time.[39] Government mistrust also influences Covid-19 vaccine acceptance. Among a study population in Nigeria, the Covid-19 vaccine acceptance rate was 28.2%, and 56.8% of study participants did not trust the government.[40] Some people believed that the government only used the vaccine as a tool to make money from the public, and foreign just wanted to take advantage of the money.[39]

The internet has a role in spreading anti-vaccination issues. According to search results about vaccination on American websites in 2009, 24% were anti-vaccination sites. An example of the website's contents was vaccines consisting of mercury, formaldehyde, and other toxic substances.[41] The Web 2.0 era makes anti-vaccination spread easily by enabling people to create abundant content online via blogs or social media. Strategies of the anti-vaccination group include supporting flawed research that supports the anti-vaccination movement and developing new theories that vaccines are dangerous.[42] The Centre for Countering Digital Hate (CCDH) reported that anti-vaccine accounts had widespread support, with 31 million Facebook followers and 17 million YouTube subscribers. Furthermore, people using social media to gather information were more doubtful to get vaccine.[43]

In the past, anti-vaccine movements have used narratives such as, "vaccine is more dangerous rather than the disease itself", "vaccine is useless", or "vaccination causes fatal disease".[44] Regarding the Covid-19 pandemic, they still use the same campaign, for instance, "vaccine is pointless", "Covid-19 is a big lie", and "Covid-19 is a staged".[45] They are spreading these narratives to reduce the confidence of the general population in the safety of Covid-19 vaccination.

Acute hepatitis outbreaks of unknown origin in children and its effect on Covid-19 vaccination

As previously mentioned, one main reason of vaccine hesitancy is fear of side effects or safety concern. Several recent studies found a very rare adverse events associated with Covid-19 vaccines. The Global Vaccine Data Network cohort study identified rare safety signals for Guillain-Barré syndrome (GBS) and cerebral venous sinus thrombosis (CVST) after viral vector-based vaccines (AstraZeneca) as well as myocarditis and pericarditis after mRNA-based vaccines (Pfizer and Moderna).[46] Another study documented a possible association with acute disseminated encephalomyelitis (ADEM) and transverse myelitis with both viral vector and mRNA vaccines.[47] These rare adverse events are often highlighted to undermine confidence in vaccine safety. One example is taking advantage of the acute and severe hepatitis outbreak of unknown origin in children during the Covid-19 pandemic to fuel anti-vaccine propaganda.

In the mid of the Covid-19 pandemic, as of April 27, 2022, about 191 probable cases of severe acute hepatitis with unexplained etiology have been reported from 15 countries, 17 of which required liver transplantation.[48] While health authorities have been examining the possible etiology of the outbreaks at that time, antivaccine activists and conspiracy believers have already disseminated false and misinformation on their websites and social media. They accuse Covid-19 vaccines as the cause of this upsurge in acute hepatitis outbreak.[49,50] They cited a scientific article published in the *Journal of Hepatology* reporting the development of bimodal episodes of autoimmune hepatitis (AIH). Each episode occurs after having the first and second doses of BNT162b2 mRNA vaccine.[51] This definitely has fueled speculation for the general population to link the outbreak of acute hepatitis (liver inflammation) with the Covid-19 vaccine rollout in children aged 5 to 11 years old.[49] This phenomenon potentially influences the efforts to control the Covid-19 pandemic.[52]

An initial case report described the development of AIH following the administration of Pfizer-BioNTech BNT162b2 mRNA vaccine in her third month post-partum.[53] Subsequently, a number of case reports and case series illustrated AIH cases following Covid-19 vaccination using different platforms, including mRNA (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) and adenoviral vector (ChAdOx1 nCov-19 Oxford-AstraZeneca) vaccines. These cases occurred in persons with and without pre-existing medical conditions.[54] Another piece of evidence came from a case of AIH with a rapid onset of liver injury after the first dose of Moderna vaccine. It led to acute, severe AIH after re-exposure during the second dose.[55] It is suggested that molecular mimicry between the Spike protein of SARS-CoV-2 and human tissues is the potential mechanism underlying the pathogenesis of the Covid-19 vaccine-induced AIH.[56] Indeed, Boettler *et al.*[51] obviously demonstrated the involvement of SARS-CoV-2 Spike-specific $CD8^+$ T cells in mediating the development of vaccine-associated AIH.

A systematic review and meta-analysis study estimated the worldwide incidence and prevalence of AIH at approximately 1.37 and 17.4 per 100,000 persons, respectively.[57] Owing to this low background incidence, AIH was not readily recognized during the previous clinical trials of various Covid-19 vaccine platforms. As hundreds of millions of people are getting Covid-19 vaccines globally, reports on AIH following Covid-19 vaccination could be increasing. The phase four post-marketing surveillance is ongoing to determine whether Covid-19 vaccines truly increase the incidence of AIH above its previous background level. Although more detailed clinical and epidemiological investigations are required to conclude the causal association, AIH is currently recognized as one of the rare cases of adverse events following Covid-19 vaccination. However, it is pivotal to emphasize that the benefits of Covid-19 vaccination to curb the pandemic are much higher than the potential risks of its (rare) adverse events. Thus, this recent paper does not deliberately promote vaccine hesitancy.[51] Numerous clinical reports in scientific papers on AIH following Covid-19 vaccination clearly demonstrate that scientific communities never withhold any potential adverse events following vaccination as long as they follow a valid research methodology. This is in apparent contrast to the believers of conspiracy theories claiming that the government and health authorities cover up the "true information" about the endangerment of vaccines.[41]

One of the most frequent tactics of antivaccine activists is "skewing the science". On the one side, they would reject scientific evidence showing the benefits of vaccination or those against their position, beliefs, and agendas. On the other side, however, they incorrectly promote scientific evidence that could be exploited to boost their ideas.[42] Definitely, Boettler *et al.*[51] presented a case report and provided an insight to the immune correlates of Covid-19 vaccine-induced AIH. However, this paper clearly did not associate the hepatitis outbreak with the Covid-19 vaccines. Based on the currently available clinical, epidemiological, and laboratory data, the leading hypothesis of the outbreak is an infectious origin of an unidentified viral pathogen and not autoimmunity.[58] Most importantly, those antivaccine activists covered up the fact that most affected children were unvaccinated against

Covid-19 since they were not yet eligible.[49] Thus, there is no reason to blame Covid-19 vaccines as the potential triggers of the upsurge in severe hepatitis cases. Similarly, there is no reason to allege adenoviral-based vaccines as the culprit of the recent mysterious outbreak.

The pediatric population is the target for Covid-19 vaccinations to acquire herd immunity against SARS-CoV-2. Conspiracy theories and misinformation about Covid-19 vaccines, together with the hepatitis outbreak, pose a threat to international efforts to combat the Covid-19 pandemic. Of note, conspiracy theories are more likely to emerge during times of (public health) crises. Health experts and government agencies should dispel any doubts regarding its connection to the Covid-19 vaccine in children by providing the public with clear and succinct facts.

The impact of Covid-19 pandemic on vaccine hesitancy

As mentioned in the previous section, vaccine hesitancy has influenced the preventive measures to control Covid-19 cases through mass vaccination. Due to massive misinformation and propaganda of conspiracy theories during the pandemic,[52] it is interesting to gather information on how it may influence vaccine hesitancy during and after the Covid-19 pandemic, not only to Covid-19 vaccines, but also to other childhood vaccines.[12] Google search analyses showed that common anti-vaccine terms, including "mercury" and "autism", were significantly increased.[59] Vaccine hesitancy is indeed becoming an important issue, as shown by a marked increase in scientific articles on the theme of vaccine hesitancy since the beginning of the Covid-19 pandemic.[60] A meta-analysis of 12 published studies showed that the pooled prevalence of hesitation towards childhood immunization throughout the Covid-19 pandemic was 18.5%.[61]

Since the start of the Covid-19 pandemic, a recent study examined the quantitative shifts in parents' hesitancy to children vaccinations.[62] Of the 310 parents of children aged 0 to 17, 11%, 12%, and 13% said that since the start of the Covid-19 pandemic, childhood immunizations were less vital, less safe, and less effective. In areas with poor Covid-19 immunization coverage, there was a greater prevalence of the perception that childhood vaccinations were less effective. In addition, this study also reported that 17%, 12%, and 16% of parents had more negative trust in health advice from the government, health professionals, and pharmaceutical firms, respectively.[62] Another study demonstrated that amidst the Covid-19 pandemic, there was a little but statistically significant rise in childhood vaccine hesitancy as measured by a vaccine hesitancy scale (VHS) scores, most commonly due to increased risk perception.[63] All these findings suggest that negative beliefs about childhood vaccination were affected by the Covid-19 pandemic.

It is noteworthy to note that parents' desire to vaccinate their children may depend on parents' perception about the severity of Covid-19. For instance, when an online poll was done when the Covid-19 pandemic began, parents' intentions to to give their children an influenza vaccination increased by 15%. Fear that their child would get Covid-19 was one among the variables influencing their decision to switch to vaccinations.[64] There was also an upward trend recorded in Saudi Arabia, where 47.3% of parents intended to vaccinate their kids against influenza the next year, up from 29.8% the year before.[65] A meta-analysis study also supported the considerable rise in parental enthusiasm to vaccinate their children against the seasonal influenza virus.[61]

Call for action: what can be done to address vaccine hesitancy in the future?

SAGE Working Group believed that addressing vaccine hesitancy cannot be done with only one strategy. Efforts to improve vaccine uptake are increasing awareness about vaccination, making better access to vaccination, involving religious and community leaders, and making vaccines mandatory.[10] Vaccine ambassadors could be a strategy to increase awareness, like in San Fransisco, which used the "Motivate, Vaccinate, Activate" campaign to promote the Covid-19 vaccine.[66] A study in low and middle-income countries (LMICs) stated that most participants would trust healthcare providers to decide on getting the Covid-19 vaccine. This suggests that health professionals have a crucial role in overcoming vaccine hesitancy.[67]

One of the examples of improving vaccine access is the recommendation to provide Covid-19 vaccines in jails. Yet, collaboration with health authorities was highly required.[68] The role of faith-based organizations successfully increased Covid-19 vaccine awareness in India by giving brochures for communities to counter vaccine misinformation. Religious leaders, such as "Imam" in the Muslim community, also helped to provide sharing sessions about Covid-19 vaccines post-Friday prayers at the mosque.[69]

In addition, the compulsory Covid-19 vaccine certification could improve vaccine uptake.[70] A Twitter survey conducted after the announcement of mandatory Covid-19 vaccination in Austria in 2021 found that 45.7% of 2,545 respondents did not support that policy.[71] Similarly, a study in the French population also revealed that 41.9% of 3,056 participants refused the mandatory Covid-19 vaccination.[72]

In addition, there is a "5Cs" strategy to overcome vaccine hesitancy: confidence, complacency, convenience, communication, and context. "Confidence", "complacency", and "convenience" are the same concept with SAGE Working Group.[10] Meanwhile, "communication" refers to information about vaccines delivered to the community, and "context" includes factors of socio-demography.[73] It is paramount to communicate vaccine information clearly; otherwise, bad communication can result in vaccine hesitancy.[10]

Social media can be used by the government to interact with the public and disseminate the Covid-19 information.[74] Along with effective communication, counteraction to anti-vaccine sentiment should be conducted. For example, social media companies made efforts not to foster anti-vaccination in 2019. Ads were deleted on YouTube videos of anti-vaccine movements; thus, the account did not earn money. When searching for vaccine-related information on Twitter in the US and the UK, the National Health Service and the Department of Health and Human Services came up as the top results. Any anti-vaccination profiles were not suggested by Facebook.[43]

Conclusion

Vaccine hesitancy has been rising since the first introduction of smallpox vaccination programs. During the Covid-19 pandemic, vaccine hesitancy influenced the rate of Covid-19 vaccine acceptance. After the Covid-19 era, it seems that the issue of vaccine hesitancy is increasing due to massive misinformation and conspiracy theories regarding the vaccines during the pandemic. Conspiracy theories are more likely to emerge during times of public health crises. Thus, health experts and government agencies should provide the public with clear and succinct facts of vaccination. More comprehensive studies are needed to examine the trend of hesitancy after the Covid-19 pandemic.

Indeed, we have to put our effort to address this issue to prevent decreased vaccination coverage that may impact the burden of vaccine-preventable disease. Healthcare workers should be well-educated on addressing vaccine hesitancy in the general population. Social media can be used to interact with the public and disseminate vaccine information. Thus, a strong and continuous collaboration between the government, international and national health authorities, academia, healthcare workers, and the community in general is highly required to maintain successful vaccination programs after the Covid-19 pandemic.

Declarations

The authors declare no conflict of interest.

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