Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 10, Page No: 145-150

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Why COVID-19 is Less Frequent and Severe in Children: Understanding the Immune Responses

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ABSTRACT

Background: Currently countries all around the globe are experiencing the pandemic caused by the deadly virus SARS-CoV-2, which is proving itself to be a huge burden on the intensive care facilities of the globe and causing a large proportion of untimely deaths all across the world. It has been seen that the number of children who come in contact with the COVID-19 virus have milder course of the disease and the extent of infection is also less frequent as that of the adult patients. We have tried to search and discover some causal evidences for this problem present in front of us.

Data sources: An extensive search strategy was designed to identify papers on COVID-19 and a systematic literature review was carried out using MEDLINE, PubMed, Google scholar, EMBASE databases.

Results: The searches assembled 60 applicable articles. The evaluation discovered that youngsters accounted for a decrease percentage of the stated instances and in addition they experienced a much less intense route of illness. Children have relatively stronger innate immunity because of trained immunity which has possibly resulted in early manage of contamination on the site of entrance. Unlike the children, older patients display a relatively depressed immunity including both cellular and humoral as well as innate immunity thereby mounting a much lower immune response. These per chance may be associated with other systemic diseases being present in the elderly. A rapid regeneration potential of alveolar epithelium in the pediatric age group might have a contributing element to a faster healing of the infection. Even so children presenting with other ailments might be a high risk unit who are in the need of cautious monitoring.

Conclusion: With all the references taken into consideration and all the data explored, the conclusion states that the pediatric population exhibit a naturally strong innate immunity and mount a relatively higher fighting response against the virus as compared to the infection and its response found in the adult population. Thus the recovery will be rapid and occur in a relatively less time frame.

Key words: Children, COVID-19, SARS-CoV-2, Adaptive immunity, Innate immunity

HOW TO CITE THIS ARTICLE: Priyadarshini Singh, Lokesh Vaishnav, Shiv Joshi, Abhishek Joshi, Ashok Mehendale, Why COVID-19 is Less Frequent and Severe in Children: Understanding the Immune Responses, J Res Med Dent Sci, 2022, 10 (10): 145-150.

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Received: 02-Aug-2022, Manuscript No. JRMDS-22-49662;
Editor assigned: 04-Aug-2022, PreQC No. JRMDS-22-49662 (PQ);
Reviewed: 18-Aug-2022, QC No. JRMDS-22-49662;
Revised: 03-Oct-2022, Manuscript No. JRMDS-22-49662 (R);
Published: 13-Oct-2022

INTRODUCTION

In the month of December in 2019, there was a sudden surge in cases of an infectious disease new to the world in Wuhan in the Hubei Province of China [1]. Coronavirus disease-2019 also known as 'COVID-19' is characterized by the severe respiratory signs and symptoms with the etiological agent being coronavirus 2 (SARS-CoV-2), it is the 7th coronavirus. SARS-CoV-2 was previously also known as 2019 nCoV. Within a year of the outbreak, the World Health Organization (WHO) declared the outbreak to be a pandemic [2]. In line with the WHO's up to date statistics of 21st April-2020, there were a total of 2,397,216 cases and 162,956 deaths all around the world. SARS-CoV-2 leads to acute respiratory infections with severity differing in various age groups, wherefore elderly tends to experience a severe course of the infectious disease, the younger generation have been proportionately spared till date. So far they have only accounted for 1-5% of total patients of SARS-CoV-19 [3-8].

LITERATURE REVIEW

This review article summarizes the findings of the current knowledge of COVID-19 infection in children and possible explanations regarding the differences among adult and paediatric infection.

Unfortunately, a detailed evaluation of statistics including the comparison about the topic was not carried out due to the substantial number of missing data [9].

Hypotheses suggesting the protective mechanisms in children infected with COVID-19

A less vigorous immune response: As the sudden rise and involvement of cytokine is proven to be essential in the rapid development of COVID infections in adults, our first end result emerges from the fact that the children are found to have a reduced exaggerated immune reaction to the organism than adult [10]. Total number of lymphocytes, $CD4^+$, $CD8^+$, memory t cells and helper T cell counts had been substantially decreased in patients with extreme sickness course, hinting to a suppressed adaptive immunity [11]. Cytokines (which includes IL-2, 6 and 10) and blood neutrophil counts had been substantially improved in seriously unwell sufferers, representing a dysfunctional immune reaction causing lung injury [12]. Children generally have a reduced pro-inflammatory cytokine reaction and have been found to have a much less capacity to develop extreme respiratory distress in an acute presentation [13-15]. It may be consequently feasible that the cytokine storm is less sensitized in the said age group [16].

A more active innate immune response: Infections with SARS-CoV-19 in mice revealed that $CD8^+$ and $CD4^+$ T cells, not to forget the antibodies, play a significant factor against the virus [17-19]. Adults with severe COVID-19 have been found to have a late and prolonged clearance of the etiological virus [20]. The innate immunological response in children is stronger. They have a greater percentage of all the immune factors like the lymphocytes, the numbers of T and B cells, and the important NKC cells, all of these will aid in the virus's fight.

Children, on the other hand, are generally been found to have a immune system which has not been matured completely and therefore might be at a very high risk for super infection with other viruses like influenza or RSV which could deteriorate the condition gradually, as well as serious sickness and hospitalization. This gives us the idea that protective immunity to SARS-CoV-2 is distinct as compared to other common respiratory illness present in the surroundings. If the disease worsened, a weaker immune response could keep them from experiencing the cytokine storm that could assist them reduce the intensity.

More trained immunity after prior infection: Trained immunity' is the re-programming of the function of the immune cells involved in innate immunity of the body following a few antigen stimulation like an infection or vaccination, to a greater activated state. This is accomplished *via* re-programming of the metabolic and epigenetic changes which includes some biochemical reactions which are of paramount importance to the body and maintains the healthy functioning [21]. Several researches have proven that children are extra liable to contamination by RSV and the atypical Mycoplasma pneumonia than the elders [22-25]. MP was found to occur in 10-40% of the instances of Community Acquired Pneumonia (CAP), the younger generation of under 15 years age being the maximum groups susceptible to the disease. However with inside the document of 2010-2011 of European epidemic statistics it was documented in kids below 4 yrs. of age. RSV is more frequent in infancy; the WHO additionally mentioned the virus as a leading etiological agent for more than 25 million new cases of infections of respiratory tract, inclusive of bronchitis in youngsters 5 yrs. of age or less. As the older siblings spend considerable time in nurseries and schools, they make a great supply of infection spreading than adults. These activities teach the immunity of the children how to make the cross reactive antibody for neutralization of MP and RSV more available. Mi B, et al. stated the affiliation among preceding occurrence of *M. Pneumoniae* and finer immune reaction in COVID-19 sufferers. The sufferers who were IgG positive had a more lymphocytic, monocytes and eosinophilia percentages and counts ($P<0.05$) than that of the sufferers of COVID-19 without MP IgG. In addition to this the Prothrombin Time (PT) and Lactate Dehydrogenases (LDH) have been improved in the group discussed. The use and necessities of oxygen delivery *via* masks was notably much less in COVID-19 MP IgG positive sufferers ($P=0.029$). The records stipulated that this positivity for igG against mycoplasma pneumonia is a defining defensive element for SARS-CoV-2 infection [26].

Orange, et al. exhibited that use of IVIG (Intravenous Immunoglobulin) obtained from the recovered patients who had exhibited antibodies of very high titres to numerous respiratory illnesses which include human metapneumovirus and several other viruses which attack the respiratory epithelium and leads to the pathogenesis of severe infection. This article advised an immediate relation among antibody status of donors to RSV and the corresponding status of the responder to different viruses ($P<0.05$). Although however, there are varieties of considerations to be examined, this could have been because of donors who mounted a relatively greater variety of viral contamination, to a superior response in the form of humoral immunity in general or specifically against antigens found intracellular and eventually to range within side the Major Histocompatibility Complex (MHC) alleles [27].

Trained immunity after previous vaccinations: Miller including their team discovered that the countries worldwide with no proper BCG immunization policies in place, such as in the United States and many others, have been damaged more than countries with proper BCG vaccination policies in place. In addition, nations with a start delayed as compared to others in universal BCG immunisation such as Iran had a higher death rate, which forms a firm base with the hypothesis suggesting that BCG vaccine protects the vaccinated older demographic. They also discovered that the BCG vaccines decreased the number of COVID infectious cases in the areas [28]. Thus, BCG is emerging to be an intriguing option for improving immunity populations who are at more risk for severe presentation of the disease, such as the elder population and those working in the healthcare department [29,30], however it is unlikely that the effect of BCG immunization

against infections will extend longer than 12 months [31]. Assessing the importance of BCG in children and new-borns with co-morbidities will be worthwhile, especially in countries without widespread BCG immunization regimens.

In children, trained immunity from routine immunizations against diseases like measles, mumps, rubella and recurrent infections of viral ethology could provide an essential preventative mechanism in defence of the SARS-CoV-2, also childhood mortality has been found to decrease substantially with the use of vaccines against diseases such as polio and measles [32].

Microbial competition limiting colonization and its effect in growth of SARS-CoV-2: Another probable explanation can be limited colonization along with the growth of SARS-CoV-2 because of better mucosal colonization by viruses and microorganism due to microbial interactions and competition amongst themselves [33-35]. In the Attili's investigation, presence of the respiratory nasal bacterial colonization is probably having a much wider and greater impact in the grownup population [36]. In comparison to this, it's far viable that duration of the different viruses which are present in the respiratory system of younger kids would possibly inhibit the development of SARS-CoV-2 thru direct virus-virus interactions [37].

Differences in RAS and ACE2 receptor: ACE-2 receptors (angiotensin-converting enzyme) are one of the important subjects of the sixth hypothesis. They are one of the principal receptors involved in SARS-CoV-2 entrance into cells of the host tissue [38,39]. ACE-2 is a viral endocytosis receptor that also modifies RAS activity from pro-inflammatory to anti-inflammatory [40]. It has also been said that those adults who take Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) for the control of hypertension may have an increased proportion of receptors to ACE-2, rendering those individuals to become more vulnerable to SARS-CoV-2 infection [41,42]. It's also been suggested that, compared to adults, the young age group have fewer receptors in addition with a reduced affinity, and hence are not much susceptible to SARS-CoV-2 [43]. ACE-2 has also proven to show in animal experiments to be a critical regulator of the immune response, particularly in the lungs, and provided protection against SARS-CoV and influenza related pulmonary infection [44-46]. The ACE degrees can be altered *via* way of means of several underlying illnesses and age [47,48], but this hypothesis has to be investigated, as Schouten and his team observed that there has been no marked distinction in ACE and ACE-2 amongst groups of various age [49]. The relationship among concentration of ACE-2 along with the quantity and its relative affinity of ACE-2 receptors is complicated, and it might also be influenced with the role of genetics [50].

Infection of 2nd or 3rd generation of etiological virus may have reduced the pathogenicity: Children usually get their infection from some adult meaning that the children are mostly infected from a 2nd or 3rd generation of the etiological agent. Following generations were defined to have decreased pathogenicity for SARS and MERSCOV [51,52]. According to a retrospective study by Y Yao, et al. in comparison with the 1st and 2nd generation of COVID-19 patients, 3rd generation patients were much older and had less number of younger population [53].

Co-morbid conditions: COVID-19 infections are linked to greater mortality in persons having some additional co-morbidities such as ischemic cardiac disease, cerebrovascular illness, and also a much common factor of obesity [54,55]. The regulation of ACE-2 among smokers, who make up the majority of the adult population, might have a role in having adverse outcomes of respiratory infections [56,57]. They have an advantageous position because most of these morbidities are not typically found in children; nonetheless, passive smoking may be a risk factor for youngsters.

Lung regenerative capacity: With advancing age, gradually lung losses its regenerative properties [58]. In a study performed on young and older mice. Influenza infection resulted in more extensive and severe damage to the alveolar surface, delayed renewal of alveolar cell of type 2 and pro-SPC-positive bronchiolar epithelial cells [59]. This high regenerating potential may explain why COVID-19 patients in children have a milder disease history and recover faster than adults.

Prevention of virus exposure: One of the many explanations in regards to the lower number of COVID-19 infections in children could be due to early isolation and movement restrictions caused by the early closing of schools and day care facilities. Because children's movement is restricted due to tight quarantine protocols, the majority of infections are transferred by infected family members. In assessments of household contacts, youngsters had a significantly reduced risk of infection than the elderly (OR: 0.26, 95% CI 0.13-0.54) [60,61].

DISCUSSION

COVID-19 has created enormous issues all across the world. Children have been relatively unscathed as of now. The various hypothesis leading to this conclusion of children experiencing a much less effect from the virus have been discussed with facts above. The younger age group have a different rather an immature immune system which will mount a relatively different response against the etiological agent as compared to the other population of adult age group. All the factors in the age group such as cross reactive neutralizing antibodies, higher lymphocytic counts and lack of lung senescence have a major and defining role in the protection of children against the devastating effects caused by this deadly COVID virus. They also have a healthier respiratory system, as well as distinct receptor expression in the lower respiratory tract. Another possible mechanism is the impact of confinement tactics such as school and day care center closures. However, more research is needed to look at other possible factors for the differential in severity of SARS-CoV-2 infection in the pediatric and older populations.

Even though, maintaining a healthy immunity amongst the children keeping in mind the spread of the virus is a must. Proper immunization and sanitization policies should be kept in check to have a fair amount of protection which will eventually lead to a natural curb in the spread of this deadly pandemic.

For better outcomes in any severity occurring in children, we need better protocols for treatment and a global approach to share knowledge and formulate a well-defined treatment against the virus. For this to occur there has to be a research on a wide basis keeping in mind several factors regarding the pathogenesis and manifestations of the disease in the pediatric age group. The threat which this deadly disease has bought to this society and all the age groups requires an extensive approach to stop the disease and put an end to the disability and mortality it brings about with it.

For the purpose mentioned above, there has to be certain evaluative factors which have to be studied in detail in all the cases of the pediatric age group which includes the parameters which are indicators of the response produced by the immune system. These include the cytokine levels obtained from the samples of the alveolar fluid from the lungs and blood samples from the affected children.

Autopsies would have to be carried out in case of death of the affected children. Along with it, post mortem biopsies from the lung should be taken to obtain the necessary patterns implicated in the pathogenesis of the lung injury sustained during the COVID infection.

In addition to the existing treatment protocol which offers symptomatic treatment and medications directed towards reducing complications and mortality in an individual, there has to be a way to include anti-viral drugs targeted against the etiological agent, the potency of which has to be evaluated in children.

As stated in the hypothesis and the subsequent discussions mentioned above, the role of ACE-2 expression and the receptors involved in the respiratory system which are involved in the host tissue has to be evaluated so that correct counter measures are carried out keeping in mind the multifactorial pathogenesis of the virus.

CONCLUSION

COVID-19 as a recent pandemic has been a long and major cause of untimely and unexpected deaths amongst a varied population. It has instilled fear within the lives of millions through its typically high rates of mortality and morbidity not to forget the several variants it has produced to sustain itself despite of all precautions and adequately followed treatment.

Throughout the entire area that the pandemic has affected, the children have been relatively less exposed as mentioned through various points and references above. Multiple strategies had been implemented to control the infection amongst the mentioned population on top of the already well existing immunity procured by the paediatric age group naturally keeping them somewhat protected against the viral agent.

Though it's a study still in progress as to determine the exact processes involved in the pathophysiology of the manifestation of the disease in paediatric population. It can be safely assured that there hasn't been any variant yet to cause profound damage to the younger age group. However to ensure that this theory is applicable multiple research strategies are in process to access and study the various investigations and the natural course of the disease in the mentioned population to have a clearer and more appropriate picture that confirms the above reviewed hypothesis.

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