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COVID-19: Cross Reactive Immunity, Herd Immunity, and Convalescent Serum Therapy

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Objective: To present various types of vaccines and viral infections which can induce cross-reactive immunity against COVID-19. In addition, this article discusses the role of herd immunity and convalescent serum therapy in preventing and controlling SARS CoV-2. The study also determined the claims and counterclaims about their protective and therapeutic effects.
Method: Non-systematic review was done using different articles done on cross-reactive immunity against COVID-19 through vaccinations, previous infections, herd immunity and the therapeutic effects of convalescence serum. The search was done on the PubMed, Google Scholar, and Science Direct, WHO, Euro-surveillance, CDC databases.
Results: Many observational correlational studies reported that BCG decreases the incidence and mortality from COVID-19. Furthermore, homology between the COVID-19 virus and the measles, mumps, and rubella (MMR) viruses was discovered. Few studies suggested the presence of cross-immunity between MMR vaccine and SARS-CoV-2. Similarly, few studies suggested protective

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effects of Oral Polio Vaccine (OPV) against SARS-CoV-2; since both viruses are positive-single-strand RNA (+ssRNA). Diphtheria, pertussis, and tetanus (DPT) vaccines, particularly those that include inactivated whole pertussis vaccine, might induce B and T cell cross-reactive immunity against SARS-CoV-2. Other vaccines against Streptococcus pneumonia, Haemophilus influenza, and Meningococcal meningitis vaccines are suggested also to induce some immunity against Covid-19. It is hypothesized that infections with other Coronaviruses may cause protection against SARS-CoV-2. However, the studies done on these suggestions were mostly observational that can carry a high chance of inherent biases. There are also claims and counterclaims about the effect of herd immunity and convalescence serum on the prevention and control of Covid-19. So, appropriately designed RCTs are needed to prove or disprove their protective and therapeutic effects.

Conclusions: There are claims and counterclaims about the protective effects of different vaccines, previous infections, and herd immunity and regarding the therapeutic effects of convalescence serum. Comparing with other vaccines, BCG was suggested to have the highest cross-reactive epitopes against SARS-Cov-2 virus. MMR, OPV, DPT, Influenza, Pneumococcal and meningococcal vaccines are suggested to protect against Covid-19. Previous infection with other Corona viruses, herd immunity and convalescence serum may play roles in the prevention and control of Covid-19. Many large clinical trials are undergoing nowadays and their results are needed to prove or disprove the cross-immunity related to SARS-CoV-2 and the effect of convalescence serum.

Keywords: SARS-CoV-2; COVID-19; cross- reactive immunity; childhood vaccination; infections; herd immunity; convalescence serum.

1. INTRODUCTION

COVID-19 pandemic becomes the biggest global crisis in the recent years [1,2]. SARS-CoV-2 (causing Covid-19) was classified as a pathogen with Risk Group 3 as it carries considerable risk to the community due to its effect on life, health, and the global economy. Covid-19 has been declared as a pandemic disease by the WHO on March 11th, 2020. The rapidly evolving global pandemic has affected almost all systems during this crisis. It presented undue challenges on all stakeholders to go online in such time constraints and resource restraint circumstances [1,2,3].

SARS-CoV-2 is structurally similar to SARS-CoV and the Middle East Respiratory Syndrome (MERS-CoV). SARS-CoV-2 is a zoonotic enveloped virus with a positive-sense single-stranded RNA (+ssRNA) belongs to genera Beta-coronavirus under the Coronaviridae family [1]. SARS-CoV-2 spread exponentially to more than 200 countries [2,4]. The pandemic has grown as the largest global catastrophe in the current years [5]. COVID-19 has a varying degree of severity ranging from non-symptomatic infections, mild upper respiratory tract infection, to a lethal disease presenting by severe pneumonia, acute respiratory distress syndrome and death [2].

Concerning the cross-immunity or reactivity, it is the ability to react with related ligands other than the immunogen. Some pathogens with pandemic potential have a previous history of infecting humans. Through *cross-immunity* an established pathogens may encounter individuals with partial immunity acquired from previous infections or vaccination with prior agent or circulating strains [6].

Regarding the herd immunity, it means the indirect protection from infection conferred to susceptible individuals when a sufficiently large proportion of immune individuals exist in a population. This population-level effect is often considered in the context of vaccination programs, which aim to establish herd immunity so that those who cannot be vaccinated, including the very young and immunocompromised, are still protected against disease [7]. Furthermore, As regards the use of convalescent plasma therapy, it is related to treat the patients with infections by using plasma collected from other recovered patients. This approach has been assessed for treating SARS, Middle East respiratory syndrome (MERS), and Ebola. The US Food and Drug Administration (FDA) recently approved the emergency use of convalescent plasma for patients with severe or life-threatening COVID-19. Although the use of convalescent plasma shows promise, the evidence supporting its use in the treatment of COVID-19 remains limited, and thus its use remains investigational [8].

The novelty of SARS-CoV-2 indicates that children are sensitized to the viral antigens even if there was no previous contact with the specific serotype of the new coronavirus [9]. Therefore, it has been postulated that childhood immunization may be attributed to the protection, mitigation of COVID-19 symptoms, and counteracts the infection via cross-immunization. It might be difficult to point out which childhood immunization is offering the proposed protection against COVID-19 [10].

Previous research had hypothesized that live vaccines lead to increasing the resistance to other unrelated diseases. It is hypothesized that vaccines increase immune responses, offering additional immunity to viruses other than those which are proposed to avoid. Research only suggested that there is a correlation between vaccines and non-specific responses, but didn't prove causation [5]. It is suggested that many available safe vaccines (including Bacillus Calmette–Guérin (BCG), Polio, Haemophilus influenza type-B (Hib), Measles, Mumps and Rubella (MMR), and pneumococcal may give substantial prevention from COVID-19 via a non-specific "innate immunity"[11[. Pawlowski, et al reported that recently vaccinated individuals with Polio, Hib, MMR, Varicella, PCV13, Geriatric Flu, or HepA-HepB vaccines have lower rates of COVID-19 infection [12].

Some reviews were done on specific types of vaccines. However, there is lack of comprehensive reviews done on different types of vaccines, previous infections and the therapeutic effect of convalescence serum and the effect of herd immunity. Thus, there is an urgent need for a comprehensive study in this area.

This paper aims to present various types of vaccines and viral infections which can induce cross-reactive immunity against COVID-19. In addition, this article discusses the role of herd immunity and convalescent serum therapy in preventing and controlling SARS CoV2. The study also determined the claims and counterclaims about their protective and therapeutic effects.

2. METHODS

The study was done through a non-systematic review of different articles done on the suggested Covid-19 cross-reactive immunity through childhood & other vaccinations, convalescence serum and herd immunity against COVID-19. The search was done on the PubMed, Google Scholar, and Science Direct, WHO, Euro-surveillance, CDC databases. The method of the review was done by articulation of the problem regarding Covid-19 cross-reactive immunity with the claims and counter-claims, accomplishment of a well-defined literature search and presentation of conclusions. The search included Covid-19, cross-reactive immunity, childhood vaccination, influenza immunization, convalescence serum and herd immunity.

3. RESULTS AND DISCUSSION

A total of 96 relevant articles were scrutinized, summarized and presented in 3 main domains with claim and counter-claims for each one.

3.1 Effects of Childhood and other Vaccinations on Covid-19

3.1.1 Bacillus Calmette–Guérin (BCG) vaccine

BCG vaccination is a live attenuated variant type, which is used routinely in some countries to prevent the complications from tuberculosis [13,14].

There is a controversial hypothesis (with claims and counterclaims) that the past BCG vaccination can reduce infection or severity of COVID-19.

3.2 Claims

BCG is known to induce a non-specific (off-target) effects or trained innate immunity against wide range of viral infections [13,14]. This effect is initiated by the enhancement of the production of pro-inflammatory cytokines such as Interleukin 1 beta (IL-1β) and tumor necrosis factor (TNF). This is done through epigenetic re-programming upon the exposure to unrelated pathogens [15].

One of the current big debate is about the role of BCG in the current evolving dilemma of Covid-19 pandemic. It was speculated that BCG might has a protective role in the immune defense against COVID-19. Comparing with other vaccines as MMR and Polio, and with the immunity that following infections with certain pathogens, BCG was suggested to have the highest cross-reactive epitopes against SARS-Cov-2 virus [16]. This can be justified by the finding of similar nine-amino acid sequences between BCG and SARS-CoV-2. Such closely-related peptides have a

moderately to high binding capacity for several common Human Leukocytic Antigen (HLA) class I molecules. These results proposing that cross-reactive T cells against SARS-CoV-2 could be generated by BCG vaccination [17]. Furthermore, the patients infected with SARS-CoV-2 have an excessive secretion of cytokines and thus increasing the disease severity and mortality, especially among patients with other co-morbidities. BCG can regulate such cytokines secretion and contribute to the development of trained innate immunity, and thus generating an early protection against the novel corona virus [18].

ACTIVATE study, a phase III randomized controlled trial (RCT), investigated the safety and the protection of BCG vaccination against several infections among elderly (2017 - August 2020). A single dose of BCG was given to the patients upon hospital discharge and followed-up for 1 year. Results found that BCG vaccination was safe and protected mainly against viral respiratory infections through innate and trained immunity. This study might indicate the potential effect protective effect of BCG. However, this needs to be proven via large RCTs [19].

Many recent ecological studies observed that countries mandating BCG immunization have lower incidence and death rates from COVID-19 compared to the nations without BCG [20]. For example, it was reported that the incidence of COVID-19 was about 0.8/million person in the countries with BCG immunization program compared to 34.8/million among those without such immunization. Similarly, the mortality rate as crude case-fatality rate were higher in countries without a BCG immunization program [21] compared to others. It was also suggested that BCG can slow down the spread of COVID-19 and resulting in lower contagion rate [22,23] and hence decreased the hospital admission24. Researchers from Egypt found a significant negative correlation between BCG coverage and both incidence and death rates from COVID-19 (using data of 183 countries) [25]. Similarly, another study reported that COVID-19 related mortalities were 5.8 times lower [95% CI: 1.8-19.0] in countries mandating BCG than others (after adjusting for country economics, proportion of elderly and the highest affected countries) [26]. In addition, there are several other studies reported also reduced COVID-19 mortality rates in countries with BCG vaccine [27,28,23,29,30,31,20,32-34]. It was also hypothesized that BCG immunization may decrease the severity of COVID-19 [35,36,37]. Akiyama and Ishida reported a significant association between the doubling times of the death toll between the countries with national universal BCG vaccination and those without. They also found significant differences in the death toll according to BCG strains that used in 42 countries applied BCG [38]. A recent systematic review, included 28 observational studies concluded that BCG vaccination can decrease the incidence and mortality from COVID-19. However, these results must be interpreted cautiously as lot of confounding factors (can affect the outcome) may be present in such studies [39].

3.3 Counterclaims Regarding the Effect of BCG on Decreasing Covid-19 Morbidities and Mortalities

All the above-mentioned studies suggested protective effects offered by the BCG vaccination against COVID-19. However, these observational studies were not confirmed by analytical designs. Arguably, the previous studies do not provide a strong proof of causality owing to many inherent biases and confounding factors such as the age proportion and the under-reporting of COVID-19 cases [40,41]. Furthermore, such observational studies used the same institutional databases with different statistical analyses and yielded different results [41].

For example, the same used database revealed that BCG vaccination was found to have no impact on COVID-19 incidence or mortality after controlling for some confounding factors. Shivendu, et al. reported protective findings of BCG when the Covid-19 testing was not considered. Conversely, such association disappeared when they added the element of testing. They concluded that there is no statistical evidence to support that inclusion of BCG vaccination in the routine immunization has any impact of COVID-19 cases or mortality, after controlling of such confounding factor [42]. Similarly, absence of significant association between BCG vaccination and COVID-19 rates were noted from another study, using the same used data from the previous observational studies, when the authors included only in the analysis the countries with high COVID-19 testing rates (> 2,500 tests / million inhabitants) [43]. These results magnifying the effect of “under-reporting bias” which might produce deceiving conclusions [44].

Similar results was achieved among people who were on the Diamond Princess ship where no significant difference was found between the rates of Covid-19 among passengers from nations with BCG and non-BCG obligatory vaccinations [45]. Meena, et al. reported absence of correlation between COVID-19 case-fatality rates and burden after controlling of many confounding factors as age [46]. They studied Covid-19 rates at three points of time. Similarly, Hamiel, et al. reported that vaccination with BCG within the childhood immunization program doesn't protect against COVID-19 during adulthood [47]. Furthermore, a cross-sectional study conducted among 123 patients diagnosed with COVID-19 pneumonia in Istanbul, Turkey, revealed that BCG vaccine was not significantly correlated to the severity of COVID-19. Instead, age and poverty remained the major actors for COVID-19 severity [48]. Li, et al. reported that at the same epidemic stage there was no difference in the severity of COVID-19 between BCG user and non-BCG user countries [8]. Finally, researchers from Sweden used a regression discontinuity approach to assess COVID-19-related incidence and hospitalization before and after BCG discontinuation for the newborn during 1975 (a drop of vaccination coverage from 92% to 2%). They confirmed that BCG vaccination at birth does not protect against COVID-19. However, this study did not account for the immigrants and inhabitants from other countries where BCG might be given following 1975 [49].

To conclude, the association between BCG and the protection from COVID-19 is currently a hypothesis; with a weak evidence. Studies about the potential protection of BCG are inconsistent. Therefore, it is logical to adhere to WHO's recommendation regarding the efficacy of the BCG vaccine on COVID-19. Appropriately designed RCTs are required to prove such a hypothesis [50]. Several RCTs are currently ongoing in the USA, Netherlands, Australia, France, South Africa, Greece and Egypt to assess whether BCG vaccine is capable to reduce incidence, morbidity and mortality from COVID-19 among health-care workers and susceptible patients or not. The trials ID are "NCT04348370, NCT04537663, NCT04327206, NCT04384549, NCT04379336, NCT04414267 and NCT04350931", respectively" [51].

3.4 Measles, Mumps and Rubella (MMR) Vaccine

MMR vaccine contains a single-stranded RNA virus. MMR is shown to have an intermediate-term of protection which might last to early adulthood [52]. Few studies suggested the presence of cross-immunity of MMR with COVID-19 [11]. In April 2020, a Cambridge Study identified homology between the COVID-19 virus and MMR viruses [53]. It was hypothesized that antibodies against measles may be cross-reactive with SARS-CoV-2. Sidiq, et al. also found a sequence similarity between the major structural proteins: Spike glycoprotein of the SARS-CoV-2 virus and the Fusion (F) glycoprotein of measles virus as well as the envelope (E1) glycoprotein of the Rubella virus [54]. Some evidence showed that the rubella virus has a sequence homology with a SARS-CoV-2 surface protein in about 29% [53]. Countries that had recent (booster) measles-rubella containing vaccines have few mortality rates from COVID-19. This finding can be noted from the aircraft carrier U.S.S. Roosevelt. All the new recruits on the aircraft must receive an updated MMR vaccination; regardless of their previous vaccination history. Among a total of 1102 people aboard who were tested positive for COVID-19, the lowest hospitalization rate was reported among them compared to the general population of the same age. One out of 955 COVID-19 positive sailors from the Roosevelt was only hospitalized [55].

3.5 Counterclaims Regarding the Effect of MMR Vaccine on SARS CoV-2

The previous observational studies might suggest weak evidence of the protective role of MMR against the poor outcome associated with the COVID-19. RCTs are still needed for further establishment of evidence MMR effect on COVID-19 incidence and outcome. Clinical trials to confirm the effect of MMR vaccine on SARS-CoV-2 are being conducted nowadays (Trial number: NCT04357028) [56].

3.6 Poliomyelitis Vaccine

Poliovirus (PV) is an enterovirus (EV) that belongs to the *Picornaviridae* family which can cause poliomyelitis [57]. Two types of polio vaccines are currently being used; Inactivated Polio Vaccine (IPV) and live attenuated Oral Polio Vaccine (OPV). Few studies theoretically suggested protective effects of OPV against SARS-CoV-2; since both viruses are positive-single-stranded RNA (+ssRNA) [11,57,58,59]. OPV has shown to be effective against respiratory and non-respiratory viruses including influenza and herpes as well as some bacterial

infections [59]. OPV seems to have a better immune response than IPV as it contains a live attenuated poliovirus. It was reported that countries that adapting only IPV vaccine have more cases and mortalities from COVID-19 compared to others that using OPV [57].

3.7 Counterclaims Regarding the Effect of Poliomyelitis Vaccine on SARS CoV-2

It was reported that PV vaccine has a poor effect for inducing cross-immunity to SARS-CoV-2 since they share scarce genetic homology [16]. An observational study, April 2020, found that PV vaccine is not attributed in COVID-19 protection [60]. However, this study did not stratify the data into IPV and OPV; as it rather generalized both polio vaccines. Furthermore, the effect of OPV is not tested extensively as done for the BCG vaccine. RCTs might be useful to understand its potential benefits. The USA, which is currently using IPV, re-introduced OPV in phase III clinical trials in November 2020 (OPV-NA831, ClinicalTrials.gov NCT04540185). Another trial in Guinea-Bissau will be done also to investigate the potential effect of OPV on COVID-19 (Trial number: NCT04445428) [58].

3.7.1 Diphtheria, Pertussis and Tetanus (DPT) vaccine

DPT vaccine is a part of childhood vaccination that contains 3 bacteria. "DTwP "w" indicates the whole-cell of inactivated pertussis or "DTaP" and "a" indicates the acellular Pertussis. Matching peptides were found between the DTaP vaccine and SARS-CoV-2. Sixteen peptides have been identified to match SARS-CoV-2 with DTP antigens, and 14 of which are in SARS-CoV-2 Spike protein (SARS-Cov-2 S) [16]. These peptides may probably interrelate to the same HLA-II molecules and might cause similar human immune reactions and cross-reactive responses [10]. Therefore, DPT vaccines, particularly those that include inactivated whole pertussis vaccine might induce B and T cell cross-reactive immunity against SARS-CoV-2. Letto, 2020, hypothesized that vaccines containing DPT could mitigate COVID-19 symptoms. It can stimulate the immune system and produce a dispersed immunity against non-self-antigens in transit (like SARS-CoV) and can stimulate the readier of the immune system to yield a specific immunity against SARS-CoV-2. It was proposed that the re-administration of the previous vaccines after the first contact with COVID-19 could enhance the CD4+ memory and boosting the immune system against coronaviruses until a specific immunity develops [9]. A possible description of the discrepancies between the frequencies, severities & mortalities of COVID-19 among children (lower rates) and adults may be due to the potential heterologous adaptive effect of the pertussis vaccines among children [16]. Many hypotheses suggested that the tetanus toxoid (TT) vaccine can reduce the severity of COVID-19 symptoms [61].

3.8 Counterclaims Regarding the Effect of DPT Vaccine on SARS CoV-2

The previous hypothesis doesn't exclude either the probability of early protection by the non-specific innate trained immunity or the possible heterologous effects of the different vaccines or stimuli [10].

3.8.1 Streptococcus pneumoniae (pneumococcus), Haemophilus influenza, Meningococcal vaccines

Reche reported that *Streptococcus pneumoniae and Haemophilus Influenzae* vaccines have 61 and 53 peptides which can match that of SARS-CoV-2, respectively. This mechanism might indicate the presence of a cross-immunity with SARS-CoV-2. It was reported also that *N. meningitides and S. pneumoniae,* contain potentially cross-reactive epitopes [16].

3.8.2 Counterclaims regarding the effect of Streptococcus pneumoniae, Haemophilus influenza, Meningococcal vaccines on SARS CoV-2

Another study reported a negative correlation of the result of the Pneumococcal vaccine and COVID-19 case rates or mortality [62]. Similarly, the meningococcal vaccine also does not show to induce antibodies against SARS-CoV-2 spike protein in a RCT done to assess AstraZeneca vaccine. In this trial participants were randomly assigned to receive either intramuscular chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) or a control vaccine which was the MenACWY quadrivalent vaccine [63].

So, big RCTs need to be conducted to prove or disprove the effects of the previous vaccines.

3.9 Influenza Vaccine

Influenza vaccines are generally safe and cost-effective. Arokiaraj hypothesized the protective effects of H1N1 influenza and *Streptococcus*

pneumonia vaccines in decreasing rates and severity of COVID-19 among the general population [64]. H1N1 type of Influenza A virus can cause a downregulation of angiotensin-converting enzyme 2 (ACE2) protein through a proteasomal pathway. The renin-angiotensin system (RAS) plays a fundamental role in the pathogenesis of acute lung injury. Angiotensin-converting enzyme 2 (ACE2), a negative regulator of the RAS, protects against acute lung injury in several animal models of acute respiratory distress syndrome (ARDS) [65]. This mechanism might explain one of the mechanisms to which H1N1 offers its protection against Covid-19. SARS-CoV-2 is shown to bind with a high affinity to ACE2 receptors leading to its entry [66]. A study from Brazil reported a negative association between the recent receiving of influenza vaccine among the elderly with the need of intensive care, or mechanical ventilation respiratory support, and the mortality rate from COVID-19. The study recommended the need for the application of mass influenza vaccinations, especially in countries at high risk of severe Covid-19. Another study conducted in Italy reported a moderate to strong negative correlation between the influenza vaccination rates and deaths from COVID-19 among the elderly. The innate immune response induced by recent vaccination could result in more rapid and efficient SARS-CoV-2 clearance, preventing progressive dissemination into lower areas of lung tissues [68].

Reche identified that SARS-CoV-2 peptides can match with several pathogens and antigens presented in vaccinations [16]. Furthermore, Wehenkel found a positive correlation between the influenza vaccination rate and COVID-19 deaths among elderly people. It is suggested that the influenza vaccine may increase influenza immunity at the expense of reduced immunity to SARS-CoV-2 [69]. In addition, downregulation of ACE-2 causes an imbalance between the renin-angiotensin system and ACE2/angiotensin-(1–7)/MAS axis which might contribute to various organ injuries among patients with COVID-19 [70]. Therefore, this effect should be further investigated to explore the effect on ACE2.

3.10 Counterclaims Regarding the Effect of *Influenza vaccine on* SARS CoV-2

Flu vaccines are numerous and few studies were conducted to test their benefits against COVID-19. In the study of Reche, the author reported that Influenza vaccines (A and B), and human rhinovirus (A, B, and C) have a poor potential for cross-reactivity to SARS-CoV-2 [16]. So big RCTs are required, and one is underway in Spain to investigate the effect of flu vaccine on reducing COVID-19 severity (ClinicalTrials.gov Identifier: NCT04367883) [12].

3.10.1 Effect of previous infections on SARS-CoV-2

3.10.1.1 Effect of infections with other Coronaviruses on SARS CoV-2

There are 7 corona-viruses recognized to produce respiratory illness in human. Four strains (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1) are known to cause a common cold; where 90% of an adult's serum contains antibodies against them [71]. These four strains share the same recognition region on their spikes with SARS-CoV-2. Therefore they may develop immunity against COVID-19. Protective immunity provided by antibodies usually wanes rapidly but the cellular immunity remains [71,72]. It is suggested that cell-surface Glucose Regulated Protein 78 (CS-GRP78), also the termed heat shock protein A5 (HSPA5), could be a possible route for SARS-CoV-2 internalization. The binding site on the spike protein of SARS-CoV-2 can recognize CS-GRP78[73]. The remaining strains, on the other hand, including SARS-CoV, MERS-CoV and SARS-CoV-2 are associated with severe respiratory symptoms [74]. Phylogenetically, these viruses share some sequence homology and antigenic epitopes which produce an adaptive immune response [75]. Furthermore, SARS-CoV-2 is closely related to SARS-CoV as they share nearly 79.6% genomic sequence identity and both types use the same receptor to invade the cell and same mechanism on the angiotensin-converting enzyme 2 (ACE2) [76,77]. Notably, MERS-CoV shares about 50% of identity with the SARS-CoV-2 [76]. It is conceivable to suggest that previous exposure to one coronavirus might generate passive immunity to another [57,75]. This finding may be due to the antibody-dependent enhancement (ADE) of this virus. This may be due to the preceding experience with other coronaviruses. ADE modulates the immune response and can provoke continued inflammation, lymphopenia, and/or cytokine storm, which have been reported in severe cases and deaths. ADE hampers the capability to cause inflammation in the lung and elsewhere. This can result in acute respiratory injury, acute respiratory distress syndrome (ARDS), and other inflammatory consequences of severe COVID-19 disease [75].

3.11 Effects of Previous Infections with other Viruses which can affect SARS CoV-2

Among the viruses without an available vaccine, herpes simplex virus (1 & 2), Epstein–Barr virus, human cytomegalovirus, human rhinovirus (A, B & C) and respiratory syncytial virus (A & B) are all prevalent in the population. These viruses were found to have poor or null sources of cross-reactive immunity against SARS-CoV-2 [16].

3.11.1 Effect of herd immunity on SARS CoV-2

Herd immunity is an indirect protection against infections that occurs when a sufficient percentage of a population is immune either through vaccination or previous infections. Hence, reducing the risk of spreading the infection to the subjects who lack such immunity. This is useful for people who cannot be vaccinated, such as immunocompromised individuals. Yet, they are protected from the infection since many subjects are immune and cannot transmit the pathogen. However, for this to occur a certain herd immunity threshold should be reached. That is when a sufficient proportion of a population is immune to a level that a sustained spread of the infection cannot occur and thus the outbreak will eventually decline [7]. Accordingly, the establishment of herd immunity towards SARS-CoV-2 depends on the protective immunity produced from the virus. A cohort of 175 patients recovered from COVID-19, due to having SARS-CoV-2-specific plasma nAbs which were detected at notable titers in the majority of the subject [78]. A study conducted in England reported that SARS-CoV-2-specific T-cell responses can last up to 6 months following the initial infection. Similarly, a study from the USA argues that SARS-CoV-2 specific immunity can remain over six months [79]. While these results might sound promising, it is unclear whether this acquired immunity will last beyond 6 months to prevent reinfection or not. If the protection from reinfection with SARS-CoV-2 diminishes over time, herd immunity would never be reached except in the presence of sufficient vaccination. The vaccination is given nowadays by several vaccines in many countries all over the world.

3.11.2 Counterclaims about the effect of herd immunity on SARS CoV-2

Many countries that adopted the concept of herd immunity at the beginning of the outbreak including the UK and Sweden had increased incidence rates or mortality from Covid-19. There was higher Covid-19 mortality from Sweden compared to countries that implemented rigorous protective measures such as Taiwan [80,81]. Additionally, the hospitals ´overload in the UK led the government to abruptly switch the strategy of herd immunity to a temporary lockdown [81]. Establishing herd immunity may not be the ultimate solution giving the crisis. In October, 2020, the WHO did not recommend reaching the herd immunity under the circumstances at that time (without vaccination). It described reaching herd immunity without vaccination as unethical, as it leads to unnecessary infections and death.

3.12 Convalescent Serum Therapy for SARS CoV-2

It is suggested that SARS-CoV-2 entry and infection may be blocked by cross-reacting the sera isolated by convalescent SARS patients [75] or from animals specific for SARS-CoV S1[82]. Many potent monoclonal antibodies were identified from SARS-CoV-2 infected patients which are particularly targeting the receptor-binding domain located on the viral spike protein [83,84]. Some of these antibodies have shown their effectiveness mechanistically in a therapeutic application by neutralizing SARS-CoV-2 infection in vitro and animal models [83,84]. Furthermore, some monoclonal antibodies identified from memory B cells from individual infected with severe SARS-CoV in 2003 potently neutralizes SARS-CoV-2 by targeting the receptor-binding domain of the Spike (S) protein [85].

Intravenous Immunoglobulin (IVIG) is a pool of immunoglobulins from healthy donors that might contain anti-CoV antibodies that might cause cross-immunization [86]. IVIG as adjuvant treatment for COVID-19 showed some evidence of clinical benefits [87]. It was tested experimentally and showed a potential effect for cross-reactivity against several beta-coronaviruses [88].

Pre-existing SARS-CoV-2-cross-reactive T-cell responses in healthy subjects, indicating a potential passive immunity from a previous infection or vaccination [89,72]. Several plasma neutralizing antibodies (nAbs) targeting spike (S) protein were isolated from infected subjects with SARS-CoV or MERS infections [1,77,82,90,91]. These antibodies might last up to 17 years after the initial infection [82].

The cross-neutralization between SARS-CoV and SARS-CoV-2 is yet needs to be proven [86]. These Abs have not been fully investigated by RCTs [1]. An ongoing phase 2 RCT (BLAZE-1) was done by recruiting the outpatients who were recently diagnosed with a mild to moderate COVID-19 infection. Patients were randomly assigned to receive either a single dose of intravenous neutralizing monoclonal antibody or placebo. This antibody is known as "LY-CoV555" and it was obtained from the plasma of COVID-19 recovered patients. The group of patients who received LY-CoV555 had slightly lower severity of symptoms relative to their placebo counterparts. Results revealed that the percentage of Covid-19–related hospitalization or visits to emergency departments was only 1.6% among those in the LY-CoV555 group compared to 6.3% among patients in the placebo group [92].

3.12.1 Counterclaims about the effect of Convalescent serum therapy on SARS CoV-2

Cross-neutralization from SARS survivors' sera against SARS- CoV-2 is not adequate to produce passive immunotherapy for patients with COVID-19 [82]. Furthermore, polyclonal anti-SARS antibodies against S protein inhibit the entry of SARS-CoV S but not SARS-CoV-2. In addition, convalescent sera from SARS and COVID-19 patients have a limited cross-neutralization activity [93]. These findings might indicate that previous coronavirus infection does not provide protection against others. Previous CoV infections do not influence the generation of immunity to SARS-CoV-2 [94]. However, the abundance of these antibodies might be useful to develop a serological test. Protection can only be provided via specific vaccination which is available nowadays.

A double-blind, placebo-controlled, multicenter trial was conducted at 12 clinical sites done in Argentina called PlasmAr. A total of 228 cases received the convalescent plasma and 105 received placebo. Results revealed that at day 30 day, no significant difference was found between both groups in the distribution of clinical outcomes by an ordinal scale (OR= 0.83; 95% CI: 0.52 to 1.35). Mortality was 10.96% and 11.43% in the convalescent plasma and placebo groups, respectively. The risk difference was −0.46 percentage points (95% CI, −7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group on day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups [95]. Another clinical trial conducted in China revealed that among severe or life-threatening COVID-19 cases, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, didn't show statistically significant better time until clinical improvement up to 28 days. The result is restricted by the prompt termination of the trial, which may possess an under-ability to notice the clinically important differences between both groups [8].

It is worth mentioning that results from studies that used convalescent plasma (CP) from recovered COVID-19 patients are conflicting. A study claims that convalescent plasma (CP) therapy has the potential to improve the clinical symptoms associated with COVID19 via neutralizing viremia [96]. While, an RCT in China found that CP does not maximize the protection against COVID-19 when added to the standard management compared to the standard treatment alone [8]. These findings are questioning the efficacy of the immunity generated post-SARS-CoV-2 infection. Especially that there is no evidence of SARS-CoV-2-specific neutralizing monoclonal antibodies from patients recovered from SARS-CoV-2 infection [1]. A study showed that CP samples collected 39 days after the onset of COVID-19 symptoms from recovered patients do not include high levels of neutralizing antibodies where only 1% of samples had high titers (above 5,000) [97]. A RCT is ongoing nowadays to determine the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma in patients with severe SARS-CoV-2 infection [98].

Therefore it can be concluded that the cross-neutralization level in the sera of SARS-CoV survivors is not sufficient to induce passive immunity for COVID-19 patients, which might indicate a different antigenicity of SARS-CoV-2 from SARS-CoV [82,78]. Moreover, a study reported a wide variability of nAb titers [93]. However, low nAbs titers were also associated with some recovery, suggesting that other, yet unknown, immune responses play a role in the recovery of these patients [78]. It is therefore difficult to establish the presence of cross-immunity between different coronaviruses, while there is plenty of room for advanced research to understand the generated immunity following COVID-19.

4. CONCLUSIONS

The reviewed studies suggested the presence of cross-reactive immunity for Covid-19 by vaccination, previous infection with other Coronaviruses. Comparing with other vaccines, BCG was suggested to have the highest cross-reactive epitopes against the SARS-Cov-2 virus. MMR vaccine is suggested also to protect against Covid-19. Regarding the Polio vaccine, OPV seems to have a better immune response (against Covid-19) than IPV as it contains a live attenuated poliovirus. Similarly, DPT, Influenza, Pneumococcal, and meningococcal vaccines are suggested to protect against Covid-19. Previous infection with other Corona viruses, herd immunity and convalescence serum may play roles in the prevention and control of Covid-19. However, the conducted studies were mostly observational that can carry a high chance of inherent biases. These biases include differences in many aspects as the genetic information of the population in different regions, adopted precautionary measures, diagnosing and reporting COVID-19 cases, the phase of the disease across countries at a given time frame, and the mean age range of the population. So, large RCTs are needed to establish the effect of the infections and vaccines on Covid-19. This is important to avoid the economic burden and the misuse of vaccinations that should be prioritized to fight against infectious diseases such as TB. Therefore, several clinical trials are now underway to investigate the effect of the established vaccines on COVID19. These studies were initiated based on the concept of non-specific immunity towards COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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