Non-specific effects of vaccines:

Questions and answers

1. What are the benefits of vaccination?

Vaccines are one of the most successful and cost-effective health interventions in history. Vaccinations have greatly reduced disease, disability, and inequity worldwide from a variety of infectious and non-communicable diseases. Every year an estimated 2-3 million deaths are prevented as a result of national immunization programmes. The impact of immunization goes far beyond saving lives and improving health, with wider benefits for society and the economy that accumulate across a lifetime.

Vaccination is one of the great achievements of the 20th century, yet suboptimal uptake in both childhood and adult programmes limits their full potential impact on public health and has been a driver of recent outbreaks around the world. For example, once common in the United States and Europe, measles was virtually eliminated in the 2000s, but has made a return in recent years. Similarly, countries like Bangladesh, Indonesia, and Venezuela have seen outbreaks of diseases such as diphtheria.

Consequently, it is imperative that we all work together to assure that a high level of coverage is obtained among populations. The scientific evidence in support of vaccination is clear for the individual and public; it is one of the most successful and cost-effective health interventions known.

2. How do vaccines work?

Vaccination works because it “trains” the immune system to recognize and successfully defend against specific or targeted pathogens. By safely working with the body’s natural defenses to develop immunity, vaccines greatly reduce the risk of infection and disease.

Vaccines not only confer protection to individuals who are vaccinated, they can also provide protection at the level of the community, by reducing the spread of infection between individuals. When a high percentage of the population is protected through direct vaccination against a virus or bacteria, it is difficult for a disease to spread because there are few susceptible people left to infect. This form of immunity is known as “herd immunity” or “community immunity”, and can effectively stop the spread of disease in a population. Herd immunity is an important indirect benefit of vaccination and functions in a specific or targeted manner.

However, if immunization rates fall and more individuals in a given population are susceptible to infection, herd immunity can break down, leading to an increase in the number of new cases. For example, measles outbreaks in Europe and pertussis outbreaks in the United States have been attributed to declining immunization coverage in the population and thus lower herd immunity.

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3. What are non-specific effects of vaccines?

Vaccines are developed to produce an immune response to protect against specific disease targets. In addition to the specific effect of vaccines in reducing illness and death due to the disease targeted by the vaccine, some researchers have argued that there are additional “off-target” or “non-specific effects” (NSE) of vaccines, based on findings from observational studies. This refers to the potential effects besides the direct protection against the disease for which a given vaccine was developed.

In other words, NSE refers to any effect of a given vaccine, other than the intended effect of preventing disease caused by the specific pathogen they were designed to protect against. If present for a vaccine, NSE could potentially be beneficial, e.g. increasing protection against non-targeted infections, or disadvantageous, e.g. by increasing susceptibility to non-targeted infections.

4. What data is available on NSEs?

NSEs are proposed to explain observations in some studies that certain vaccines may have an impact beyond the direct protection against infection with a specific pathogen for which the vaccines were designed. Besides these epidemiological studies, there are no published studies that demonstrate a mechanistic link between immunological mechanisms and markers and clinically relevant NSE in humans.

Overall, existing data on the NSE of vaccines on all-cause mortality (i.e. all of the deaths occurring in a population, regardless of the cause) is not conclusive and the methods used to collect and analyze the data have been deemed to be at high risk of bias (e.g. unfairly prejudiced for or against a result). Therefore, further studies using more robust methods are needed to assess the potential NSE on all-cause mortality. This would offer further insights into the eventual importance and implications of such effects.

The current data on NSE on all-cause mortality for specific vaccines are discussed in more detail in question 6.

5. How was the evidence on NSEs evaluated by WHO?

WHO makes recommendations to Member States on the basis of a transparent and systematic evidence review process led by groups of independent experts.

In recent decades, and most recently in 2013-2014, WHO reviewed and critically appraised the evidence on NSEs, to assess whether available evidence is sufficient to lead to adjustments in policy recommendations, or if further scientific investigations are warranted. This review was conducted through three independent advisory bodies: 1) The Global Advisory Committee on Vaccine Safety (GACVS); 2) The Strategic Advisory Group of Experts (SAGE) on immunization and its working groups on NSEs; and, 3) The Immunization and Vaccines-related Implementation
Research Advisory Committee (IVIR-AC), whose role is to provide advice and recommendations to SAGE.

These independent groups of experts each have carefully examined the existing evidence on NSEs of vaccines on a number of occasions (e.g. most recently by IVIR-AC in February 2017; SAGE in 2017 and 2014; IVIR-AC in 2014; GACVS on multiple instances between 2000 and 2008). During these evidence reviews, an assessment was made of the NSE results reported and the study design and research methods used. It was ensured that the quality of evidence was considered using globally accepted standards and methods. Therefore, during the reviews, experts evaluated factors such as the study type (e.g. randomised trials provide, in general, more robust and unbiased evidence than observational studies) and the potential risk of bias across the entire research process.

6. **What conclusions can be made from the available evidence?**

On the basis of the available evidence, the SAGE conclusions were published in 2014. These conclusions were not updated by SAGE in their subsequent review because all new publications were reanalyses of data already reviewed and/or did not have any implications for changes to recommendations.

Regarding the possible NSE of BCG vaccine on all-cause mortality, the epidemiological review suggested possible beneficial effects on all-cause mortality. The available data suggest that the current WHO recommended schedule for BCG vaccine has a beneficial effect on all-cause mortality. SAGE concluded that the evidence does not support a change of the current policy for BCG immunization as soon as possible after birth.

Regarding the possible NSE of DTP vaccine on all-cause mortality, the available data neither exclude nor confirm the possibility of beneficial or deleterious (harmful) NSE of DTP vaccines on all-cause mortality. SAGE concluded that the evidence does not support a change in policy for DTP, and highlighted the benefit of DTP in preventing disease and the importance of the existing recommendation.

Regarding the possible non-specific effect of measles-containing vaccines on all-cause mortality, the review suggested possible beneficial effects on all-cause mortality (i.e. possible lower rates of death in those vaccinated). SAGE concluded that the evidence does not support a change in policy for measles vaccine. The available data suggest that the existing WHO recommended schedule for standard titre measles-containing vaccine has a beneficial effect on all-cause mortality in children.

On an ongoing basis, WHO continues to regularly monitor and critically appraise emerging data on NSEs of vaccines. To date, none of the recent publications, several of them including re-analyses of the cohorts included in the 2014 review, indicate that the existing immunization policy recommendations should be adjusted.
7. What considerations will guide future research?

While SAGE emphasized that based upon the evidence the existing immunization schedule should be maintained, it also considered that hypothesized NSE on all-cause mortality warrant further research. Accordingly, in 2014, SAGE tasked IVIR-AC with providing advice on which priority research questions need to be addressed in order to inform policy decisions, and what types of studies and study designs would provide answers to these questions.

Following a review of almost 50 potential research questions, IVIR-AC presented SAGE in April 2017 with two proposed questions whose results may help to inform policy, and outlines of study protocols to further evaluate the hypotheses that have been proposed regarding NSEs (subsequently published in the Weekly Epidemiological Record).

SAGE reiterated the value of definitive robust evidence to confirm or refute the existence and magnitude of the impact of vaccine NSE on susceptibility to severe childhood infection, particularly attributable mortality, and the potential implications for national immunization schedules. SAGE highlighted the need to implement these studies as a step to obtain robust evidence on the potential NSE of vaccines, but also recognized the high cost involved, given the very large numbers of participants needed.

The two protocols on randomised clinical trials developed based on the SAGE recommendations to assess NSEs can be accessed here. Implementation of these protocols would also address if different vaccine schedules could impact the hypothesised NSE. All SAGE meeting reports are available here.

Global child mortality continues to fall thanks to reductions in deaths from pneumonia, diarrhoea, malaria and measles. However, some countries and regions will doubtless continue to suffer considerable infectious disease morbidity and mortality over the next few decades and all efforts to maximize the benefits of vaccination, should continue. WHO continues to monitor all relevant evidences on this subject matter.