https://doi.org/10.46344/JBINO.2021.v10i04.13

INFANTS IMMUNIZATION: CHALLENGES OF OTHER VACCINES DUE TO COVID-19 PANDEMIC

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 related diseases (COVID-19) is now responsible for one of the most challenging and concerning pandemics. By August 2020, there were almost 20 million confirmed cases worldwide and well over half-million deaths. Since there is still no effective treatment or vaccine, non-pharmaceutical interventions have been implemented in an attempt to contain the spread of the virus. During times of quarantine, immunization practices in all age groups, especially routine childhood vaccines, have also been interrupted, delayed, re-organized, or completely suspended. Numerous highincome as well as low- and middle-income countries are now experiencing a rapid decline in childhood immunization coverage rates. We will, inevitably, see serious consequences related to suboptimal control of vaccine-preventable diseases (VPDs) in infant's concurrent with or following the pandemic. Routine pediatric immunizations of individual infants at clinics, mass vaccination campaigns, and surveillance for VPDs must continue as much as possible during pandemic.

Keyword: vaccine, infants, immunity, covid-19

INTRODUCTION

Unlike many infectious diseases, such as endemic malaria and common flu where infants are known to have the highest mortality rates and to drive transmission in households and communities it appears as it could be that SARS-CoV-2 just does not translate into severe disease as frequently in infants, specifically for young children, below 10 years of age (1). Moreover, infected infants suffer milder symptoms of COVID-19, with much lower case-fatality rates (CFR), and recover quickly from the infection (2). In an initial assessment from Wuhan, China, among 50 infants identified with COVID-19, the severity varied between asymptomatic and mild in 96% of the patients (3). While diagnostic findings were similar to those of adults, fewer infants developed severe pneumonia. Neonates, on the other hand, have developed symptomatic and more severe COVID-19 (4).

1 The Immunological Basis for Potential Effect of Childhood Vaccines in Disease Expression

In many countries, infants are routinely vaccinated against a number of bacterial and viral diseases. Vaccines may have non-specific physiologic effects when they alter the immune response to unrelated organisms, called heterologous immunity. The non-specific effects of vaccines are usually more pronounced in girls and appear to be maximal in the first 6 months of life when passed maternal immunity is further supplemented by newly introduced vaccines, starting at 2 months. There are several theories as to why heterologous immunity may occur (5).

Salman and Salem suggest that cross-immunogenicity of childhood vaccines for multiple viruses could potentially be a reason for the relatively milder infection and severity of COVID-19 among infants (1). Most routine viral vaccines are either inactivated or killed viruses that stimulate T Helper 1 cells (CD4+) to secrete many different types of cytokines as interferon gamma, interleukin-2 (IL-2), and IL-12, improving the cytotoxicity of natural killer cells to recognize and destroy cells infected with new cross-reactive viruses. For example, warts that are caused by human papilloma virus (HPV) could be ameliorated using intralesional MMR vaccine (6).

Furthermore, neutralizing antibodies produced against the foregoing vaccine-preventable microbes might cross-react with the antigenic epitopes of the spike (S) and nucleocapsid (N) proteins and prevent COVID-19 in infants (7). An investigation of this hypothesis, using the BLAST search tool, showed no significant sequence similarity between these proteins and those in the childhood vaccine-preventable microbes, inferring that memory T-cells, rather than vaccine neutralizing antibodies, may be involved in the protection of infants against COVID-19 owing to them having a larger number of naive T-cells that can be programmed to protect them against the disease (8).

Potentially, the low immunity in infants that doesn't exaggerate the immune response against the virus as in the case of adults, could explain the lesser severity of SARS-CoV-2 in this age group. Infants have less

adults-like memory cells specific to other circulating coronaviruses and therefore, are less capable to mount a devastating and vigorous cell-mediated attack on alveoli and interstitial tissue of the lung upon new infection (9).

1.1 The Bacille Calmette–Guérin (BCG) Vaccine

O'Neil and Netea suggest that induction of trained immunity by BCG vaccine could provide protection against COVID-19, and the use of oral polio vaccine and new recombinant BCG-based vaccine VPM1002 may be some of the approaches to induce resistance to SARS-CoV-2 (10). The authors hypothesize that induction of trained immunity is at least partly the mechanism through which BCG vaccination induces its beneficial effects and might protect against SARS-CoV-2. A retrospective study compared countries that do not have BCG vaccination policies (Italy, USA, Lebanon, the Netherlands, and Belgium), to countries that have such policies (11). The results showed that while middle-high and high-income countries with current universal BCG policies had 0.78 COVID-19 deaths per million, those without such policies had 16.39 COVID-19 deaths per million people and the difference was statistically significant. In countries, such as Italy, where BCG vaccine was never given, the mortality rate was significantly higher compared to Japan where BCG vaccination has been implemented since 1947. In countries, such as Iran, with BCG vaccination starting in 1984, mortality was higher since today's elderly population did not receive the vaccination.

COVID-19 mortality rates in New York, Illinois, Alabama and Florida states without BCG-vaccination policies in the US, were significantly higher than locations with BCG-vaccine policies, namely Pernambuco, Rio de Janeiro, and Sao Paulo in Brazil, or Mexico State and Mexico City in Mexico.

1.2 The Measles, Mumps, and Rubella (MMR) Vaccine

Two potential mechanisms for higher COVID-19 cases per population ratio and higher death rate in Italy (no MMR vaccine) compared to China: (1) by generating bystander immunity the measles vaccine increases ability of immune system to combat non-measles pathogens, including coronaviruses, and (2) due to shared structural similarities between measles and coronavirus the cross-reactivity and immunity between the measles vaccine and coronavirus leads to partial protection against COVID-19 (12). Franklin et al., identified that the macro domains of SARS-CoV-2 and rubella virus and the MMR vaccine, share 29% amino acid sequence identity (13). This finding suggests the viruses possess the same protein fold. Patients with high illness severity had high levels of rubella IgG (161.9 + 147.6 IU/ml) compared to patients with a moderate severity of disease (74.5 + 57.7 IU/ml). The authors suggest the MMR vaccine could result in potentially reduced severe outcomes with COVID-19. In their commentary, Fidel and Noverr support the use of live attenuated MMR vaccine as a preventive measure against the pathological inflammation and sepsis associated with COVID-19 infection (1).

1.3 The Hepatitis-A (HEP-A) Vaccine

Sarialioglu et al., reported on the differences in the rate in which COVID-19 had affected some countries such as China, US, Italy, Spain, France, England, the Netherlands, and Belgium more severely than some others such as India, Pakistan, countries of the African continent, and South America which had lower rates of infection and mortality at the time of their study (15). The authors hypothesize that routine vaccination for hepatitis A virus (HAV) causing high seroprevalence among populations in countries in the low COVID-19 prevalence group, while it is rather low in the industrialized countries. The authors conclude that immune response caused by the hepatitis A vaccine may be protective against COVID-19 infection by a possible adaptive immune cross-reaction. Patients with asymptomatic COVID-19 disease could indirectly indicate those with protection from HAV seropositivity. The HEP-A vaccine may help to keep the COVID-19 infection at mucosal colonization levels and prevent lower respiratory tract involvement and fatality (1).

2 Scenario of Routine immunizations during the COVID-19 pandemic

COVID 19 is disrupting life-saving immunization services around the world, putting millions of infants in industrialized as well as in low- and middle-income countries – at risk of vaccine-preventable diseases. Because of the risk of infection and the need to maintain physical distance during the early stages of the COVID-19 pandemic, many countries have temporarily and reasonably suspended preventive mass vaccination campaigns against diseases such as measles, polio, diphtheria, pertussis, polio, tetanus, meningitis (16). Causes of the delayed/interrupted immunizations are due to parents' fears, restrictions of movement/lockdown policies, changing priorities for COVID-19 among health-care personnel, and logistics delivery issues (i.e., vaccine transport delays). The World Health Organization (WHO), UNICEF, and GAVI, the Vaccine Alliance have reported that routine immunization programs have been substantially disrupted in at least 68 countries, affecting around 80 million infants (15). A further 24 million people are at risk of losing out on vaccines including measles, polio, rotavirus, meningitis, rubella, and human papillomavirus in GAVI-supported low-income countries (16). Vaccines are of critical importance in these areas, which also have limited access to health services and treatments. Due to the risk of inadvertently contributing to the spread COVID-19, global health organizations have not been able to continue to support mass vaccination campaigns in some countries (17).

3 Global Suspension of vaccine service

Of the 129 countries in which data were available, more than half reported moderate to severe disruptions, or total suspension of vaccination services during March – April 2020. There was a full cessation of routine immunizations from April 1–15, 2020 in Vietnam. In India, routine immunizations were disrupted due to health-care workers being re-organized in response to the pandemic. In Pakistan, polio catch-up immunization campaigns

were postponed until June 1st, 2020(18). A number of countries postponed immunization campaigns in the first 5 months of the pandemic, including: measles or measles-containing vaccines in 27 countries, inactivated polio vaccine in 7 countries, bivalent, or monovalent oral poliovirus vaccine in 39 countries, meningococcal conjugated A vaccine in 2 countries, yellow fever vaccine in 4 countries, typhoid vaccine in 2 countries, oral cholera vaccine in 5 countries, and Td (tetanus–diphtheria) vaccine in 7 countries (19). While several mass immunization campaigns have been stopped to prevent the virus spreading, the results have been alarming. Diphtheria has recently resurged in countries like Venezuela, Pakistan, Nepal, Bangladesh, and Yemen where conflict and/or population displacement have seriously affected public health systems (20). Cholera is now present in Bangladesh, Cameroon, Mozambique, South Sudan, and Yemen (15).

4 Outrage of polio

Polio is an important concern, and suspending polio immunizations is a particularly relevant issue where the virus is likely to spread (e.g., Afghanistan and Pakistan) due to active circulation. The risk of polio spreading to other countries is real, and could negatively affect global polio eradication efforts (21).

The Global Polio Eradication Initiative recommended suspending polio vaccination campaigns until the second half of 2020 (22). As a result of the coronavirus pandemic, 46 poliovirus immunization campaigns in 38 countries, mostly in Africa have been suspended. During this time, a mutated vaccine-derived strain of poliovirus has been reported in >30 countries (23). Following the suspension of these immunization activities, there has been a new polio outbreak in Niger (24). In Pakistan and Afghanistan, wild poliovirus Type 1 have been reported, and cases of Type 2 poliovirus, mutated from the oral vaccine, have appeared in Chad, Ethiopia, Ghana, and Pakistan (25).

5 Measles outrage

Measles is a disease that can cause serious morbidity and has a casefatality rate of 0.2%, it is more highly contagious (basic reproduction rate; R0 as 12–16) than COVID-19 (26).During the pandemic, 37 countries (home to 117 million unvaccinated imfants) suspended scheduled measles campaigns, and more will be postponed (27). Before the pandemic, and despite the availability of an effective vaccine, the highly contagious measles virus continued to spread around the globe. In 2018, cases surged to an estimated 10 million worldwide, with 140,000 deaths, a 58% increase since 2016 (28). Measles outbreaks have been reported in diverse settings, including Madagascar and Ukraine (29). In 2019, measles outbreaks infected more than 6,500 infants in the Democratic Republic of the Congo where one-dose measles vaccine coverage was 57% (30). In 2019, in many countries faced vaccination coverage rates below the minimum needed for herd immunity; this posed a serious risk to infants who were not vaccinated and indirectly threatened immunocompromised infants and others

who could not be vaccinated for other medical contraindications. Eighteen countries reported measles outbreak due to suspended measles campaigns. By 2020, 178 million people are at risk of skipping measles vaccines, according to the Measles and Rubella Initiative, even as measles flares across the globe, including in Afghanistan, Brazil, Cambodia, the Central African Republic, Iraq, Kazakhstan, Nepal, Nigeria, and Uzbekistan (31).

Measles weaken the immune system for months or years, causing immune amnesia that leaves infants susceptible to other infections (32).

6 Potential effects of existing vaccines on COVID-19 pandemic

A majority of countries include conjugated pneumococcal vaccines in their national childhood immunization programs and recommend conjugated and/or polysaccharide vaccines for high-risk groups and elderly people. Routine immunizations that include pneumococcal vaccines for infants and high-risk adults should continue according to previously developed schedules, to reduce the need for hospital admissions for vaccine-preventable diseases. High influenza vaccine coverage would reduce influenzarelated mortality while also helping to preserve the capacity and function of the health system during circulation of both influenza and COVID-19 viruses. The goal should be to attain high influenza vaccine coverage, including near-universal coverage among health-care personnel and other high-risk groups for COVID-19 (33).

7 Routine immunizations in infants and adults with suspected or confirmed COVID-19 infections

There is currently no evidence that vaccination would increase the risk of a child becoming infected with COVID-19, or affect the course of the disease in a child who has been inadvertently vaccinated during the asymptomatic phase or incubation period (34). In cases of mothers with a laboratory-confirmed diagnosis of COVID-19, asymptomatic newborns could be vaccinated according to local recommendations with BCG and hepatitis B vaccine. If the newborn presents COVID-19 symptoms, the BCG vaccine should be postponed and the hepatitis B vaccine might be administered within the first 24 hours of life (35). Here is no clear guidance on the administration of routine vaccines in infants with COVID-19, or those who have tested positive for the virus but who have no symptoms or known contact. Individuals with signs of acute respiratory infection, including mild symptoms such as sore throat or runny nose, may postpone regular immunization until they have recovered during the COVID-19 pandemic. The presence of fever may cause confusion concerning vaccine side effects or the progression of the illness; therefore, vaccines can be postponed until illness resolution, in cases of acute febrile illness (34). The CDC recommends deferring vaccinations of anyone infected with SARS-CoV-2, regardless of symptoms, until they meet the criteria to discontinue isolation. It is also prudent to delay the administration of any live vaccines among COVID-19 patients who have been treated

with immunoglobulin or plasma, according to routine live vaccine use protocols.

8 Immunization measures by WHO during the COVID-19 pandemic

The WHO recommends that all routine vaccinations be administered as scheduled, even during the COVID-19 pandemic. Routine immunization sessions should continue, using special measures and precautions, to the extent possible and as permitted within the local COVID-19 response context. This includes routine immunization for infants, children, adolescents, pregnant women, high-risk groups, and adult healthcare providers (36). Any interrupted immunization services should be resumed and catch-up vaccinations offered as quickly as possible (34). New vaccines should be delayed from introduction to national immunization schedules. It should be communicated clearly to the community and healthcare professionals alike the rationale for the inclusion of immunizations among the priority health services provided during the COVID-19 pandemic. The risks from VPDs and the benefits of vaccination should also be reiterated (37).

9 Myths about vaccination

Vaccine hesitancy/refusal has been one of the most important health problems in recent years, and during the COVID19 period, the most radical groups have continued to share false and non-evidence-based opinions with the community (38). Many of these theories posed during the pandemic have the risk of increasing future vaccine refusals. One of the most important observations during the period has been that the speed of transmission of false information about the disease is much faster and more dangerous than the speed of the spread of the virus (39).

Reduced access to critical health-care facilities and medications is known to establish circumstances in which patients use substandard drugs and/or dosages. This could lead to increased morbidity and mortality caused by human immunodeficiency virus infection, tuberculosis, and malaria, as well as leading to the rise and spread of drug-resistant diseases (40). These populations need protection not only from the pandemic, but also from the consequences of non-pharmaceutical interventions. In addition to low- and middle-income countries, other vulnerable populations for the pandemic and mitigation strategies consequences are refugees and migrants. The pandemic has had an enormous effect on mobility, border and migration management, and on global migrant populations' health, social, and economic situation. There now needs to be an immediate concerted effort to link these communities with national and global responses to COVID-19 (41). During the pandemic, immunization program for refugees and immigrants should not be neglected.

10 Causes of outbreaks

In many countries, vaccine hesitancy and refusal have become an important problem in recent years.30 Due to school closures, serious immunization disruptions may occur in countries where routine immunizations have been delivered in school settings. According to UNESCO

data from April 15, 2020, 91% of the world's school-age children have stopped their education due to the pandemic (42). If children are left unvaccinated, case numbers could quickly surge following a drop in the optimal population immunity and the suspension of these vaccination programs. Parental fears about potentially exposing their infants to COVID-19 during routine follow-up visits may have led to the declines observed (43).

11 Cross talk of previous vaccination immunity and covid-19 infection

Previous studies showed that live vaccines (i.e., BCG, oral polio vaccine, measles) induce heterologous protection against infections, likely by inducing interferon and with a long-term boosting of innate immune immunity mechanisms (44). Measles and smallpox vaccines have also been associated with pronounced nonspecific protective effects against infectious diseases. Both poliovirus and coronavirus are positive-strand RNA viruses; thus, specific innate immunity mechanisms are likely to induce and affect these viruses.

Conclusion and future perspectives

Vaccination and immunization is responsible for protection from severity of disease. COVID-19 is creating hurdles in the field of immunization, so we should take proper measures regarding this. As no proper vaccine for covid-19 for children and infants is launched that's why BCG, hepatitis and polio vaccines have proved beneficial to create protective antibodies against corona virus. Through these useful information we can make strategies for formation of COVID 19 vaccination in future by using previous FDA approved Infants vaccines.

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