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RESEARCH HIGHLIGHT

COVID-19 vaccines and beyond

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Hundreds of vaccines have been developed worldwide for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of Coronavirus disease 2019 (COVID-19), since the beginning of the pandemic. These vaccines have saved innumerable lives and contributed to partial control of the COVID-19 pandemic. Most of the vaccines approved for clinical use exhibit satisfactory initial protection rates against corresponding strains. However, vaccine protection declines over time, with almost all vaccines falling below 50% protection after 6 months [1]. In the case of natural infections, protection lasts longer, but the incidence of reinfection is also quite high.

Unsatisfactory vaccination coverage against SARS-CoV-2 is not the first challenge of vaccinology. Over many decades, influenza vaccines have never been able to elicit long-lasting immunity against seasonal influenza virus strains. The RSV vaccine, which was approved by the FDA of the USA a few months ago, provides favorable protection against severe lower respiratory tract disease, but its efficacy in preventing infection remains unsatisfactory. Experts in the field have categorized viruses such as influenza, RSV and SARS-CoV-2 as nonsystemic respiratory viruses because they have only mucosal replication periods and no subsequent systemic spread of infectious virions. A commonality of non-systemically replicating respiratory viruses is that they tend to repeatedly reinfect people, closely linked to the fact that none of the predominantly mucosal respiratory viruses have ever been effectively controlled by vaccines.

An explanation for reinfection by nonsystemically replicating respiratory viruses is that this type of mucosal virus does not elicit complete protective immunity against reinfection [2]. The advantages of viruses that evolve from host–virus relationships, such as mucosal tolerance, could be the cause of repeated infections. However, these factors may not be obstacles for developing vaccines because vaccines can be developed artificially by eliciting complete immunity rather than solely a mucosal response. There is a consensus in the field that the next-generation SARS-CoV-2 vaccine will take advantage of enhancing secretory mucosal immunity and bursting protective IgA responses, but an incomplete understanding of the immune response against mucosal respiratory viruses is still a major limiting factor for developing new strategies to effectively control viral spread. Here, we discuss a few likely neglected views on SARS-CoV-2 prevention and management. One commonly heard comment is that the short protection period of SARS-CoV-2 vaccines is due to the rapid decrease in the anti-SARS-CoV-2 antibody level after vaccination. It is true that protection with some immunizations, such as measles and EBV, can be lifelong, whereas the protection provided by others could be much shorter. Studies have also shown that the rate of decrease in serum antibodies is not consistent during different periods after vaccination and tends to decrease over time [3]. Although not as dramatic as that of measles and EBV, the vaccines for HBV and HPV elicit excellent protection against related infections. A half reduction in the serum antibody level against HBV takes approximately 60–100 days within the first six months, that against HPV takes approximately 70–120 days, and the decay rate is significantly lower at later times [4, 5]. There is no long-term serum antibody tracking data for SARS-CoV-2, but several short-term studies have revealed that the half-life of serum SARS-CoV-2 antibodies within six months of vaccination is approximately 40–90 days [1, 3, 6]. These findings suggest that the rate of decrease in the serum antibody concentration against SARS-CoV-2 is not obviously faster than that against HBV or HPV. Thus, the rapid decrease in protection afforded by the SARS-CoV-2 vaccine is unlikely to be attributed to the more rapid decrease in the titer of anti-SARS-CoV-2 antibodies than other vaccines.

The high receptor affinity of SARS-CoV-2 poses challenges for vaccine protection. The spike protein of the SARS-CoV-2 Alpha strain has an affinity for the ACE2 receptor of 3–7 nM, approximately 10 times greater than that of the original strain. Similarly, the affinities of the spike proteins from the Beta, Gamma, Delta and Omicron strains for the ACE2 receptor are approximately 2~5 times greater than that of the original strain. Overall, SARS-CoV-2 has receptor affinities ranging from 3 to 40 nM [7], which are higher than those of HBV (67.1 nM) [8], measles (80~400 nM) [9], and poliovirus (110~670 nM), which have persistent vaccine efficacy [10]. By reasoning, the greater the affinity of a virus for a receptor is, the more difficult it is to use neutralizing antibodies to prevent the virus from binding to host cells. Thus, the threshold titer of antibodies for protecting against SARS-CoV-2 infection should be higher than that for most other viruses.

Differences in the incubation period may also contribute to variations in vaccine effectiveness across different viruses. The short incubation period of SARS-CoV-2 makes it difficult to protect against this virus by immunization. Influenza viruses have an incubation period of approximately 1–3 days. SARS-CoV-2 has an incubation period of approximately 2–10 days. The incubation period of the hepatitis B virus is approximately 50–150 days, that of the measles virus is approximately 9–14 days, and that of HPV is approximately 50–150 days. It is generally believed that a certain

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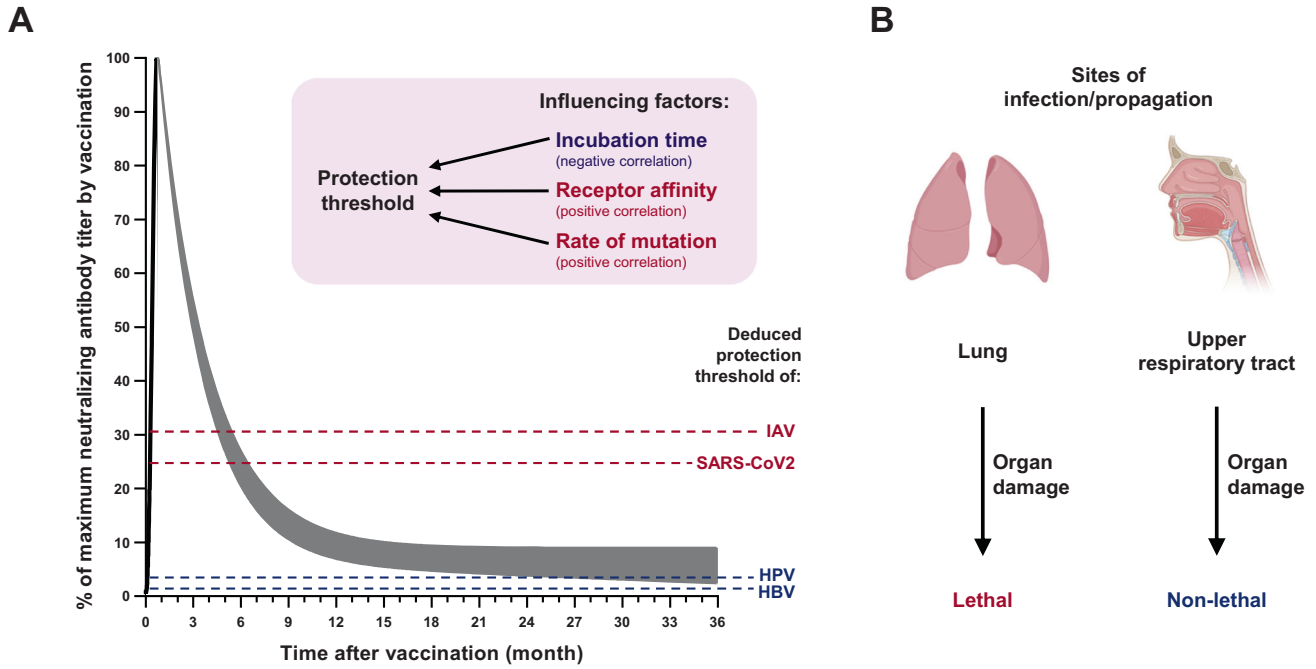

Fig. 1 Factors that may influence the protection of viral infection and the outcomes of COVID-19 patients. **A** The schematic diagram of neutralizing antibody titer relates to time after vaccination and deduced threshold levels of neutralizing antibodies for the protection against SARS-CoV-2, influenza, HPV or HBV infection are shown. Factors that can increase or decrease the threshold are summarized in the box. **B** Different viral infection/propagation sites, such as the lung and upper respiratory tract, could result in different survival/mortality outcomes of infected individuals

incubation period of a virus is required for host serum antibodies to neutralize the virus and for adaptive immunity to occur. The short incubation time of SARS-CoV-2 is a disadvantage against protection by vaccination.

The continuous variation in SARS-CoV-2 strains is one of the major reasons for the reduction in vaccine protection and virus reinfection. Antibodies generated in response to previous strains of the virus may not effectively bind to the newly emerging mutated antigen sites, resulting in a rapid decrease in the actual neutralizing antibody titers. This effect is particularly pronounced with the emergence of the Omicron variant. After vaccination, the neutralizing antibody titers against Omicron are approximately tenfold lower than those against the Delta variant [6]. Even though the vaccine provides approximately 90% protection against Delta, it offers only approximately 50% protection against Omicron [11].

All SARS-CoV-2 vaccines used in the clinic can effectively prevent the infection of corresponding strains in approximately a half-year period. As expected, a correlation between serum antibody levels and protective efficacy was observed [1], and the initial antibody levels raised by various vaccines were greater than the protective threshold. Maintaining the neutralizing antibody titer above the threshold is required for protection. The threshold level of antibodies for protecting against HBV infection is ~10 mIU/mL, and the antibody levels can exceed this threshold by several hundred times after complete vaccination [4]. The threshold of protection of antibodies against measles is considered to be 120 mIU/mL [12], and vaccine immunization increases antibody levels to approximately 1000 mIU/ml [13, 14]. The titer of neutralizing antibodies for protecting against poliovirus infection is approximately 1:4–8, and vaccine immunization raises the neutralizing antibody titer to approximately 1:400–5000 [15, 16]. Many studies have shown that there is still a fairly high protective effect even years after HPV vaccination, with serum antibody levels falling below 100 mMU/mL [5]. In the case of SARS-CoV-2, the neutralizing antibody titers corresponding to 50% protection against SARS-CoV-2 infections ranged from 1:10–40 [1], and the serum antibody levels from infected or vaccinated individuals were approximately 1:200–1000 [3, 6]. The hemagglutination inhibition (HAI) titer corresponding to 50% protection against influenza infections was approximately 1:18–40 [17], whereas the HAI titers in vaccinated individuals ranged from 1:300–1200 [18]. Due to inconsistent measurement units and experimental standards, the evaluations and comparisons above are very rough, but these data indicate that a much higher initial antibody titer than the threshold is linked to long-term protection (Fig. 1A). Thus, to develop an ideal vaccine for SARS-CoV-2 that can maintain a titer above the threshold of protection, a new vaccination strategy that can produce many additional and/or super high-affinity neutralizing antibodies is needed.

SARS-CoV-2 variants, particularly Omicron, have evolved to become less virulent. Although other viral proteins, such as nsp6, may also play a role, the Omicron spike (S) protein is the main driver. Mutations in the S protein increase the attachment potency of the virus but decrease its ability to fuse with host cells. The Omicron S protein is less dependent on TMPRSS2 (transmembrane protease, serine 2) [19]. Since the expression level of TMPRSS2 is greater in the lung, whereas ACE2 expression gradually decreases from the upper respiratory tract to the lung [20], Omicron tends to infect/propagate through the upper respiratory tract rather than the lung. Since the tissue/organ damage of the respiratory tract is not life-threatening, but rather that in the lung is, what makes the Omicron variant less dangerous is most likely because the lung is not attacked as often as by past variants (Fig. 1B).

From the current perspective of SARS-CoV-2 vaccines, no vaccine can provide long-term protection. By comparing various vaccines and their corresponding viruses, we believe that the reason is the nature of the virus but not the rate of anti-SARS-CoV-2 antibody decay. The rapid mutation of SARS-CoV-2 driven by global-scale infection contributes to the unsatisfactory long-term protection afforded by SARS-CoV-2 immunization, but its high affinity for host cells and short incubation period are major obstacles to the development of satisfactory vaccines (Fig. 1A). As we reasoned

above, long-term protection against such viruses requires a very strong antibody response. Current knowledge and technology are insufficient, and the future of an effective new generation of vaccines for SARS-CoV-2 infection remains uncertain.

Although the long-term protection afforded by vaccines is not satisfactory, the current vaccines have substantially reduced the risk of death and contributed greatly to the control of the COVID-19 pandemic. Preventing severe sickness by vaccination may result from immune responses that last longer than the short incubation time of SARS-CoV-2. The success of immunization and the ability of SARS-CoV-2 vaccines to activate adaptive immunity have been demonstrated by the reduced sickness in infected individuals. It is fair to say that the evolving low-virulence Omicron variant is one of the major factors that led to the end of the pandemic. The reduction in mortality associated with Omicron infection is likely to result primarily from the switch of the infection/propagation site from the lung to the upper respiratory tract; thus, we must remain vigilant, as danger is a possibility if mutations switch the infection site back to the lung (Fig. 1B). To provide long-term protection against SARS-CoV-2, we may have to develop a strategy that can induce much more effective immunization than any of the currently used methods. On the other hand, vaccination-induced T-cell immunity deserves additional study because reducing mortality is the most important part of controlling the COVID-19 pandemic.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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