Vaccine non-responders and severe adverse events

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Eyer Klaus, an Associate Professor at Aarhus University's Department of Biomedicine, explores the causes, impact, and potential resolutions of vaccine non-responsiveness and severe side effects

Vaccination has had a tremendous net positive effect on individual and public health and remains a crucial and cost-effective preventive pharmaceutical intervention. While most vaccine recipients develop protective immunity, some individuals do not, and rare severe side effects may occur. Both occurrences represent key problems in vaccination, not only at the individual level but also beyond. This discourse delves into the complexities surrounding these issues and highlights interconnected challenges alongside prospective resolutions from a basic researcher's perspective.

Measuring vaccine protection

Understanding and quantifying vaccine protection, while conceptually straightforward, poses substantial challenges. Scientists, therefore, attempt to define so-called correlates of protection (COP) during vaccine development and assessment. [1, 2, 3] The identification of COP holds principal importance for determining vaccine efficacy, optimizing dosing regimens, and ensuring adequate population immunity, as the right COP corresponds to a measurable indicator that is used to measure and predict immunity post-vaccination reliably.

However, finding COP represents a formidable challenge in vaccine development and assessment. One major difficulty lies in the multifaceted nature of the immune response and the definition of a sole individual parameter that correlates with protection.

Successful immune responses encompass various mechanisms and elements, including antibodies, T cells, memory cells, and cytokines, each contributing distinctively to the response and pathogen defense. Determining which of these components are reliable correlates requires comprehensive understanding, meticulous experimentation, and exact and resolved measurement methods. Furthermore, the correlation between immune response and protection can exhibit variability across different pathogens and vaccine modalities. Additional factors such as genetic predispositions, age, hormones, and underlying health conditions further introduce complexity and variability, making it challenging to generalize COP across subpopulations.

Overcoming vaccine non-responders

Vaccine non-responders, denoting individuals who fail to develop a protective immune response following vaccination, represent a notable challenge in vaccine-mediated prevention. [4] Non-responsiveness not only imperils the health of the affected individuals but also diminishes the fraction of protected individuals in the immunized population. Non-responsiveness can stem from many factors, encompassing genetic predispositions, underlying health ailments, age-related factors, immunosuppressive therapies, or individual variations in immune system reactivity.

While the precise prevalence of vaccine non-responders remains a topic of ongoing scientific discourse, a notable proportion of initially unresponsive individuals may eventually mount a protective immune response following supplementary booster doses. Nevertheless, estimates typically suggest that around 3-7% of vaccinated people may not develop immunity even after such intervention. While this implies a vaccine efficacy rate of about 93-97%, it also highlights that many people do not respond to current vaccination. These vaccine non- responders might not be uniformly distributed across the general public and may aggregate within disease- susceptible subpopulations.

Current strategies to address vaccine non-responders primarily hinge on attaining herd immunity. In this case, the individuals are passively protected by the limited disease transmission within the community. However, the issue of non-responsiveness can also be directly addressed. Utilizing straightforward clinical scores aids in the identification of potential non-responders, allowing for the specific scheduling of follow-up in-depth assessments and interventions. [5] Active interventions in identified non-responders include changes in vaccination schedules and different vaccine designs or administration routes, and many initial non-responders will mount a subsequent protective immune response after such regimens.

Nevertheless, addressing the residual cohort of vaccine non-responders requires a multifaceted approach as they likely also represent a subpopulation with compromised or modified immunity. Comprehensive screening protocols will help identify non-responding individuals to study their immune restrictions and, if possible, unveil potential ways to overcome these. A deeper understanding and precise evaluation of the distinct mechanisms underpinning immunological impairment is needed in these groups. Such understanding would allow for a more personalized approach to vaccination strategies in different risk groups, enhancing vaccine responsiveness. Genetic testing and baseline immune status assessment may offer insights, but environmental factors and biases must be considered. Functional analysis of pivotal immune pathways is integral in augmenting these investigations. Understanding the intricacies of their immunity and deviations from typical immunity may inform the development of vaccines capable of overcoming such limitations alongside optimized vaccination regimens, formulations, adjuvants, alternative administration routes, and optimized vaccine delivery methods. Ultimately, defining indicators and markers of non-responsiveness, together with simple and rapid test systems allowing the determination of these markers reliably and cost-effectively, could aid in determining the individuals that will profit most from these modified vaccination regimens.

Overcoming/reducing severe adverse events and vaccine hesitancy

Rare yet severe side effects following vaccination emerge as a critical concern for individual wellbeing and public health. Such occurrences inflict profound harm on affected individuals and their immediate environment, burden healthcare systems, erode trust in vaccination initiatives and fuel broader vaccine hesitancy. [(6)] Despite rigorous pre-approval safety assessments, extreme adverse events may only surface once vaccines are administered to large populations due to their rarity and the inherent variability in individual responses. [(7)]

Robust surveillance systems are in place to swiftly identify and address any adverse events post-vaccination, facilitating prompt reporting and comprehensive investigation. This diligent monitoring aims to pinpoint potential safety signals and ascertain their causation with vaccination. Once identified, research into vaccine safety and the underlying mechanisms of rare severe adverse events is crucial.

Ideally, individuals predisposed to such risk would be identified preemptively, allowing for adopting alternative immunization approaches devoid of such risks. While this approach remains aspirational today, ongoing efforts by researchers and clinicians focus on delineating and understanding the various immunological causes of severe adverse events. This entails exploring potential risk factors, devising means of early or preemptive identification, and formulating strategies to mitigate or prevent these events while preserving the overall benefits of vaccination.

Although the success of such an approach may not be universal, and the path forward presents difficult scientific and economic challenges, advancements in this realm hold promise, given the involved relationship between vaccine hesitancy and rare, severe side effects. Realizing these aspirations likely demands innovative breakthroughs in development, manufacturing, and regulatory approval processes to enable such advances. Ultimately, the overarching objective remains the preservation of vaccines as a cornerstone of public health efforts by minimizing risks, maximizing benefits, maintaining public confidence in vaccination programs, overcoming vaccine hesitancy, and promoting acceptance.

References

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7. For more information, visit www.VAERS.hhv.gov, the vaccine monitoring program VMP (EMA/EDCC).

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