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Safety of the COVID 19 Vaccines: Implications for Future Vaccine Development

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ABSTRACT

The past few years have witnessed development of new vaccines especially for highly pathogenic viruses like the SARS CoV2 and Ebola. Rollout of the vaccines against SARS CoV2 was the fastest ever recorded in the history of modern medicine and it was indeed a creditable feat achieved by the basic scientists and manufacturers to develop and actually administer a vaccine within months of the detection of a virus. These developments have been made possible and informed by advances in basic biology and vaccine science, including new vaccine antigens, newer and advanced vaccine platforms and newer vaccine adjuvants. While the EUA (emergency use authorization) for the developed vaccines by authorization agencies listed them as safe and effective but questions have been raised about the extent the safety of these vaccines, given their speedy development and a perceived 'less than optimal' time for long term safety.

Keywords: SARS CoV2; Vaccine science; Medicine; Biology; Pathogenic virus

INTRODUCTION

Some people have side effects from the vaccine, which are normal signs that their body is building protection. These side effects may affect their ability to do daily activities and are generally self-limiting. Speedy introduction compared to the previously introduced vaccines was used by anti-vaxxers as a reason for advocating against the use of COVID-19 vaccines, leading to an epidemic of mis- and dis-information. A number of adverse effects have been reported through various reporting agencies including the Vacccine Adverse Event Reporting System (VAERS) and other similar such systems in various countries. These have among others included anaphylaxis, thrombosis with thrombocytopenia syndrome (VITT), Guillain-Barre syndrome, myocarditis and pericarditis. In the US, VAERS has also received 14,180 preliminary reports of death (0.0025%) the COVID-19 vaccine recipients [1].

Continued monitoring has identified 9 deaths causally associated with Johnson and Johnson/Janssen COVID-19 vaccination. Pertinently, programs like the VAERS are well armoured to identify isolated major vaccine related adverse events with defined phenotypic definition with a clear temporal relationship with the administration of the vaccine, they are inherently not well adapted to recognize adverse events without strong phenotypic markers or temporal associations or those VAE that may be subclinical [2].

LITERATURE REVIEW

Whenever confronted with a public health emergency like the COVID pandemic, a balance has to be between rapid development and deployment of a potentially life-saving vaccine and investigation of less severe adverse events. How can adverse events be identified and quantified if they cannot be measured by standardized diagnostic tests? Similarly, we have only embryonic understandings of the theoretical effects of vaccines, such as effects on epigenetics, trained immunity, antigenic imprinting and longer-term mutational pressure [3]. Similarly vague isolated side effects like tinnitus, sudden elevation of blood pressure, intense myoarthralgias have been reported without clear assessment of causality. Such grey areas call for significant and focused research for understanding the novel adverse effects of newer vaccines.

Vaccines have traditionally been known to have both local and systemic side effects mediated by various mechanisms. A crucial property of vaccines is the ability to elicit a sufficiently strong

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innate immune response to enhance antigen presentation and stimulatory signals required for cellular immune activation. Inappropriate immune response to the administered antigens can also drive vaccine-induced adverse effects through overstimulation of innate immunity, cross-reactive adaptive immune responses to host epitopes or the generation of autoimmune responses [4]. Thus immune responses are also responsible for most of the common, transient side effects after vaccination, such as injection site pain, fever and myalgia. While all vaccines are tested for adverse effects during preclinical development, it is possible that these reactions may only occur in specific situations or in rare population groups and therefore will not be apparent until larger clinical trials or after widespread use in the general population. This is especially true when there is intense public health pressure to introduce a vaccine where the fast turnaround could have resulted in less than desired follow-up of the recipients for long term adverse effects. Vaccine developers must therefore find the right balance to achieve the minimum reactogenicity necessary for optimal immunogenicity and efficacy [5].

Vaccine induced cross-reactive cellular immune responses, involving T cells or B cells, is responsible for the cross protection of the vaccines against non-vaccine pathogens. For example, BCG vaccine (containing *Mycobacterium bovis*) cross reacts against *Mycobacterium tuberculosis* [6]. Similarly, cross-reactivity related immune responses to rotavirus, pneumococcal, meningococcal, human papillomavirus and other vaccines provide broader protection against pathogen strains not included in the vaccine. This cross-reactivity, on occasion, may target host proteins and lead to adverse effects [7]. An example of this effect is the development of narcolepsy in few recipients of the AS03-adjuvanted influenza A/H1N1 vaccine, associated with the HLA-DQB1 haplotype. The similarity in sequences between the influenza nucleoprotein and the receptor for hypocretin (sleep regulating neurotransmitter) has been proposed as the potential mechanism for narcolepsy as a result of the immune response to the adjuvenated vaccine [8]. Antibodies from affected individuals have been demonstrated to cross-react with both proteins. In the context of the COVID-19 vaccines, few recipients of the adenovirus-vectored vaccine developed VITT [9]. While no clear mechanism has been put forth to explain the rare adverse effect, cross reactivity between the vaccine induced antibodies and platelet factor 4 have been proposed as a mechanism. Recently 1E12, a chimeric anti-PF4 antibody with a human Fc fragment and VITT antibodies have been demonstrated to recognize overlapping epitopes on PF4 [10].

DICUSSSION

Another possible mechanism for vaccine induced adverse effects is the autoimmune response as a result of excessive or chronic inflammation induced by the vaccine. Strong data suggest a link between infection and the development of autoimmune disorders [11]. Multiple large, observational and epidemiological studies have been carried out to examine the link between vaccines and allergic or autoimmune diseases. Although these studies have limitations, there is a consistent lack of evidence linking vaccines to autoimmune disease. Nevertheless, in the era of novel vaccines on novel platforms, the possibility deserves continued attention [12].

Safety is a primary consideration in vaccine development and because vaccines are typically given to healthy individuals to protect against a possible future disease, the bar for safety is necessarily much higher than for other medical interventions [13]. Vaccine safety is an area in which continued support is essential in basic, translational and clinical research. The most important of these is an enhanced surveillance during clinical trials and post-marketing. This should include a better understanding of the background rates of potential complications, as well as syndromic surveillance, recognizing the importance of identifying collections of adverse events. Also, increased basic research into the molecular and immunological mechanisms elicited by vaccines will provide crucial information regarding the pathways that drive adverse events [14]. Such knowledge could potentially help obviate such problems in future vaccines. A case in point would be the research into the mechanisms of VITT that can be used to modify future iterations of adenovirus-vectored COVID-19 vaccines.

Since adjuvants are routinely being used in the development of vaccines, an inquiry into the effect of these adjuvants on innate and adaptive immune responses to optimize protection against different pathogens, while minimizing potentially pathological reactogenicity [15]. An increased use of systems biology approaches will be needed to fully characterize, assess and understand the complex interactions between cells, tissues and molecules that constitute immune responses, both protective and aberrant or pathological. Against this backdrop, robust safety surveillance systems that serve the public agenda are essential for public trust and acceptance of vaccines. These are especially important in countries that have less developed surveillance systems for monitoring or recording vaccine related adverse effects. Identification of safety issues allows for the identification of mechanisms involved in such events and thereby the reverse engineering of new vaccine candidates to avoid activating such mechanisms. Surveillance systems can also help us understand as to who will experience vaccine-related adverse events and under what conditions and if safety issues can be predicted at the individual level in the future?

CONCLUSION

This would help inform new vaccine development and vaccine public health policy. While we must understand that no vaccine can be completely free of adverse effects, the critical question to answer in all of these settings if to see whether the frequency and severity of the adverse effects can be justifiably balanced against the benefits of the vaccine. Pathogens will continue to emerge and surprise us. We just need to have pre-emptive robust systems in place to balance the rollout of novel vaccines against their potential adverse effects.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare in relation to the manuscript.

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