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Mini Review

Immunopathologic basis of Confer Hypothesis: Other Wild Viral Exposure and Immunization can possibly Confer Protection against Coronavirus Infections

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Abstract

Despite having limited healthcare resources and high infectious diseases burden, some regions of the world have lower CoVID-19 case incidence and case-fatality indices. Epidemiological studies suggest that pediatric age group is relatively spared by SARS-CoV-2 outbreak and those children affected don't seem to develop serious clinical illness as seen in the adult population. Children worldwide are covered under WHO Expanded Immunization Program. As children age, the antibody titers of several vaccines also start to decline which coincide with increasing trend of CoVID-19 attributed mortality in the adult population. These observations have resulted in the "Confer Hypothesis". This hypothesis states that one of the existing vaccines such as Measles and / or past viral infections can potentially confer immunity against CoVID-19. In this review, pathophysiological basis, merits, criticism and future directions of Confer Hypothesis is discussed.

ABBREVIATIONS

MMR: Measles, Mumps, Rubella; MMR-V: Measles, Mumps, Rubella, Varicella; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome

INTRODUCTION

As of 22 April 2020, more than 2.5 million confirmed cases of COVID-19 have been reported from 190 countries, areas or territories. With an approximate mortality rate between 1.5% and 12%, there have been at least 190,000 confirmed deaths making this outbreak a global health emergency. This ongoing situation is evolving with undetermined SARS-CoV-2 pathophysiology or clinical manifestations. Interestingly, some population subsets seem to be doing better than the others in terms of disease incidence and disease severity. For example, Bangladesh with a population of 170 million, reported only 4126 CoVID-19 cases with 127 deaths, whereas Italy with a population of 60.5 million has reported nearly 190,000 cases and more than 25,000 deaths. Similar pattern can be seen on comparisons between USA-India, Spain-Pakistan and France-Sri Lanka. Secondly, pediatric population worldwide seems to be protected from severe manifestations of CoVID-19. This pediatric age group sparing follows the epidemiological pattern of past coronavirus infections of MERS (2012) and SARS (2002-2004). Cytopathological and immunopathological basis of these trends and better resistance against coronaviruses in certain sections of population is still debated. In view of these observations "Confer Hypothesis" has been proposed which states that past infections or past immunization may confer complete or partial immunity against the coronavirus infections.

Clinical Spectrum of SARS-CoV-2 Infection

The current understanding of COVID-19 symptoms is limited. The disease presentation can range from asymptomatic to severe pneumonia. Based on recent results reported by Wu et al., 2020; most common symptoms are fever (98%), cough (76%), myalgia or fatigue (44%), and atypical symptoms include sputum (28%), headache (8%), hemoptysis (5%) and diarrhea (3%) [1]. About half of the patients have dyspnea (the median from onset to dyspnea was 8 days) and over 60% of patients have lymphocytopenia. Observed complications include acute respiratory distress syndrome (29%), acute heart injury (12%), and secondary infections (10%). Approximately one-third of patients require to be treated in the ICU. Therefore immediate steps are needed to be taken to understand the natural history of disease to limit the disease spread.

Immunologically unique Pediatric Population

Only a small number of cases of SARS-CoV-2 infection have been described in children and understanding of the spectrum of illness is limited. Xu et al., 2020 reported that as compared to adult patients, SARS-CoV-2 infected pediatric patients have clinically milder symptoms and show fewer alterations in radiological and laboratory testing parameters [2]. Data on individuals aged 18 years old and under, reported by the World Health Organization (WHO) China Joint Mission on COVID-19 suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). These observations are in agreement with epidemiological pattern of 2003 Coronavirus SARS-CoV outbreak when 8,098 cases of SARS were diagnosed worldwide and only <5% of all cases were diagnosed in patients <18 years of age [3]. Similarly in 2012 Middle East Respiratory Syndrome (MERS) Coronavirus outbreak, few cases of MERS-CoV in children were detected and it remained mainly a disease of adults. In contrast, non-Coronavirus 2009 flu pandemic of (H1N1)pdm09 virus primarily affected children and young and middle-aged adults [4]. Immunologically, the pediatric population is uniquely built in the sense that children have an immature but a robust immune system. This character of childhood immunity makes this population susceptible to various infections as evidenced by high under 5 years morbidity and mortality due to infectious diseases. At the same time, a maturing humoral immune system is thought to adapt and learn more rapidly as compared to the adult population. An immunological explanation for relative sparing of young population in Coronavirus outbreaks including the current SARS-CoV-2 pandemic is lacking.

Childhood immunization

All United Nations member states have been extensively covered under Expanded Programme on Immunization by the World Health Organization (WHO). Some of the viral infections which are vaccine preventable include Measles, Mumps, Rubella, Chickenpox, Rabies, Japanese Encephalitis and Hepatitis. The Measles, Mumps and Rubella (MMR) vaccine is known to also protect against other viral infections including causes of respiratory diseases [5]. It is believed that host genetic factors, including both major histocompatibility human leukocyte antigen genes (HLA) and non-HLA genes, as well as other variables modulate immunity following measles vaccination. Twins studies have revealed a strong genetic influence on the variance in measles vaccine-specific humoral immune responses. A large body of evidence has demonstrated that several markers in HLA genes (highly polymorphic gene region on human chromosome 6p21.31) are associated with the heterogeneity of antibody responses to measles vaccination [6].

Franklin et al. 2020, identified sequence homology between the fusion proteins of SARS-CoV-2 and measles and mumps viruses [7]. They reported a 29% amino acid sequence homology between the Macro (ADP-ribose-1-phosphatase) domains of SARS-CoV-2 and rubella virus. The rubella Macro domain has surface-exposed conserved residues and is present in the attenuated rubella virus in MMR. These findings are in agreement with the confer hypothesis that MMR could protect against poor outcome in COVID-19 infection.

Measles and COVID-19 Pneumonia

Chen et al., 2020 described clinical and epidemiological features of COVID-19 Pneumonia in 99 patients [8]. These clinical features are similar to the extensively studied features of Measles pneumonia. Like SARS-CoV-2 virus, Measles virus infects the respiratory tracts of nearly all affected persons and it is the most common severe complication of measles and accounts for most measles-associated deaths. In studies of unselected hospitalized children with measles, 55% had radiographic changes of bronchopneumonia, consolidation, or other infiltrates; 77% of children with severe disease and 41% of children with mild disease had radiographic changes [9]. This similarity in disease presentation can be linked to a possible pathophysiological similarities between Coronavirus and Measles virus. Measles virus (MV) attachment to its receptor is mediated by the hemagglutinin (H), and H protein is the primary target of the MV specific T cell response during measles and after vaccination. Analogous to H, Coronavirus spike protein is the main mediator of virus entry into the target cells. This Spike protein is also the most promising and one of key targets for the development of vaccines and therapeutics. Based on limited literature, a possibility of immunological proximities between the two RNA viruses can be raised.

Measles, Mumps and Rubella declining Antibody Levels

A higher incidence and prevalence of COVID-19 has been reported in adults which coincides with declining trends of Measles, mumps, and Rubella IgG antibody levels as age advances. Carryn and colleagues reported that although satisfactory immune response is elicited upto 10 years after the MMR immunization, there is reduction in both the measles seropositivity rates and the measles antibody geometric mean concentrations (Figure 1) [10]. A study from one of the major epicentres of current

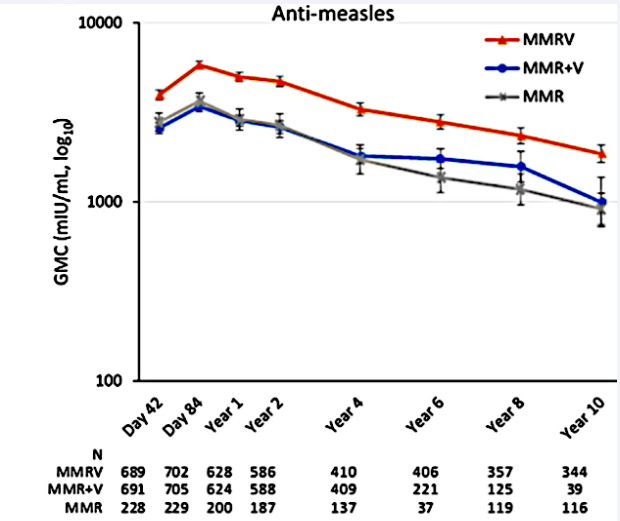

Figure 1 Anti-Measles antibody Geometric Mean Concentrations trends upto 10 years. Anti-measles antibody geometric mean concentrations from Day 42 to Year 10 for the MMRV, MMR+V and MMR groups, GMC, antibody geometric mean concentrations; IU, international unit; mIU, milli international unit; U, unit; N, number of children with available results.

pandemic – Italy, reported that an important proportion of subjects immunized for measles do not show a protective IgG titers 10 years after vaccination. During the first 8 years after the second dose, the decline in levels of antibodies against all 3 viruses was 50%, 69% and 58% for measles, mumps and rubella respectively [11]. Based on these observations, possible role of measles Containing Vaccine (MCV) has been suggested in preventing serious complications of CoVID-19 [12].

Regional variations in CoVID-19 incidence

Developing countries such as India, Pakistan, Egypt, South Africa, Bangladesh and Mexico have fewer CoVID-19 cases per million population in contrast to developed countries such as USA, France, Italy, Spain, Germany and United Kingdom (Table 1 and Figure 2). Despite having significantly higher population densities and limited healthcare resources – for some reason these countries seem to be doing better than the developed world. One possible explanation is that, SARS-2-CoV virus strain in these countries might have mutated to a less virulent strain. Also, these countries are home to highly prevalent tropical diseases and viral respiratory tract infections. Confer hypothesis states that recurrent viral infections has modulated the herd immune response of these populations, making them more adjusted to resist pathophysiological complications of CoVID-19. Caution must be exercised in making assumptions because of two important factors. First, mentioned developing countries got ample time to prepare and learn from the developed nations as they were affected only in the later part of the pandemic. Second, the testing facilities are limited in these countries, so the actual number of cases might be underreported.

The Hypothesis and its Limitations

Here, the "Confer Hypothesis" is proposed that a more robust immune response can be elicited against Coronavirus in a previously immunized child, or in an individual with prior coronavirus like viral infection. This hypothesis is primarily

Table 1: CoVID-19 attributable total cases, CoVID-19 attributable total death and country population on 24 April, 2020. (Source: https://www.worldometers.info/coronavirus/countries-where-coronavirus-has-spread)

High CoVID-19 Burden Countries	Total Cases	Total Deaths	Total Population (in million)
United States	886709	50243	331
Spain	219764	22524	47.1
Italy	189973	25549	60.3
France	158183	21856	67
Germany	153307	5575	83.78
United Kingdom	138078	18738	67.88
TOTAL	**1746014**	**144485**	**657.06**
Low CoVID-19 Burden Countries	**Total Cases**	**Total Deaths**	**Total Population (in million)**
India	23502	722	1369.5
Mexico	11633	1069	127
Pakistan	11155	237	210
Bangladesh	4689	131	167.5
South Africa	3953	75	58.8
Egypt	3981	287	100
TOTAL	**58913**	**2521**	**2032.8**

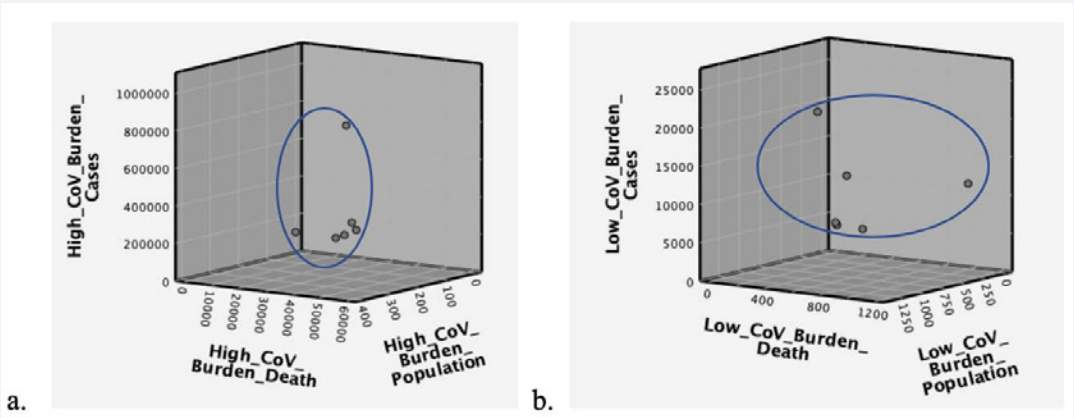

Figure 2 CoVID-19 attributable depiction of total cases and total deaths in countries with high disease burden (a) and low disease burden (b). X-axis represents number of COVID-19 cases, Y-axis represents total number of deaths attributable to CoVID-19 and Z-Axis represents total population of country. Note that the scale on all three axis is different. This figure is based on data collected on 24 April, 2020.

based on retrospective analysis of epidemiological data and limited clinical-pathophysiological features of COVID-19 which are not fully understood. Hence, this hypothesis carries all the inherent limitations that accompany assumptions based on incomplete observations. SARS-CoV-2 virus is a new entity and our knowledge is constantly evolving. There is no substitute for a detailed structural analysis of coronavirus, basic science experiments eliciting molecular mechanisms of the virus, long term follow up studies of patients and rigorous scrutiny of scientific literature. However, in view of unprecedented outbreak of this pandemic, loss of patient lives, exhaustion of healthcare resources, poor understanding of virus behaviour and grave economic impacts – premature but eligible observations can be assessed for validity, to obtain "quick and doable" solutions for the present crisis.

Summary

Evidently, there is a selective sparing of paediatric population in terms of severity of clinical symptoms during Coronavirus outbreaks in recent times. Some developing countries have reported better outcomes and lower case incidence rates as compared to developed countries. Pathophysiological and immunological explanation for this observation is lacking. Confer hypothesis proposes that one of the available vaccines such as MMR and / or past viral infections may confer immunity against the CoVID-19 infection.

DISCUSSION & CONCLUSION

Evidently, there is a selective sparing of paediatric population in terms of severity of clinical symptoms during Coronavirus outbreaks in recent times. Some developing countries have reported better outcomes and lower case incidence rates as compared to developed countries. Pathophysiological and immunological explanation for this observation is lacking. Confer hypothesis proposes that one of the available vaccines such as MMR and / or past viral infections may confer immunity against the CoVID-19 infection.

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