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Do vaccines increase or decrease susceptibility to diseases other than those they protect against?

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Abstract

Contrary to the long-held belief that the effects of vaccines are specific for the disease they were created; compelling evidence has demonstrated that vaccines can exert positive or deleterious non-specific effects (NSEs). In this review, we compiled research reports from the last 40years, which were found based on the PubMed search for the epidemiological and immunological studies on the non-specific effects (NSEs) of the most common human vaccines. Analysis of information showed that live vaccines induce positive NSEs, whereas non-live vaccines induce several negative NSEs, including increased female mortality associated with enhanced susceptibility to other infectious diseases, especially in developing countries. These negative NSEs are determined by the vaccination sequence, the antigen concentration in vaccines, the type of vaccine used (live vs. non-live), and also by repeated vaccination. We do not recommend stopping using non-live vaccines, as they have demonstrated to protect against their target disease, so the suggestion is that their detrimental NSEs can be minimized simply by changing the current vaccination sequence. High IgG4 antibody levels generated in response to repeated inoculation with mRNA COVID-19 vaccines could be associated with a higher mortality rate from unrelated diseases and infections by suppressing the immune system. Since most COVID-19 vaccinated countries are reporting high percentages of excess mortality not directly attributable to deaths from such disease, the NSEs of mRNA vaccines on overall mortality should be studied in depth.

Introduction

Human vaccines were created to protect againstinfectious diseases such as measles, smallpox, polio, and tuberculosis. Edward Jenner (1749–1823) is generally referred to as father of vaccination technology, as his smallpox vaccine heralded the era of vaccination as a major preventive therapeutic strategy, which eventually culminated in the eradication of smallpox [1], [2]. It is often not highlighted that Jenner's small pox vaccine and all those who followed fitted within the framework of the "magic bullet" concept in chemotherapy given later by Paul Ehrlich (1854–1915) [3]. Jenner's first use of cowpox virus clearly indicated that vaccines can result in collateral advantages in diseases other than those which results from the pathogen, which is used for the design of the vaccine. The functioning of the biological world has classically been viewed and interpreted in terms of the biological specificity at the cellular and molecular levels [4]. In the context of enzymes and antibodies, the specificity concept changed to accommodate "cross-reactivity". Recognition of this trait quite early has resulted in our not especially concerning ourselves with immune response to cowpox virus protecting against smallpox virus.

The "lock-and-key" hypothesis has been the anchor of the one structure – one biological function paradigm, which has had overarching impact on our views on the way biological specificity operates in both *in vivo* and *in vitro* worlds of biological systems. Over the time, all this has turned out to be over-simplification. For example, proteins can be highly non-specific as seen in the phenomena of protein promiscuity and moonlighting. These phenomena have been exploited in drug designs and have led to the concept of drug repurposing [5], [6], [7], [8]. Hence, it is not surprising that even vaccines turn out to be non-specific in the sense of influencing immune responses of the diseases for which they were not designed. Just to be unambiguous, these non-specific effects are not based upon cross-reactivity of antibodies etc. They are seen in diseases which are, unlike cowpox and smallpox, quite unrelated.

In more recent times, these non-specific effects have assumed great importance with wider perspectives. This overview is about the lack of specificity observed with many vaccines which is generally described as ''Non-specific effects'' (NSEs) of vaccines. We also discuss that while looking at NSEs, we get drawn into the hugely controversial and debatable issue of using live attenuated viruses vs. killed (inactivated) viruses as vaccines. This debate has not still ended and continues to impact policy decisions in many countries in the world. This debate started seriously in the case of Polio and now has got enmeshed with the discussion on NSEs of vaccines. NSEs of vaccines have also raised few other questions, which merit a closer attention. We hope that an updated information and a critical look at NSEs in this review would be helpful in future vaccination programs.

Section snippets

Methodology

Research reports from the last 40years were compiled. PubMed was searched for the epidemiological and immunological studies on the non-specific effects (NSEs) of the most common human vaccines. To this end, we used the "non-specific effects of child vaccines" and "non-specific effects of vaccination" search terms to find corresponding articles. These searches generated 345 results, from which most review articles and research studies not related to the human vaccines were excluded. Resulting…

Impact of NSEs on overall benefits of vaccination

Anecdotal data from the past indicates that the smallpox vaccine decreased the probability of developing several illnesses [9]. As early as in 1931, Albert Calmette, co-inventor of the Bacillus Calmette-Guérin (BCG) vaccine noticed that "The general mortality of 8,075 vaccinated children exposed to tuberculous infection, aged from one month to one year, controlled by 114 dispensaries, has been 4.6%, whereas in non-vaccinated children of the same age, living under similar conditions, it is at…

Live and killed pathogens and other vaccine designs

Broadly, the various designs of vaccines, which are in use, are as follows [27], [28]. An important class is where live but attenuated organisms have been used. Viruses of measles, mumps and rubella (together to form MMR vaccine), yellow fever, varicella-zooster, and Sabin's polio vaccine are examples of this. The classical Bacille Calmette-Guérin (BCG) vaccine for tuberculosis also uses a live nonvirulent strain of *Mycobacterium bovis*. The organisms, when used as a vaccine in such cases, do…

Live vaccines induce beneficial NSEs

An interesting pattern appeared in which the effects of live attenuated vaccines and non-live vaccines differed. The live attenuated vaccines have generally positive non-specific benefits that are noticeable when they are the most recent immunization [26]. For instance, African children who were injected with live vaccines had much lower all-cause mortality than children who did not, and this disparity cannot be explained by variations in mortality resulting from the infection that the vaccine is…

Non-live vaccines induce negative NSEs

As opposed to live vaccines, non-live vaccines, while protecting against the disease for which they were designed, in some circumstances may also enhance the risk of other diseases, especially in females [88]. For instance, in low-income environments, girls who received the non-live diphtheria-tetanus-pertussis (DTP) vaccine died at a rate that was 1.5–2 times greater than girls who did not receive the vaccine, and a comparable enhanced risk above that of male recipients of the DTP vaccine [88]. The …

The effect of vaccination sequence on the mortality rate

According to the present vaccination model, the order and combination of the vaccines do not really matter; for instance, it is of little significance if DTP is administered before MV, MV is administered before DTP, or DTP and MV are administered simultaneously in terms of pertussis or measles immunity [26]. Nonetheless, studies on DTP, inactivated polio, and hepatitis B vaccines, indicate that non-live vaccines injected after live attenuated vaccines impair the positive non-specific effects of…

The influence of vaccine antigen concentration on the measles mortality rate

Significantly favorable NSEs have been linked to four live vaccines. An early intriguing observation was that the high antigen concentration (with more than $10^{4.7}$ plaque-forming units) in the high titer measles vaccine (HTMV), which isalso a live vaccine, induced detrimental NSEs. In addition, the standard measles vaccine (MV), which had 10^3 to 10^4 plaque-forming units, inducedmore significant beneficial NSEs for females, whereas HTMV was linked to higher female mortality [12]. The MVis often…

Immunological mechanisms for non-specific effects (NSEs) of vaccines

We had compared the live and inactivated viruses for the design of the oral vaccines in case of Polio virus. The key lessons from that historical case have mostly turned out to be general in nature. In this section, we amplify the mechanistic insights into the limitations of the non-live virus-based vaccines. The main attraction of these vaccines is their better safety. Hence efforts continue to overcome their limitations and disadvantages. We will also briefly outline these strategies so that…

Could the possible NSEs of COVID-19 mRNA vaccines include IgG4-mediated immune suppression?

People who received 2 or more shots of the COVID-19 mRNA vaccines have been reported to have unusually elevated concentrations of IgG4 antibodies, according to recent studies [176], [177]. It has also been shown that the HIV, malaria, and pertussis vaccines elicited higher-than-normal IgG4 production, which has been related to decreased protection against infections [178], [179], [180]. A rise in IgG4 levels has been hypothesized to provide protection by reducing immunological hyper-activation, …

Proposed solutions

Some proposals have been made to diminish the harmful NSEs of non-live vaccines: First and foremost, it has been recommended that every child in Africa needs to be immunized against BCG at birth [154]. However, less than 50% of children in Africa currently receive the BCG vaccine during the first month of life, although this has been demonstrated to reduce newborn mortality by more than one-third [15]. To strengthen the infant's immune system, the BCG vaccine should be marketed as a…

Conclusions and future perspectives

The current vaccination model presupposes that vaccines only provide protection against a specific infection, that effective vaccines diminish mortality concerning the proportion of all deaths attributable to the target infection, and that the outcomes of vaccines are the same for both boys and girls. Epidemiological vaccine investigation, nonetheless, has produced findings that defy these presumptions and imply that vaccines have significant non-specific impacts on population health [26]. It…

CRediT authorship contribution statement

Alberto Rubio-Casillas: Conceptualization, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Cesar Manuel Rodriguez-Quintero:** . **Elrashdy M. Redwan:**

Validation, Formal analysis, Data curation, Writing – review & editing. **Munishwar Nath Gupta:** . **Vladimir N. Uversky:** Conceptualization, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Mikolaj Raszek:** Formal analysis, Data…

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Recommended articles

References (196)

M.N. Gupta *et al.*
Protein promiscuity in drug discovery, drug-repurposing and antibiotic resistance
Biochimie (2020)

P. Aaby *et al.*
Developing the concept of beneficial non-specific effect of live vaccines with epidemiological studies
Clin Microbiol Infect (2019)

P. Aaby *et al.*
Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies
Lancet (2003)

C.S. Benn *et al.*
A small jab–a big effect: nonspecific immunomodulation by vaccines
Trends Immunol (2013)

C.S. Benn *et al.*
Vaccinology: time to change the paradigm?
Lancet Infect Dis (2020)

S. Prentice *et al.*
BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial
Lancet Infect Dis (2021)

A. Schoeps *et al.*

No effect of an additional early dose of measles vaccine on hospitalization or mortality in children: a randomized controlled trial
Vaccine (2018)

P. Welaga *et al.*
Fewer out-of-sequence vaccinations and reduction of child mortality in Northern Ghana
Vaccine (2017)

E. Seppälä *et al.*
Viral interference induced by live attenuated virus vaccine (OPV) can prevent otitis media
Vaccine (2011)

P. Aaby *et al.*
Routine vaccinations and child survival in a war situation with high mortality: effect of gender
Vaccine (2002)

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