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Over one year of immunity?Reviewingthe durability and determinants of adolescent responses to SARS-CoV-2

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Abstract. COVID-19 is a new disease spreading and causing harm across the world. The lack of research on adolescent immunity limits treatment options, which affects the health status of this age group and society as a whole. This article summarised recent evidence regarding immunity response in adolescents and found that the immunity duration lasts more than one year. However, other factors influencing long-term immunity remain debatable. These results could guide more reasonable vaccine policies and improve treatment plans for adolescents, leading to better control of the spreading of COVID-19.

Keywords: adolescent, immunity, SARS-CoV-2

1. Introduction

The SARS-CoV-2 virus was first detected in Wuhan, Hubei province, China, in late 2019 [1]. The disease it causes, later named COVID-19, started to spread across the world in 2020. While a substantial body of research has focused on the immune response of adults to SARS-CoV-2 [2], relatively few studies have investigated this response in adolescents [3]. As a result, treatments offered to adolescent patients are often similar to those designed for adults. However, adolescents undergo significant hormonal changes during their developmental stages, suggesting that the treatments for them should be tailored to their age groups. Consequently, applying the general research findings from adults to adolescents could be problematic, potentially leading to reduced diagnostic accuracy and less effective clinical management of COVID-19 in this population.

In the past 2 years, COVID-19 vaccines have become widely available across the world [4]. Many countries have started to pay attention to the COVID-19 vaccine policy for younger age groups, as this population is highly active and could serve as significant transmitters of the virus. Hence, investigations regarding the adolescents' immunity patterns are crucial for informing policy updates aimed at improving the vaccination rates globally, enhancing vaccine efficiency, and minimising side effects.

In summary, this article presents a literature review that examines recent insights from scientific studies and provides a comprehensive summary of adolescents' immunity to COVID-19, focusing on long-term immune response to COVID-19 in adolescents.

2. Overview of immune response to COVID-19

The human immune system can be divided into innate and adaptive immunity [5].

The innate immunity response serves as the first line of defence against the SARS-CoV-2. It involves in neutrophils, natural killer cells and macrophages which engulf or kill viruses. However, these cells can barely be tested as a reference to measure the immunity for SARS-CoV-2, as these are non-specific defences.

After the innate immunity response, the adaptive system plays an essential role. T cells, antibodies and B cells are the three key components of adaptive immunity involved in the defence against SARS-CoV-2. T cells are eventually detectable in almost all infected individuals, especially Anti spike IgG, which is a type of immunoglobulin G antibody. Anti-spike IgG represents the past exposure to the virus or successful immunisation. Another key element to test in SARS-CoV-2 is the neutralising antibodies. The presence of neutralising antibodies illustrates the infection or vaccination of COVID-19. Beside Anti-Spike IgG and neutralising antibodies, other types of antibodies such as nucleocapsid protein, IFN antibodies and inflammatory biomarkers are also detectable and could be considered as a measurement of immunity level for SARS-CoV-2 immune studies.

According to the WHO, adolescence refers to individuals aged 10-19, a stage of human development that is unique both physically and mentally [6]. During this period, the immune level of adolescents develops rapidly, including an increase in the

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number of white blood cells, an increase in insulin-like growth factors, and fluctuations in sex steroids. Further investigations are needed to better understand the impact of adolescent immune function on their physical health [3].

3. Overview of reviewed literature

This review summarises 11 studies exploring the immune response of adolescents against COVID-19, spanning various countries —including China, Switzerland, the United States, Germany, and Italy—as well as a range of age groups and research designs. While these regions already represent a significant portion of the global population, they do not capture all possible adolescent COVID-19 immune conditions. Country-specific policies and differing timelines (May 2020 to February 2024) contribute to variability, reflecting the impacts of different virus variants and vaccination conditions.

The 11 articles focus on examining three main types of immunity: humoral, cellular, and antibody. These immune responses are often examined in relation to various factors—such as age, disease severity, and more—within a single study. Factors influencing these immunity types are also analysed, providing particular insights. Sample sizes range from 1 to 2,500, employing cohort, cross-sectional, or case report designs. While larger samples enhance generalisability, findings remain influenced by local policies, COVID-19 prevalence, and regional differences, limiting comparability across studies.

Additionally, the definition of "adolescent" varies across studies, with few adhering to the WHO standard of 10–19 years [6]. This inconsistency may lead to inaccuracies, due to the rapid developmental changes in immunity and growth that occur during adolescence [7].

4. Result

4.1. Immunity duration

Four studies have analysed the duration of IgG antibody immunity inadolescents [9-11].Two cohort studies in Zurich found that anti-spike IgG antibodies were detectable in 99% of students by the 6th months, but this declined to 68.8% by the 24th month[8, 9], which indicates that the detection rate generally decreases over time. This result is further supported and detailed by two American cohort studies, which show that IgG levels increase during the first two months of acute infection, then decline from the second to the fourth month. However, IgG remains detectable at 12 months post-infection [10, 11]. This suggests that the acute immune response period lasts approximately 2-4 months.

Regarding the half-life of IgG, the study by Raineri et al. suggests that it is estimated to be 305 days [95% Cl 263-363 days] [8]. However, another cohort study reported an average half-life of 121.6 days [12]. These disagreements may arise from variations in sample size and detection methods.

Overall, IgG antibodies produced by most individuals after infection or vaccination can persist for more than one year, with more than half lasting beyond 2 years. It is also important to note that testing is conducted some time after infection due to the incubation period, so the actual duration of IgG presence may be longer than recorded.

4.2. Age

In relation to the age and the IgG antibodies level, a cross-sectional study in Germany reported average IgG levels of 600 BAU/ml in children under 10 and 6,500 BAU/ml in those aged 10–21, suggesting a positive correlation with age [13]. However, Yang et al. found the opposite: adolescents aged 11–18 had higher IgG levels (473 [CI: 233–656] RFU) than young adults aged 19–24 (85 [CI: 38–150] RFU) [14]. These studies, conducted in different U.S. states using different methods, suggest immune responses may vary by population and variant.

Two studies found no significant difference in nAB levels across age groups [8, 9]. However, Rothoeft et al. reported higher levels in the 10–21 age group (1,300 RLU) than in those under 10 (230 RLU) [13], suggesting a positive correlation. In contrast, U.S. cohort and cross-sectional studies found adolescents had higher nAB levels than adults at various time points post-infection [11, 14], indicating a negative correlation. Overall, no consistent pattern has been identified; factors beyond age, such as region and timing, likely influence nAB levels.

A case-control study in Hong Kong found no significant differences in CD4+ T cell frequency across age groups using M/N/S peptide pools (Cohen's $d = 0.071$), but S-peptide-specific CD4+ T cells were negatively correlated with age in minors (Cohen's $d = 0.306$). No CD8+ T cell difference was found (Cohen's $d = 0.032$) [15]. In contrast, Paniskaki et al. reported higher CD4+ and CD8+ T cell responses in children and adolescents than adults [9]. These discrepancies may due to regional and methodological differences.

Another German cross-sectional study also showed a positive correlation between age and IFN-γ/NCP antibody levels. IFN-γ averaged 0.7 IU/ml in children under 10 and 0.9 IU/ml in those aged 10–21, with a 15-year-old vaccinated outlier reaching 10 IU/ml. NCP antibodies averaged 25.0 IU/ml and 40.0 IU/ml in the same groups, respectively [13].

4.3. Intensity and hybrid immunity

A study from Hong Kong found that T cell responses in adolescents decay much more slowly than antibodies, with no correlation between IgG decay (−0.0377 anti-RBD IgG ratio/day; $R^2 = 0.58$) and T cell decline ($CD4^+$: −0.0022%/day, $CD8^+$: −0.0001%/day) [15]. This suggests that T cells offer more stable, longer-lasting immune protection. A case report from Shanghai further supports this, showing that cellular immunity can play a crucial role in COVID-19 defence, even compensating for the absence of antibodies in some cases [16]. Additionally, 30% of asymptomatic adolescents tested positive for N-antibodies, indicating that immune responses can develop without noticeable symptoms [12]. These findings suggest that immune response intensity is not strongly tied to infection severity.

Hybrid immunity—resulting from both infection and vaccination—has been shown to produce higher neutralising antibody levels [17]. However, these levels often wane by around six months post-infection unless the immune system is re-stimulated. High antibody titres in such cases are also linked to increased IFN-γ release. Despite this, most studies agree that symptom severity is not closely correlated with antibody levels; adolescents with mild or no symptoms can still develop strong and lasting immune responses.

A rare case involving a 15-year-old patient who failed to produce detectable IgG even 53 days post-infection highlights individual variation in immune response and the potential role of underlying immune system differences [16].

5. Implication

To summarise, majority of studies confirmed that the immunity duration following SARS-CoV-2 infection in adolescents can last for over 1 year, with this finding supported by substantial evidence. However, conflicting findings were reported regarding the relationship between long-term immunity and factors such as age, severity, intensity, indicating no obvious consensus, and highlighting the need for more researches. There is also a notable case indicating that some individuals may be unable to produce any antibody response, highlighting the importance of additional protection for adolescents.

6. Limitation

Several limitations exist in this review. First, differences in study results may be due to things like sample size, testing methods, age groups, and health conditions such as high BMI, high blood pressure, or diabetes. One common issue is the definition of adolescence. Although the WHO defines adolescents as those aged 10–19 [6], most studies don't treat this group separately, which makes age-related data unclear. Also, because vaccines were given to different age groups at different times, it's hard to tell if differences in antibody levels are due to age or the timing of vaccination. This review only looked at some major and well-known studies, and does not include all published data.

7. Future research

There are still many areas of disagreement in current studies, especially regarding the relationship between immunity and infection intensity or symptom severity. Future research should involve more precise age groupings, larger and more diverse sample sizes, longer time frames, and varied detection methods.

In addition, further research on other non-COVID vaccines is needed, as they may have cross-over effects on the new coronavirus, though there is currently insufficient evidence to support this.

8. Vaccination strategies

Vaccines play a crucial role in enhancing immune responses across all age groups. Most studies suggest that adolescent immunity lasts around one year post-vaccination, supporting the need for a booster within 12 months. However, since T-cell immunity declines more slowly than antibody responses, both humoral and cellular data should inform vaccination schedules to ensure lasting protection. Variability across studies indicates that immune responses may differ due to developmental stages, highlighting the need for more tailored, age-specific vaccination strategies.

According to World Health Organization (WHO), adolescents aged 12 and older should receive two COVID-19 vaccine doses spaced 4–8 weeks apart, followed by a booster 4–6 months later (Pfizer BNT162b2 and Moderna mRNA-1273) [18, 19]. Updated WHO guidance from March 2023 recommends administering boosters 6–12 months after the primary series. However, as adolescents are considered a lower-priority group, national strategies may vary [20].

Global data reveal major differences in vaccine uptake: Mexico reports the highest acceptance rate among adolescents (95.2%), while Turkey reports the lowest (36.3%) [21]. These disparities suggest that many adolescents are not vaccinated as recommended, often due to social, political, or economic barriers.

To address this, public health efforts should focus on improving awareness of vaccine safety and effectiveness. Offering free doses through schools could also potentially boost uptake by reducing financial barriers.

9. Conclusion

In general, it is widely agreed that the duration of long-term immune response in adolescents can last for around 1 year on average, but other factors influencing the duration and strength of immunity have yet to be confirmed. COVID-19 severely affected our lives, more research on adolescent immunity could help guide better protection strategies.

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