What does immunogenicity mean in the context of COVID-19 vaccines?

In response to the COVID-19 pandemic, scientists all over the world have been working with determination and perseverance tirelessly to develop vaccines against the SARS-CoV-2 virus. As part of the development process, vaccines must undergo rigorous clinical trials before they can be assessed and approved by regulatory authorities for use by the wider public. Vaccine clinical trials are designed to build an understanding of the safety of the vaccine and to determine how well they work, their efficacy and immunogenicity, across a wide span of people[1].

Efficacy is a measure of how well a vaccine works, and can be measured by investigating a vaccine's ability to prevent disease[1]. For COVID-19, which presents with a range of severities, measures of efficacy (endpoints) can include reductions in asymptomatic infections, symptomatic infection, hospitalisations and deaths. For each of these endpoints, efficacy is determined by comparing a group of people who received the vaccine with a group who receive a placebo. If the number of infections, hospitalisations or deaths in the placebo arm of the trial is significantly higher than that of the COVID-19 vaccine arm, then efficacy can be conclude[2].

Immunogenicity however, is a more complex measure of how well a vaccine works, and measures the type of immune responses that the vaccine generates and their magnitude over time[2].

Vaccines work by teaching the body to recognise a foreign invader (a pathogen) by priming the immune system, by introducing either part or an inactivated form of a pathogen and allowing the body to develop an effective response without danger of disease. This priming of the immune system means that, should the pathogen be encountered naturally, the immune system is able to react more quickly and effectively than if it were unprimed[3]. When we measure immunogenicity, we look at which types of immune responses are activated and their magnitude over time. This analysis provides valuable information not only on how well a vaccine is working, but can support aspects such as the determination of dosage and immunisation schedules[1].

Measuring immunogenicity is, however, a complex process and poses challenges for scientists. In the case of the SARS-CoV-2 virus, which is a new infection, these challenges are amplified. The first of these challenges comes in defining what good looks like with regards to a vaccine-induced immune response.

In order to determine if a vaccine is able to effectively produce a strong and sustained immune response, a vaccine-induced immune response would typically be compared to the immune response found in people who have known immunity to a disease. Where the response is comparable or greater, then the vaccine shows promise of being effective[1]. However, for COVID-19, scientists are still working to learn what constitutes an effective natural immune response. Until this has been defined, it is difficult for scientists to state definitively what a good vaccine-induced immune response would

look like. Initial research combined with our knowledge of other coronaviruses such as SARS has, however, provided a guide. Antibodies, specifically those that are able to bind to the spike of the SARS-CoV-2 virus and prevent it from entering cells, which are known as neutralising antibodies, have been shown to be associated with protection against infection in preclinical disease models. While it is believed that these types of antibodies are important for protection, it is not yet known what level, or titre, is needed for protection. Recent studies have also suggested that the magnitude of neutralising antibodies generated from natural infections may wane over a period of months. While this is not unexpected, it is as yet unknown what impact this will have on the longevity of immunity. T-cells, which work to activate other parts of the immune system or to directly kill invading pathogens, are also thought to play a role in immunity to the SARS-CoV-2 virus, due to their presence in people who have had either asymptomatic infection or who have recovered. Again, the specific type and number of T-cells required for protection is still unknown[4].

When measuring immunogenicity, scientists look at two key aspects of the immune response:

Antibodies

Antibodies are able to bind to the surface of invading pathogen. This binding can flag the pathogen for destruction by immune cells and can stimulate the development of proteins known as compliment which further promotes pathogen destruction. Antibodies are also able to inhibit infectivity by binding to the pathogen and blocking the molecules it needs to enter cells, thereby neutralising it[5]. It is the second type of antibodies, the neutralising antibodies, which have been implicated as a correlate of protection, but other types of antibodies are also seen in response to natural infection with the SARS-Cov-2 virus[6]. People who have never been exposed to a pathogen will have extremely low background levels of antibodies that are able to bind to the virus, and they are said to be sero-negative. People who have previously been exposed to a pathogen either naturally or through vaccination may have high levels of antibodies able to bind it and are said to be sero-positive. The overall level of antibodies a person has produced can be measured through techniques such as ELISA (enzyme-linked immunosorbent serum assay), and specific neutralising antibodies can be screened for via virus neutralising assays

Antibody assay infographic

T-cells have many roles in the immune response, including activating other immune cells, producing cytokines - secreted factors which can activate or inhibit other immune activity - and even directly killing infected or abnormal cells[5]. Measurement of T-cell responses can be more complex than the measurement of antibody levels, but through assays such as enzyme-linked immunospot assays it is possible to define which types of T-cells are present and at what level.

T Cell assay infographic

The second major challenge that scientists face when measuring the immunogenicity of vaccines, is the lack of global standardisation across the measurement process. Due to the speed at which scientists across the world have worked in response to the pandemic, it has not been feasible to pre-align on the exact methodologies of the tests used. As shown in the diagram, there are several types of immunoassay which may be used to measure a single aspect of the immune response e.g. neutralising antibodies and for each variation, a different set of reagents and screening processes will be used. Due to the diversity in testing methodologies being carried out in various laboratories around the world, there is currently no definitive set values for a protective immune response. This variation in measurement also means that it is currently not possible for scientists and regulatory authorities to effectively compare vaccines based on their immunogenicity data, as the data for each vaccine may be

generated through a different testing methodology, in different laboratories and with no comparative standards available[2].

In time, standardisation of assays will occur, allowing the scientific community to build a greater understanding of the immune response to the SARS-CoV-2 virus and further development of vaccines and therapeutics for COVID-19[2]. AstraZeneca is committed to collaborating with scientists, governments and multilateral organisations around the world, to ensure robust scientific standards are met and to further scientific knowledge into the SARS-CoV-2 virus.

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