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Short Communication

Immunity Debt: Something New is Old Again

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Immunity debt is a theory that sounds like it has always been around. However, it was very recently published in 2021 describing French children. The concept of immunity debt is that the body, and specifically the bodies of children, needs exposure to viruses to build up the immune system [1].

Cohen et al. noted that COVID-19 public health measures including masking, school closures, isolation, and stay-at-home mandates sharply under-stimulated the immune systems of children. This understimulation, lasting a year or more, increases the severity when the individual is finally exposed to a virus, and this concept is responsible for the rise and virulence of viruses we see currently, especially in pediatric wards [1].

The concept of immunity debt postulates immune defenses do not work as well when the immune system is not active, making the body more vulnerable to both viral and bacterial infections. Frequent exposure provides "training" to the immune system, and reprogramming leads to a stronger response when the individual is exposed again [2]. Immunity debt proponents are concerned that increased hygiene in children has reduced exposure to viral infection and has led to decreased immune training in this population.

Cohen et al. noted several common pathogens and illnesses that affect children including respiratory syncytial virus (RSV), rotavirus, varicella, measles, bacterial, and other viral infections that dropped dramatically during the protective measures placed during the pandemic [1]. In the United States, seasonal influenza rates were almost non-existent during the first year of the pandemic, prompting the Centers for Disease Control and Prevention (CDC) to state, "Estimates are not available for the 2020-2021 flu season due to minimal influenza activity" [3]. As schools reopened, stringent health measures were minimized or eliminated, people resumed regular social activities, and viruses began circulating again, especially in children.

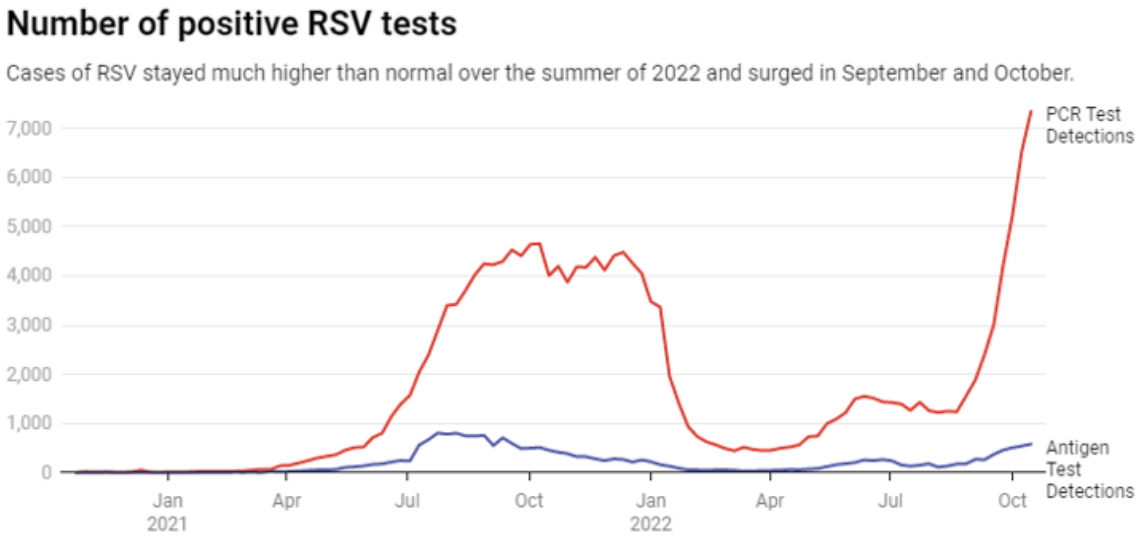

Chart: The Conversation CC-BY-ND. Source: Centers for Disease Control and Prevention [12]

The immunity debt theory has found a champion in the press; they are proposing that social distancing, virtual schooling, plastic barriers, and masking left the children without "trained" immunity. It is not just the press that are touting this theory. Immunity debt may also be a cash cow. Abbott Nutrition, makers of PediaSure, has a full page in their brochure about immunity debt stating that, "kids staying indoors for long prevents exposure to common bacteria causing immunity debt." Additionally, they advise that using two scoops of PediaSure can help bolster the pediatric immune system [4].

Is our immune system like a muscle—if you don't use it, you lose it? Does constant exposure to viruses strengthen the immune system? Did we set up our children for viral and bacterial infection by understimulating their immune systems and by restricting their socialization?

A Quick and Dirty Review of the Immune System

The immune system is a large complex network that keeps the body healthy and is a defense system against germs, bacteria, viruses, and parasites. Organs of the immune system include the skin, mucous membranes, spleen, thymus, tonsils, and bone marrow. Macrophages, T and B lymphocytes, and granulocytes are some of the specialized cells that are part of the immune system. The lymphatic system carries immune cells that are found in lymph nodes throughout the body [5].

The immune system detects and neutralizes harmful substances from the environment. This happens when it encounters a new antigen or activates memory cells that remember old antigens. It also maintains a healthy equilibrium of cell death and cell regeneration. These actions are done by several mechanisms [5].

The innate immune system is the first line of defense to prevent infection and attack pathogens, and a response occurs fairly quickly, within minutes to hours. Innate immunity first uses the barrier response to prevent pathogens from entering the body. These include skin and mucous membranes in the nose, eyes, mouth, and intestinal tract. The second response is the non-specific immune response. The innate response only recognizes a few of the invaders and treats all invaders the same way. The cells involved in innate immunity do not remember the specific antigens, do not remember when they attacked previously, and do not give continued ongoing protection against infections [5].

A third response is an acquired or specific immune response. This type of immunity is not present at birth but is learned by the body, and the learning period begins when an antigen enters the body and the body recognizes it as a foreign invader. The body creates special cells that learn the best way to attack this antigen and develops a memory for that particular antigen. In fact, acquired immunity can also be called specific immunity because it attacks the specific antigen it has met before. Acquired immunity takes some time to develop after it is first exposed to a new antigen. These cells literally learn what the antigen is, adapt themselves to be able to attack it, and remember that exact antigen. Once these cells remember, future responses to that particular antigen are much faster and more effective as compared to an initial exposure [5].

The Wonder of Vaccines

Innate immunity is the type of immunity that may be understimulated by lack of exposure. Though it is not specific, it is not an unintelligent, automatic response to pathogens. Researchers and scientists who worked on the tuberculosis vaccine noted a decrease in overall deaths as well as protection against other respiratory infections. The Bacille Calmette-Guérin (BCG) vaccine was first introduced in the 1930s to target tuberculosis, and in the 1970s, the World Health Organization (WHO) launched a BCG immunization campaign in African and European countries. Multiple studies showed that although this vaccine was developed specifically to prevent tuberculosis, it had many nonspecific effects. Some of these effects "bestowed a type of immunological memory" on the innate immune system, and this innate training was shown to protect against viral infections [6].

Vaccines can have a protective effect, in addition to the specific immunity induced, by reprogramming and stimulating the innate immune system. Scientists and researchers were well aware of the training for the adaptive immune system, and they are now researching how the innate immune system also receives training. There is increasing evidence that our innate immunity can be enhanced by training the immune system. Certain live attenuated vaccines had already demonstrated this form of trained immunity, for example, smallpox, yellow fever, and live polio stimulated both the specific and innate immune response. Currently, this reprogramming is believed to be epigenetic. Scientists are researching how the epigenetic changes wrought by infection and vaccinations train the innate immune system to be more protective [7].

Should we look at these new studies into the innate immune system and conclude that the marked rise in viral illnesses in children is due to immunity debt? Partially this might be true.

Most children have been infected with RSV by the time they are two years old, as it is the most common cause of acute respiratory infection in infants and children [8]. Many young children who would have been exposed to RSV but had not due to isolation measures are being infected now. Without the protective pandemic measures, the virus would have been staggered in this pediatric population. However, now these children all are getting RSV at the same time. It is not just RSV that is landing children in the hospital; several different viruses including influenza, parainfluenza, and respiratory enteroviruses are affecting children as well.

What Should We Do?

Cohen et al. argue for vaccination and a "reinforced catch-up vaccination program" of French children to avoid a dispute over public health measures including masking and school closures [1]. The success of vaccines for many childhood killers including diphtheria, measles, hepatitis, polio, and others prevented these infectious viruses from encountering our immune systems, and the marked difference of life expectancy for children in the past two centuries stands testament to vaccine effectiveness. For every thousand babies born 200 years ago, 462.9 died before age five, and in 2020, only seven deaths were noted per 1000 births [9].

Scientists are currently researching trained immunity-based vaccines that would have a multi-pronged approach. The first is to increase protection by using both the innate and adaptive (B and T cell response) immune systems, and the second is to provide protection to unrelated pathogens using innate training. Future vaccines could help prevent infections for viruses that currently do not have vaccines, and this would help the most vulnerable patients such as newborns, the elderly, or those with an autoimmune disorder. Lastly, this type of vaccine would pre-condition the innate immune system and it would strengthen sub-optimal vaccines or be beneficial for those who do not respond efficiently to vaccines [10].

A Final Word

Many studies on COVID-19 and long COVID have found that close to one in five recovered individuals suffer from persistent symptoms for many months afterward, even those who experienced a mild infection. These reports seem similar to other post-infectious syndromes and point to long-lasting deregulation of the immune response in those who are recovering from COVID-19 [11]. There are some who suggest that children who are so ill from RSV now may have had asymptomatic COVID-19 infections previously which caused the deregulation of their immune systems. It is not necessarily immunity debt that is causing a rise in pediatric cases as it may be a deregulated immune system caused by a prior asymptomatic COVID-19 infection.

There is hope! Progress on an RSV vaccine is promising, and the better we can protect our children with targeted vaccines that help bolster both the innate and adaptive immune system, the healthier they will be.

TL:DR Immunity Debt

- There are those that believe that public health measures for COVID-19 made children sicker. Lack of socialization, masking, virtual school, and staying at home understimulated children's immune systems. This created immunity debt and as the world opened up, children are much sicker now than had they been exposed throughout the pandemic.
- Immunity Debt is a recent theory published in Infectious Disease Now in 2021 about French children. It is important to note that this paper has no evidence cited to back up the theory.
- Conclusion: Normally, children are exposed to viruses in a staggered manner. With lockdowns and stringent public health policies in place, their exposure was restricted. They are now exposed all at once. Others say that these children may have had asymptomatic COVID-19 infections. There is some evidence that post-viral COVID-19 deregulates the immune system. This lack of protection has increased the virulence and rates of RSV, influenza, and other viruses in children.

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