Review

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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 40 years, showing 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.

Keywords: non-specific effects of vaccines; tolerance; immune training; excess deaths; IgG4 antibodies

1. Introduction

Human vaccines were created to protect against certain diseases such as measles, smallpox, polio, and tuberculosis. The standard procedure for evaluating novel vaccines has been disease-specific: does it produce clinically effective protection against the targeted infection and generate protective antibodies or cellular immunity? This belief about vaccinations is fading away, as more epidemiological [1–3] and immunological [4–6] investigations identified either positive or negative non-specific effects (NSEs) of vaccines (also known as **heterologous** or un-targeted effects). In simple terms, vaccination may have an impact on illnesses that it is not intended to protect [7]. The mortality rate for children has significantly dropped since 1990. The number of children under the age of five who died globally has reduced from 12.8 million in 1990 to 5 million in 2021. Globally, the mortality in kids less than five years old has fallen by 59%, from 93 fatalities per 1000 live births in 1990 to just 38 in 2021 [8].

A portion of this reduction can be attributed to a decrease in pediatric ailments that can be prevented, many of which are frequently credited to the success of vaccinations [9]. Vaccines are

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developed to defend against particular pathogens [10], but they can also have additional effects because live vaccines can boost immune function and reduce mortality in ways that go beyond what can be elucidated by just halting a specific infection [4,11–13]. Because of these positive non-specific effects (NSEs), live vaccinations might have had a greater impact on the drop in childhood mortality than is typically thought [14]. Numerous studies suggest a pattern in which live vaccines (like the smallpox vaccine, the Bacillus Calmette-Guérin (BCG) vaccine, the measles vaccine (MV), and the oral polio vaccine (OPV) enhance immunity to vaccine-unrelated infections, primarily sepsis and pneumonia, and thereby decrease global mortality far beyond what was anticipated from preventing the disease they were designed for [15].

The fact that these live vaccines protect against both target and non-target illnesses confers a greater beneficial effect. In opposition, non-live vaccines, such as "diphtheria-tetanus-pertussis (DTP) vaccine, the pentavalent vaccine for DTP, hepatitis B virus (HBV), and Haemophilus influenzae type b, the inactivated polio vaccine, single hepatitis B virus (HBV) vaccine, the RTS,S/AS01 Malaria vaccine, and the H1N1 influenza vaccine" enhance vulnerability to diseases not related with the vaccine, particularly in females. So, non-live vaccinations may protect against the target disease but have unfavorable effects by making people more susceptible to infections that are not the target [15]. Current vaccination guidelines are solely focused on the disease-specific results of vaccines, which frequently depend on assessments of the potential for preventing targeted illnesses. Nevertheless, it should be also investigated if vaccines change susceptibility to other illnesses [14].

2. Live vaccines induce beneficial NSEs

Anecdotal data from the past indicates that the smallpox vaccine decreased the probability of developing several illnesses [16]. Calmette, co-developer of the BCG vaccine, observed that in Paris, mortality decreased by 75% among infants who had received the vaccine, which was significantly more than could be provided by tuberculosis prevention. He hypothesized that the vaccine might also have added advantages by boosting overall resistance to other infections [17]. The Russian virologist Voroshilova carried out extensive studies in the 1960s and 1970s on live enteroviruses, which included the oral polio vaccine, and discovered that they dramatically decreased the probability of contracting influenza [18].

In the 1980s, Danish scientists performed systematic research into the effects of routinely administered infant immunizations on overall health., the conclusion was that the majority of vaccines had an impact on overall mortality that was greater than what was caused by the disease they were intended to prevent. The phrase "non-specific effects" of vaccines was used to describe such outcomes [7]. 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 [15]. 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 intended to protect [15].

Since infectious diseases are the primary reason why people die in such environments, vaccines may reduce the susceptibility to independent infections or their seriousness, and in cases in which studies have been able to categorize by cause of death, investigations have demonstrated a specific protective action against infectious diseases [19,20]. For four live vaccines, all-cause mortality that is lower than anticipated has been consistently found [15], and randomized studies have mainly confirmed the positive non-specific outcomes of the BCG vaccine [19,21], the measles vaccine [22,23], and the oral polio vaccine [24].

2.1. The oral polio vaccine

It was reported that the oral polio vaccine (OPV) specifically decreased diarrhea morbidity and mortality in Latin America when it was first given in the 1960s [25], and investigations in the Soviet Union demonstrated that the OPV had a prophylactic impact on respiratory infections [18,26]. Additionally, some investigations from Bangladesh, Burkina Faso, Ghana, and Guinea-Bissau have

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discovered that OPV was linked to significantly lower rates of child mortality [27–30]. Campaigns administering only OPV dramatically decreased the probability of passing away from respiratory illnesses by 62% post-natally (1-35 months) according to a recent study conducted in Bangladesh [31].

An investigation from Denmark reported the same advantageous result. Investigators looked at the rate of admissions for infectious diseases among kids who received the live attenuated OPV as their latest vaccination versus infants who received the inactivated diphtheria-tetanus-pertussis-polio-Haemophilus influenzae type b vaccine (DTaP-IPV-Hib) or the live measles-mumps-rubella vaccine (MMR). Similar to the MMR vaccine, having the OPV vaccine as the latest immunization was linked to reduced admissions for lower respiratory infections [32]. In Finland and Bangladesh, randomized control trials (RCTs) contrasting the OPV with the inactivated polio vaccine (IPV) discovered that the OPV safeguarded against upper respiratory infections and diarrhea [33,34].

When BCG, which is frequently administered along with the OPV, or the MV was the last vaccination administered, these protective effects have been noticeably beneficial [1,2,35]. The combined injection of the OPV and the diphtheria-tetanus-pertussis (DTP) vaccinations, however, has not been linked to a lower mortality rate in multiple studies from West Africa [1–3,35,36]. Because DTP and OPV vaccines are generally given jointly, it was challenging to discriminate between their individual effects [37].

The researchers used the sporadic scarcity of the DTP vaccine in Bissau city to evaluate the distinct influence of OPV on mortality at the pediatric hospital because the DTP vaccine had been inconsistently provided in Guinea-Bissau. The case fatality ratio (CFR) was 0.29 (95% confidence interval (CI) 0.11-0.77) for 719 infants under the age of five whose vaccination cards were evaluated when admitted and who had not received a measles vaccination yet. Only receiving the OPV vaccine was linked to a case fatality rate of 6%, as opposed to 15% for kids who had the DTP and OPV vaccines together [37].

The outcomes of administering live attenuated vaccinations simultaneously were studied in two RCTs. One compared BCG and OPV to BCG alone. Until participants received campaign OPV, BCG, and OPV immunizations were linked with a 32% (range 0-55) decrease in newborn mortality [24]. In contrast to receiving only the MV, the co-administration of OPV and the MV decreased diarrhea morbidity in the other RCT [34,38]. In Bangladesh and Finland, RCTs comparing OPV and inactivated polio vaccine (IPV) discovered that OPV was linked to a decreased incidence of otitis media and diarrhea [33,34]. These findings cast doubt on the concept that OPV only prevents polio infection and raise questions about the decision to substitute the OPV with the IPV [34].

2.2. The Bacillus Calmette–Guérin (BCG) vaccine

Tuberculosis (TB) vaccine, also known as BCG, is a live attenuated vaccine and it is one of the most often used today, having been administered more than 4 billion times worldwide, plus an extra 100 million neonatal BCG immunizations annually [39]. Unexpectedly, epidemiological research soon after the BCG vaccine's debut in the 1920s showed that it decreased child mortality regardless of its impact on tuberculosis (reviewed in [40,41].

Children who received the BCG vaccine experienced a 50% decrease in overall mortality, according to various observational surveys conducted in West Africa. The result was too significant to be attributed to tuberculosis immunity alone [2,42,43]. Comparable effects were found in other nations, and lately, they have been confirmed by randomized controlled trials (RCTs) and a meta-analysis of three RCTs [19,44,45]. The induction of protection against unrelated pathogens seems to be the cause of the BCG-induced decrease in infant mortality [39].

According to some investigations [46–48], the BCG vaccine has positive NSEs on child survival, which are more pronounced in females [49]. The campaign to prevent tuberculosis (TB) was the initial primary endpoint of BCG studies conducted in the US and the UK in the 1940s and 1950s, and a reanalysis of those trials revealed that BCG immunization was linked to a 25% decrease in non-TB and non-accident mortality [41]. A further mechanism through which BCG immunization can safeguard babies from sepsis was just uncovered. The BCG vaccine stimulates the growth factor granulocyte colony-stimulating factor (G-CSF) a few hours after its injection, which consequently

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triggers a mechanism termed "emergency granulopoiesis", that boosts the creation of neutrophils prepared to fight pathogens [50]. The characteristics of this rapid reaction to the BCG vaccine provide solid proof for the epidemiological evidence that the BCG vaccine can safeguard infants after a few days after its administration [20,51].

2.3. The measles vaccine

There is a growing consensus that the measles vaccine (MV) causes advantageous NSEs. According to studies on the introduction of MV in Africa, mortality decreased by 50%, which was greater than the predicted **prophylaxis** of ±10% of measles-related deaths [52,53]. Later observational research and randomized controlled trials (RCTs) confirmed these results [54]. A "booster" dosage may also enhance the favorable NSEs for several live-attenuated vaccines [54–58]. In 1963, an RCT in West Africa showed that 27 in the group of control children who were immunized with the Diphtheria-Tetanus-Pertussis (DPT) vaccine had three deaths reported, whereas, in the cohort of 26 young children who had received the MV, there were no deaths when monitored for 18 months [59].

The Kasongo Project in Zaire, which was completed in 1981, produced the first prospective cohort study. The research showed that measles immunization led to a 48% relative decrease in global infant mortality between 7 and 35 months of age. The total mortality rate was found to have decreased by 3.0% according to the same study, yet the total decrease was greater in young children [60]. More significant death reductions have been attributed to the implementation of the measles vaccine than those accounted for by preventing measles infection and its prolonged repercussions in numerous countries, including Guinea-Bissau [1], Bangladesh [61], Senegal [62,63], and Haiti [64]. What is the support for the outstanding argument that the Schwarz vaccine's normal doses decrease mortality from diseases different than measles? First off, while measles *per se* accounts for 10% of infant deaths worldwide, the vaccine lowers mortality in underdeveloped nations by at least 30% [61]. Second, compared to unvaccinated children, immunized children without measles had a much lower mortality rate [1,65]. Girls had a higher decline in non-measles mortality than boys did [61].

The Bandim Health Project kept records of all kids from the studied region who were admitted to the pediatric section of the major hospital in Bissau, Guinea-Bissau, between 1990 and 1996. 2079 hospitalized kids from the Bandim study area, ranging in age from 1.5 to 17 months, were included in the research. The case fatality ratio registered for measles-immunized infants versus un-immunized infants was 0.51 (0.27-0.98), with females benefiting significantly more than boys (test of interaction, p=0.050). Children with pneumonia and suspected malaria responded most favorably to the measles vaccine (MR=0.28 (0.07-0.91) and MR=0.40 (0.13-1.18), respectively). In summary, measles vaccination was linked to a decreased risk of death from non-measles infections, with a higher positive effect for girls than boys [66]. The favorable outcome of vaccination protocols indicates that measles can be eradicated [67]. It has been advised to continue administering the MV to children in low-income nations even after the illness is eradicated because there is compelling evidence that it offers protection against death from diseases other than measles [68].

2.4. The smallpox vaccine

Following the discovery of the last case in Somalia in 1977, smallpox was declared extinct in 1980 [69]. Older People in Guinea-Bissau's city and rural areas were examined for smallpox scars to determine whether immunization against smallpox continued to have health advantages after the disease had been eradicated. Results were significantly above what was anticipated [70,71]. A 40% (95%CI: 13-59%) decrease in mortality for persons over 25 years of age was found in the urban trial when smallpox scars were compared to no scars over the following 4 years [70]. The mortality decrease in the rural study was 78 % (39 to 92 %) [71]. Scientists examined the vaccination history described on the school vaccination certificates of youngsters in Copenhagen to look into the effects of halting the BCG and smallpox vaccinations in Denmark. They centered on the 47,622 kids born between 1965 and 1976, the cohort that underwent the simultaneous discontinuation of the BCG and smallpox immunizations [72].

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Being immunized with both smallpox and BCG vaccines was linked to a 46% (19-64%) lower mortality rate from natural causes between the start of school and the age of 45, after controlling for socioeconomic status, year of birth, and sex. Receiving smallpox and/or BCG was linked to a 34% (4-54%) decreased chance of contracting HIV-1 in a different study that used data from Guinea-Bissau and Denmark [73]. Thus, in both high- and low-income countries, the smallpox vaccine was linked to positive NSEs that persisted for decades after the smallpox extinction. No study has documented harmful NSEs following smallpox immunization. Therefore, it is likely that discontinuing vaccines against measles, polio, and smallpox had a detrimental impact on survival [74].

3. 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 [75]. 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 [75]. The DTP vaccine [15], the H1N1 influenza vaccine [30], the pentavalent vaccine [76], the DTP plus hepatitis B and Haemophilus influenzae type B vaccines [77], the hepatitis B vaccine [77], the inactivated polio vaccine [78], and the RTS,S malaria vaccine [79] are six non-live vaccines for which this pattern has been identified.

Whenever a certain vaccine is the most recent, these non-specific side effects are more evident. Little research has been done on how long non-specific effects last if no further vaccines are administered because the majority of research has been conducted on children who were frequently vaccinated. Nevertheless, non-specific effects appear to persist for at least six months [15,80] and occasionally for years [72,81]. The non-specific outcomes of vaccines were first discovered in low-income nations with high infectious disease mortality, but non-specific outcomes were reported in some investigations from high-income nations that assessed the risk of hospitalizations for infectious diseases that are not specifically targeted [82,83], confirming that vaccines can influence the likelihood of contracting unrelated infections [84]. Studies from Europe and the USA demonstrated that the live MV and the BCG vaccine reduced hospital admission for unrelated diseases in high-income nations, whereas the non-live DTP vaccine increased it [82,83].

3.1. The DTP vaccine

The diphtheria-tetanus-pertussis (DTP) vaccine has a high level of effectiveness in lowering morbidity and death from diphtheria, tetanus, and pertussis. However, observational studies have discovered that, despite this specific protective benefit, a link between whole-cell DTP immunization and elevated total mortality when DTP is the last vaccine applied [78,85–87]. Girls are more likely to be affected by this effect, which may be linked to higher risks of contracting unrelated diseases [75,76,88,89]. Girls' cytokine reactions to irrelevant stimuli are reduced in West African newborns who received the whole-cell DTP vaccine [90]. Despite protecting against particular diseases, the implementation of the diphtheria-tetanus-pertussis vaccination (DTP) in the 1980s was linked to greater total mortality [91–93].

Later investigations comparing the mortality of DTP-vaccinated infants with that of DTP-unvaccinated children corroborated deleterious NSEs, particularly in girls [2,78,86,94,95]. According to the WHO review of NSEs, there is insufficient evidence to confirm or disprove whether DTP-related NSEs are beneficial or harmful [13,96]. Nevertheless, the WHO report included trials with severe survival bias; whenever the meta-analysis was limited to investigations with continuous follow-up and vaccination status validation, children who received the DTP immunization had mortality rates that were twice as high as those of infants who did not receive the DTP vaccine [87].

The World Health Organization (WHO) advises administering BCG followed by DTP, and potential negative effects have been reported in Senegal [47], Guinea-Bissau [86], Gambia [97], and Malawi [98]. In contrast, kids who were immunized with BCG and DTP at the same time as their first vaccinations had a lower death rate than kids who began the immunization plan with BCG-only and

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then DTP according to further research from Senegal [47], Bangladesh [99], and India [100]. According to some investigations, administering BCG and DTP simultaneously lowers mortality compared to the immunization plan suggested by the WHO, which administers BCG first and then DTP/Penta [98].

Children in Bangladesh who were injected with the DTP1 vaccine (first dose) after receiving BCG had a mortality rate that was two times greater than those who were immunized with DTP1 and BCG at the same time 98. In comparison to children who initiated their immunization plan with BCG first or DTP1 first, infants in rural India who were injected with BCG and DTP1 at the same time had a fourfold decreased mortality rate until 9 months of age [99]. Similar to this, a Senegalese study discovered that children who received BCG and DTP1 at the same time had lower mortality compared with those who received BCG or DTP1 first [47].

Combining data from these three studies, the Strategic Advisory group of Experts on Immunization (SAGE) evaluation predicted that giving BCG and DTP at the same time may result in mortality that is 48% (20%-66%) lower than giving BCG first and then DTP [101]. While other studies revealed few deaths, they were consistent with the notion that giving BCG and Penta at the same time rather than BCG then Penta would lower mortality in infants between the ages of 6 weeks and 9 months. It was discovered in that study that if the Penta vaccine was the most recent vaccine administered, it was linked to higher mortality for girls than for males [102].

Ten countries, including Bangladesh, have recently shown higher than predicted rates of under-5-year-old female mortality [103,104], which they attribute to differing treatment of girls and boys [105–107]. The sex-differential under-5-year mortality, however, may have at least two causes: sex-differential therapy and immunizations. It was found that while BCG was the most recent vaccine delivered, girls died at lower rates than boys, but when Penta was the most recent vaccine applied, girls' mortality was greater than in boys. The idea that some additional female deaths are caused by Penta vaccination could be supported by the reversal of the female-male mortality rate ratio (F/M MRR) from BCG as the most recently applied vaccine to Penta as the most recently applied vaccine [102].

The existing data demonstrate that, in low-income countries, the DTP vaccine could cause the death of more infants from other illnesses than it prevents from diphtheria, tetanus, or pertussis. Although a vaccine defends kids from the disease it is intended to prevent, it may also make them more vulnerable to unrelated infections [91]. This study showed that in comparison to children who had not gotten the DPT vaccine, mortality was five times higher among kids who had received the vaccine. Unexpectedly, the same study discovered that children who were immunized only with DPT and no OPV had a mortality rate that was ten times greater [92].

3.2. The Influenza vaccine

An H1N1 influenza outbreak started in Mexico and the USA in March and April of 2009. On June 11, 2009, the virus spread in many countries and the WHO proclaimed it as a pandemic, because, according to that organization, it reached Phase 6, the highest level [108]. Vaccine research was quickly started [109], and a vaccine was ready in August 2009 [108]. Researchers in Guinea-Bissau examined the hypothesis that children who received the H1N1 vaccine would consult with doctors more frequently than children who did not receive the vaccine, despite having immunity to the H1N1 influenza. Although Guinea-Bissau did not perform any influenza monitoring, data from Senegal, a nearby nation, showed that H1N1 influenza was present in the area in October 2010 [110].

If H1N1 influenza was prevalent, vaccinated kids (who are less susceptible to H1N1 influenza) would be predicted to have a smaller number of influenza consultations with physicians. Children who received the H1N1 vaccine should have experienced a greater drop in consultation rates if the vaccine had no NSEs. Since the opposite happened, researchers concluded from those results that the non-live H1N1 vaccine, along with other non-live vaccines, could render children more susceptible to other infectious diseases [111]. This is also applicable to Hepatitis B [77], inactivated polio [78], and DTP vaccines [87], all of which have resulted in increased overall mortality rates for females notwithstanding conferring immunity to the intended illnesses [111]. Importantly, the study

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found no evidence that a possibly detrimental outcome of H1N1 was greatest for females, contrary to what research for other non-live vaccines demonstrated [111].

The impact of H1N1 influenza vaccines on overall mortality has not been thoroughly studied. One of them recently discovered that children monitored in Guinea-Bissau's randomized vaccine trials had higher age-adjusted mortality rates following the H1N1 immunization campaign [55]. In Kenya, hospital employees who had received the trivalent inactivated influenza vaccine (including the H1N1 strain) had higher rates of self-reported respiratory symptoms and absence from work than hospital personnel who had not received the vaccine [112], and children in a small randomized controlled trial in Hong Kong who had received the vaccine suffered a higher incidence of respiratory illnesses other than influenza [113].

The biological process underlying NSEs is unresolved. Though mechanisms for heterologous immunity have been identified in both the innate and adaptive immune systems, according to an increasing number of studies [4,5,114]. It is interesting to note that the live BCG vaccine and the non-live trivalent seasonal influenza vaccine have recently been contrasted for their impact on the innate immune system. According to the research, the trivalent influenza vaccine causes negative NSEs, which is in contrast to the overall immunostimulatory effect that was seen after BCG immunization. Influenza vaccination was linked with reduced IFN-gamma and IL-1beta production in response to heterologous pathogen stimulation, or "innate tolerance," which may be a sign of negative NSEs [115]. More investigation into the mechanisms of non-live vaccine NSEs is required [111].

3.3. The Malaria vaccine

According to calculations, there were 247 million clinical cases of Malaria and 619,000 fatalities from it in 2021 [116]. 10% of all pediatric fatalities in Africa occur in children under the age of five due to malaria. In phase III clinical studies with young children, the RTS,S/AS01 malaria vaccine was found to be 18 to 36% effective in preventing clinical malaria [117]. The vaccination may be somewhat effective against the disease, but it has little effect on total mortality [79]. The non-live RTS,S/AS01 malaria vaccine increased by two-fold the all-cause mortality in African girls in a randomized study. Additionally, there was a propensity for RTS,S to be connected to a lower risk of malaria mortality in boys (malaria mortality ratio, 1.07 [0.52 to 2.18]), but not in girls (malaria mortality ratio, 1.90 [0.82 to 4.37]) [79].

Contrary to popular belief, RTS,S was not related to a decrease in malaria deaths, but rather to a case fatality ratio that was twice as high in children who contracted severe malaria [118]. According to the WHO, the increased death rate among girls "could be due to chance" and was "largely due to the low female mortality in the control arm" 118, despite a P value of 0.0006 for girls and a mortality rate of 2.4% in girls versus 1.8% in boys following RTS,S vaccination (risk ratio, 1.33 [1.02 to 1.74]). The WHO may be right to speculate that this discovery was the result of randomness, but these data point to a call for precaution and more investigation. Before RTS,S is included in normal immunization regimens, it must be established whether RTS,S/AS01 enhances mortality in girls, and plausible pathways involved should be also investigated [79]. Findings from numerous trials of non-live vaccines, such as DTP and the inactivated polio vaccine (IPV), demonstrate that females are more adversely affected by these non-live vaccines than boys are [3,78]. The higher female mortality following RTS,S/AS01 vaccination should therefore not be considered an unexpected discovery that was randomly produced [79].

3.4. The hepatitis B vaccine

Research performed in high mortality areas has demonstrated that the DPT, Influenza, and Malaria vaccines were linked with enhanced mortality of girls in comparison to boys. Hence, scientists looked into how sex-specific variations in mortality in Guinea-Bissau were also related to the hepatitis B vaccine (HBV). A sub-cohort of 876 kids received HBV at 7½, 9, and 10½ months of age as a part of a measles vaccination randomized study. The researchers wanted to determine if this cohort's death rate and female-male mortality ratio changed from the previous and subsequent birth cohorts recruited in the same study [77].

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The mortality rate (MR) for children aged 7½-12 and 1½–7½ months in groups that did not get the HBV was 0.97, while the MR for the group that was injected with the HBV at 7½ months was 1.62. Children who got the HBV vaccine between the ages of 7½ and 12 months who were participating in the measles immunization experiment had higher mortality than both the prior and following groups who were not immunized with the HBV vaccine (MR = 1.81; the effect was especially substantial for girls (MR=2.27). The female-male MR between 9 and 24 months of age was 2.20 in the cohort that was injected with the HBV and MV, as opposed to 0.96 among trial subjects who were only given the MV. Longer monitoring showed no change in these trends. In conclusion, although HBV vaccination protected children against this disease, it induced higher mortality in girls, as reported for the other non-live vaccines [77].

4. 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 [15]. Nonetheless, studies on DTP, inactivated polio, and hepatitis B vaccines, have demonstrated that non-live vaccines injected after live attenuated vaccines impair the positive non-specific effects of the live attenuated vaccines [15]. DTP given after MV, for example, is linked to twice as much mortality as when MV is given before DTP [15,101,119].

Observational investigations [3,29,76,86,94,119,120] and RCTs [46,95] showed that the sequence of immunizations is crucial since NSEs are most significantly correlated with the most recent vaccination. Inactivated vaccines given after medium- or high-titer MV have been contrasted with standard-titer MV following an inactivated vaccine in RCTs. According to a meta-analysis of studies, being immunized with an inactivated vaccine after a live MV was linked with a mortality rate ratio (MRR) of 1.38 (95% CI 1.05 to 1.83) compared to being immunized with a live MV after an inactivated vaccine, with the unfavorable effect being especially high in females [44]. When DTP was given after MV, more females died, according to other research [46,78].

The number of injections of the DTP vaccine increased the relative female-male mortality rate ratio (F/M MRR) by 50% (95% CI: 10-106%), however, the ratio decreased thrice after receiving the MV. When DTP was administered following MV, it considerably spiked once more [119]. When Tdap (the use of capital letters in this acronym denotes the presence of full-strength antigen concentration for Tetanus bacteria in the vaccine. The lowercase "d" and "p" indicate that a fewer concentration of diphtheria and pertussis antigen is used in this vaccination. The "a" in Tdap stands for "acellular," which denotes that the component of whooping cough only consists of some of the bacteria rather than the entire bacteria) and BCG are administered concurrently, their nonspecific immunological effects interact, indicating that the sequence in which vaccines are administered is essential for the result of nonspecific immune consequences.

This is consistent with epidemiological investigations that show the BCG vaccine, given concurrently with or after DTP, is linked with decreased mortality, as opposed to receiving DTP after BCG (as per the recommended schedule by the WHO), implying that the most recent vaccination given is of the utmost importance in determining the positive or negative nonspecific effects [11,13,99]. This reinforces the hypothesis that giving live-attenuated vaccines to young children as their last immunization can elicit protective, non-specific benefits [121].

Compared to in-sequence immunizations, out-of-sequence vaccinations were linked to greater mortality. It was discovered that DTP not followed by MV was associated with increased mortality and that children who received their immunizations out of order had a higher mortality rate compared to those who received them in order. As a result, the current evaluation criteria, which place a strong emphasis on DTP3 coverage, may not maximize the effect of the vaccination scheme on children's health. Such findings suggest that more priority should be given to enhancing the MV coverage and receiving DTPs and MV in the suggested order [14].

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5. The influence of vaccine antigen concentration on the measles mortality rate

Significantly favorable NSEs have been linked to four live vaccines. From this stance, it was intriguing that the high antigen concentration (with more than $10^{4.7}$ plaque-forming units) in the high titer measles vaccine (HTMV), which is also a live vaccine, induced detrimental NSEs. In addition, the standard measles vaccine (MV), which had 10^3 to 10^4 plaque-forming units, induced more significant beneficial NSEs for females, whereas HTMV was linked to higher female mortality [7]. The MV is often administered between 12 to 15 months of age in high-income countries since seroconversion rates are greater at that age than in younger kids. The MV is often administered between 6 and 9 months of age, although many children in developing nations succumb to the disease before 12 months old [64].

Due to its significantly greater seroconversion rates than the regular doses of the Schwarz vaccine administered at 6 months, the World Health Organization recommended large doses of the Edmonston-Zagreb vaccine in 1990. This advice was then withdrawn after it was demonstrated that girls who received the high-titer Edmonston-Zagreb vaccine had a greater mortality rate than those who received the regular Schwarz vaccine. The girls did not contract more measles, and they did not die at a faster rate than children who were not inoculated, proving that the higher mortality was not the result of vaccine malfunctioning. The rationale appears to be that the high-titer Edmonston-Zagreb vaccine was not protective against death from illnesses other than measles (a consequence that was more pronounced in girls than boys [64].

The high-titer measles vaccine (HTMV) was discontinued by the WHO in 1992 because it was linked to a rise in female mortality [122]. The WHO advised HTMV to start at 6 months of age in 1989. When administered at this early age, HTMV proved protective against infection with measles in both boys and girls [123,124]. Nevertheless, HTMV compared to standard-titer MV at 9 months of age was linked with twice as much increased female mortality when children in Guinea-Bissau and Senegal were followed up to age 5 [3]. For boys, HTMV had no impact. The WHO withdrew the HTMV when a comparable pattern was discovered in Haiti [122].

It had not been clarified how an efficient live vaccine may be connected to increased female mortality. Finding an answer that matched all of the available facts took ten years. The non-live DTP vaccine had been linked in several studies to greater female mortality [1,78]. The majority of kids received doses of DTP or inactivated polio vaccine (IPV) after receiving HTMV, which was administered around 4-5 months of age. It was investigated if the non-live DTP and IPV vaccines injected after HTMV contributed to female mortality [3]. Female mortality was greater in Sudan, Senegal, and Guinea-Bissau if DTP/IPV was given after HTMV but not in the control group of children who were immunized with the MV at 9-10 months and were prone to acquire a non-live vaccine after MV [125]. Female mortality did not raise when kids were not vaccinated with the DTP/IPV after HTMV [3]. Therefore, rather than HTMV specifically, the sequence of a non-live vaccine after early MV explained the enhanced female mortality. Numerous investigations conducted after the HTMV incident revealed that DTP and other non-live vaccines have been linked to greater mortality rates in girls compared to boys [3,75,78,86,125].

In addition to this hypothesis, we have an alternative explanation. These results suggest that the antigen concentration in the vaccine also has an important influence on the immune response not yet recognized. This concept has been excellently summarized with the following maxim "A little bit of vaccine does you good—but a lot of vaccine is not so good" [68].

6. Repeated vaccination with the DTP vaccine increased female mortality

The third injection of DTP (DTP3) is utilized as an indicator of the percentage of one-year-old children who survive after receiving three doses of the DPT vaccine and is commonly employed to evaluate the efficacy of the immunization system. To reinforce the National Expanded Program of Immunization (EPI), it has been customary to set goals for DTP3 coverage, evaluate the effects of different interventions, and quantify effectiveness by a rise in DTP3 coverage [126]. Lately, the Global Alliance for Vaccines and Immunization (GAVI) provided extra funding to EPIs in accordance with growing DTP3 coverage [127]. Although MV coverage is now taken into account when allocating

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performance-based funding, the Global Vaccine Strategy solely evaluates coverage according to DTP3 [128].

Even though DTP3 requires three immunizations while MV coverage just requires one, its coverage has grown more as a result of the focus on DTP3. Children who had DTP3 as their most recent vaccination had a 66% (32-109%) greater female mortality rate than male mortality rate. Shifting from DTP1 to DTP3, the female-male MRR increased by 50% (10–15%). The female-male MRR decreased three times after standard MV vaccination compared to DTP; the reduction in the F/M MRR from DTP to MV was always lower for females than for men. The F/M MRR raised again if the DTP vaccine was administered after the MV [119].

For DTP and MV, opposite-sex-differential outcomes have been described in several prior research, including the SAGE review [13,86]. Girls' mortality was lower than boys' mortality in the first eight weeks of life whenever BCG prevails; after 3–4 months of age, when DTP was likely to be the prevailing vaccine, girl´s mortality exceeded boys' mortality, according to research that compared girl and boy mortality rates by monthly age cohorts. Female mortality drops below male mortality after 9 months when MV predominates [11,97,100,129,130]. It is important to note that this pattern is not present when vaccination percentages are low or when vaccinations are administered at various times. For instance, in Niakhar, Senegal, where DTP coverage was poor and MV practically absent in the late 1990s, infant death rates were not greater for females than for males [47].

Two prior investigations revealed that the adverse outcome of DTP-vaccinated versus DTP-unvaccinated infants was exacerbated by further DTP doses [131,132]. The same phenomenon was discovered in other investigations of DTP [77] and pentavalent DTP-containing vaccines [129,130]. Boosting with live vaccines improves the favorable NSEs, according to prior work [57]. In opposition, since most non-live vaccines induce negative effects with boosting, this is essential because the WHO intends to administer more non-live vaccines in the 2nd year of life, e.g. booster DTP and booster RTS,S malaria vaccine.

Although there is currently a lack of clarification for why non-live vaccines have more harmful effects on girls, there is mounting proof that sex-specific immunological responses exist. Additionally, it is unclear why the mortality is enhanced with each additional immunization [119]. When compared to one dose (DTP1), the Female/Male Mortality Rate Ratio considerably increased after three doses of the DPT vaccine (DTP3), demonstrating that repeated inoculation with non-live DTP vaccines further exacerbates the harmful NSEs for girls [119].

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

Possible explanations for the NSEs of vaccines are now beginning to emerge from immunological investigations of innate immune training [6,11]. Live vaccines, such as BCG and vaccinia, elicit epigenetic alterations that train the innate immune system and increase immunity to unrelated infections. In opposition, non-live vaccines may promote "tolerance" that increases susceptibility to unrelated illnesses [133].

It is hypothesized that both Th1 and Th2 immunity may be involved, as a live vaccine such as the MV induces Th1 and an inactivated vaccine like DTP induces a Th2 profile [34]. According to a study, after controlled human malaria infection (CHMI), a group of healthy participants who received the BCG vaccine exhibited increased natural killer (NK) cell and monocyte activation, which is correlated with decreased numbers of parasites in their blood. These results support the hypothesis that BCG vaccination could produce trained immunity with functional responses toward a different human pathogen in vivo [134]. Additionally, there is proof that BCG immunization lowers parasitemia in rodent malaria models [135–138], and in endemic locations, BCG immunization has been linked to lower malaria mortality [43].

Training of the innate immune system has been confirmed for live vaccines such as the BCG and smallpox vaccines [139], as well as the adenovirus-based COVID-19 vaccine [140], and could elucidate why they have favorable non-specific outcomes. On the other hand, various non-live vaccines (DTP vaccine [89], typhoid vaccine [141], and non-replicating smallpox vaccine [142] have been demonstrated to promote innate immune tolerance to unrelated pathogenic stimuli. The

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connection between non-live vaccines and greater vulnerability to other diseases may be explained by the enhanced innate tolerance toward other pathogens [83].

The DTP vaccine may enhance susceptibility to infections in females because it has been demonstrated to inhibit innate immunity and promote T cell exhaustion in girls but not in boys. Reduced post-vaccination pro-inflammatory responses to TLR4 stimulation in DTP-vaccinated children suggest compromised innate immunity against gram-negative bacteria, while responses to TLR2, TLR5, and TLR7/8 were unaltered. This notion is further supported by the reduced levels of mostly type 1 interferon genes in DTP-vaccinated girls but not in boys. This is because the STAT1 pathway, which relies extensively on type 1 interferons, is an important pathway for "trained immunity" leading to altered innate memory [89].

The Tdap vaccine caused modifications in some immune cell subsets in peripheral blood, which likely caused the short-term activation of monocyte-derived cytokine responses and the short-term repression of T-cell responsiveness. Tdap suppressed nonspecific T-cell responsiveness three months after immunization and suppressed innate immunological reactions to unrelated pathogens. Ex vivo, re-stimulated, PBMC-derived, cytokine reactions following inoculation with a live vaccine, like the BCG, as opposed to a non-live vaccine, such as Tdap, may be different. In an *in vitro* model of trained immunity, it was discovered that a live smallpox vaccine produced trained immunity while the non-replicating Vaccinia Ankara promoted tolerance [142].

In conclusion, heterologous innate and T-cell-derived cytokine synthesis is affected in a nonspecific manner by the BCG and Tdap vaccines, and these outcomes overlap with one another. These findings are in line with the hypothesis that vaccination with an inactivated vaccine, such as DTP [89], suppresses heterologous immunity, while vaccination with a live-attenuated vaccine, such as BCG [5,29,143], enhances trained immunity. Up to months after immunization, BCG enhances cytokine reactions to unrelated pathogens [5,115,144]. BCG caused monocyte-derived cytokine responses to be both temporarily and permanently potentiated. Immuno-tolerance to unrelated pathogens was brought on by Tdap and was only partially reversed by BCG vaccination given concurrently or afterward. The BCG vaccine reversed the immunosuppressive effects of Tdap vaccination when administered together or after Tdap [133]. In conjunction with epidemiological evidence demonstrating contrary outcomes of live and inactivated vaccines on total morbidity and mortality [43,69,85,98], the results emphasize the relevance of improving our knowledge of the biological processes underlying these effects to achieve the best health results by improving currently vaccination programs [40].

8. The negative NSEs induced by COVID-19-mRNA vaccines could be the result of IgG4-mediated immune suppression

People who received two or more shots of the COVID-19 mRNA vaccines have been reported to have unusually elevated concentrations of IgG4 antibodies, according to recent studies [145,146]. 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 [147–149]. A rise in IgG4 levels has been hypothesized to provide protection by reducing immunological hyper-activation, similar to that seen following effective allergen-specific immunotherapy, by blocking the effects of IgE [145].

The described rise in IgG4 levels found following repeated administration of the mRNA vaccines, nevertheless, might not correspond to a protective mechanism, according to new findings. Instead, it may represent an immune tolerance mechanism to the spike protein, which might encourage unrestrained SARS-CoV2 infection and replication by inhibiting natural antiviral responses [150]. Excessive antigen concentration, repeated vaccination, and the particular kind of vaccine administered are three important variables that influence the class turn to IgG4 antibodies, according to a thorough analysis of the literature [150].

It is important to mention that while adenovirus-based vaccines did not result in long-lasting IgG4 responses, mRNA vaccines did [146]. Detailed examination of the literature revealed that only vaccines utilizing a portion of the virus—the spike protein for mRNA vaccines, the gp120 protein for

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HIV, and the EBA-175 antigen for the malaria vaccine, respectively—produced an increase in IgG4 levels [145,147,148]. Additionally, other investigations have demonstrated that IgG4 antibody production was stimulated by acellular (aP) but not whole Pertussis (wP) vaccines, which was similarly associated with compromised immunity [149,151].

Is the excessive mortality reported in highly COVID-19-vaccinated countries related to the deleterious NSEs induced by the mRNA vaccines?

There is not enough information regarding the NSEs of COVID-19 mRNA vaccines. By analyzing the randomized control trials (RCTs) of mRNA and adenovirus-vector COVID-19 vaccines, a recent investigation evaluated the potential non-specific outcomes of these vaccines [152]. Researchers estimated mortality risk ratios (RRs) for COVID-19 vaccines in participants receiving mRNA vaccines in comparison to placebo receivers and contrasted them to RRs for COVID-19 vaccine recipients receiving adenovirus-vector vaccines compared to controls. The risk ratio (RR) of mRNA vaccines compared to placebo for overall mortality was 1.03 (95% confidence range [CI]: 0.63-1.71). The RR for overall mortality in the adenovirus-vector vaccination RCTs was 0.37 (0.19-0.70). The mortality risk ratio was 3 times higher for the mRNA vaccines than that of the adenovirus-vector vaccine. Unfortunately, the COVID-19 RCTs were quickly unblinded, and controls received vaccinations; as a result, the chance to conduct extensive RCTs vaccine-vs.-placebo trials that would have offered significant data was eliminated [152].

Since the canonical view is that vaccines only provide immunity against the disease they were designed for, then the significant mortality decrease linked to adenovirus-vector vaccines may be challenging to accept. It is crucial to remember that these non-specific outcomes and their immunological underpinnings have been demonstrated for many different vaccines [4,11,12,15,153]. It was recently demonstrated that the AstraZeneca vaccine enhanced monocyte counts and frequency up to 3 months after immunization in comparison to their pre-vaccine levels [140]. In addition to having improved antigen presentation abilities, monocytes were more competent to create important cytokines and chemokines in reacting to unrelated pathogens. Therefore, it appears that the adenovirus-based vaccine promoted trained immunity [140]. The viral vector may stimulate the immune system similar to a "live" vaccine, even though it lacks replication [152].

9. Proposed solutions

Some proposals have been made to diminish the harmful NSEs of non-live vaccines: First and foremost, 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 non-specific shot. Second, it is necessary to reverse the intention to discontinue the live OPV [154]. With only 68 children needing to receive the OPV vaccine to save the life of one kid, vaccination programs with this vaccine have significantly decreased infant mortality in low-income nations [56].

Therefore, the positive effects of OPV exceed the relatively low risk of polio infection caused by vaccination [154]. Third, children should receive a live vaccine soon after getting a non-live vaccine [154]. For instance, all of the investigations found that inoculating the DTP vaccine after MV resulted in a higher rate of female mortality than giving MV after the DTP vaccine [7]. Because HTMV was administered at such a young age and most kids received the DTP vaccine after HTMV, this may also help to explain why the live, high-titer measles vaccine (HTMV) had been linked to higher female mortality [3].

10. Conclusions

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 men and women. Epidemiological vaccine investigation, nonetheless, has produced findings that defy these presumptions and imply that vaccines have significant non-specific impacts on population health

[15]. It can be understandable that, in a time of increasing vaccination hesitancy, numerous researchers are reluctant to even contemplate the possibility that such harmful NSEs might occur [155]. Recognizing that non-live vaccines have negative effects does not mean that they should stop being used, and should not encourage people who believe that vaccines only cause harm to continue to refuse them. Like any medicine, non-live vaccines can in some circumstances induce iatrogenic effects, which can be effectively neutralized when the last to be applied is a live vaccine. Since they promote immune training and enhance resistance to unrelated infections, they should not be replaced by non-live vaccines. We encourage the WHO to take into account the important discoveries made by Danish scientists in the last 4 decades.

Regarding the detrimental NSEs of non-live vaccines, an inevitable question arises: why is there higher mortality in low-income countries linked with the administration of such vaccines? Apparently, the same vaccines had been also used in high-income countries, where such higher mortality has not been reported. We suggest that malnutrition, lack of medical doctors and well-equipped hospitals in rural areas, and an inadequate supply of antibiotics and antivirals have caused higher mortality from diseases that are promptly and appropriately treated in high-income countries.

A final suggestion is that the high IgG4 antibody levels generated in response to repeated inoculation with COVID-19 mRNA vaccines are associated with a higher mortality rate from unrelated diseases and infections by suppressing the immune system. Since most vaccinated countries are reporting high percentages of excess mortality not directly attributable to deaths from COVID-19 [156], the NSEs of these vaccines on global mortality should be studied in depth.

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