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COMMENTARY

Non-specific effects of vaccinations in high-income settings: How to address the issue?

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ABSTRACT

"Non-specific effects" of vaccines go beyond the specific protective effects against the targeted diseases. They, if real, could theoretically be beneficial, neutral or negative.

This article intends to answer the following questions:

- Do the non-specific effects of vaccines exist? Almost certainly yes, and they can be important in low-income countries
- Are non-specific effects also present in high-income countries? At least to some extent, it seems quite logical
- Can non-specific effects be systematically identified by the current systems of side effects/unintended reactions monitoring? Most likely not
- Could the Institute of Medicine proposals and some ongoing attempts solve the issue? It seems unlikely
- Could there be better, feasible and ethically acceptable ways to achieve the aforementioned objective?

A proposal is presented about this issue, with the potential both to solve the problem with the most valid methods, and to overcome the ethical problems that have so far precluded the adoption of RCTs to study possible vaccine non-specific effects, monitored by long follow-up.

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Introduction

"Non-specific effects" of vaccines (also called "heterologous" or "off-target" effects) are defined as effects that go beyond the specific protective effects against the targeted diseases. They should not be confused with "side effects" of vaccines, such as local reactions in the site of injection (tenderness, pain, swelling, erythema, induration, bruising), or systemic reactions (fever, headache, rash, joint and muscle pain), which usually resolve within days to weeks – or in rare cases anaphylaxis.

The non-specific effects might theoretically be beneficial, increasing protection against non-targeted infections and conditions relevant to health, or they might be real but negligible. However, in other circumstances they could be harmful, increasing susceptibility to non-targeted infections or to some health drawbacks.

This manuscript will address the following questions: their existence and possible magnitude, if they show up also in high-income countries, whether they can be systematically identified by the current systems of monitoring the side effects/unintended reactions, and if there could be better, feasible and ethically acceptable ways to achieve this goal.

It will critically examine some attempts to identify and quantify these effects, describing the study designs suitable for these purposes, able to reach non-disputable conclusions, and how to overcome the ethical problems that have hindered their implementation so far.

Are there any non-specific effect of the vaccines?

When the smallpox vaccine was introduced, an unexpected protection was observed against several other conditions as atopic diseases, measles, scarlet fever, and syphilis[1]. With BCG vaccine was noticed a much lower mortality among BCG-vaccinated children, not explained only by the prevention of tuberculosis[2].

The hypothesis of a "non-specific immunity" was relaunched in the 1990s in West Africa[3], following randomized clinical trials/RCTs of a new high-titer measles vaccine in Guinea-Bissau and Senegal. This formulation could be administered starting from 4–5 months of age and it was effective against measles, but it was associated with an unexpected doubling of mortality for females compared with the standard measles vaccine given at 9 months[3]. This negative effect led to investigate other routine vaccines for potential

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non-specific and sex-differential effects. Some observational studies found non-specific effects for all the routine childhood vaccines, and this allowed to perform some RCTs, that confirmed beneficial non-specific effects of the standard measles[4] and BCG vaccines[5,6], against sepsis and respiratory infections.

On the contrary, diphtheria-tetanus-pertussis (DTP) vaccine, although protective against the target diseases, increased female mortality from other infections[7]. Many studies suggest that DTP has effects opposite of BCG and measles vaccine on child survival. In two natural experiments, DTP-vaccinated (particularly girls) had significantly higher mortality than DTP-unvaccinated children[8]. This could explain the increased female mortality in the above high-titer measles vaccine trials[3,8], in which inactivated DTP vaccine, or inactivated polio vaccine (IPV) for different children, were administered *after* the measles vaccine.

Indeed, these effects may be persistent until the administration of another type of vaccine, and might last even longer. In low-income countries these outcomes can be very important, with significant effects on overall morbidity and even on all-cause mortality. In some situations the vaccine non-specific effects might be more important for health than the specific ones[2].

Some Authors estimated that millions of child deaths in low-income countries could be prevented every year if the non-specific effects of vaccines were taken into consideration in immunization programs[9], for instance reducing time of exposure to DTP as the most recent vaccination with BCG or measles vaccines[2].

However, the evidence for these effects mainly derives from studies in countries with child health characteristics very different from those of high-income countries.

The position of the WHO

BCG vaccine. A WHO-commissioned review of RCTs and observational studies concluded for a likely beneficial effect of BCG on overall mortality in the first 6–12 months of life; but the confidence in the findings was "very low" according to the GRADE criteria. The WHO's Strategic Group of Experts on Immunization concluded that "the non-specific effects on all-cause mortality warrant further research"[10].

Measles vaccine. The aforementioned WHO-commissioned review on RCTs and observational studies concluded for a consistent evidence of a beneficial effect of measles vaccine, although with a GRADE rating of "low confidence". Girls seemed to benefit more than boys from measles vaccination. The WHO's Strategic Advisory Group again concluded that "the non-specific effects on all-cause mortality warrant further research"[10].

DTP vaccine. A WHO-commissioned review on observational studies concluded that the findings were inconsistent, with a majority of the studies indicating a detrimental effect, and two a beneficial effect of DTP, with a GRADE rating of "very low" confidence.

However, three observational studies suggested that the contemporary administration of DTP and BCG might lead to better results than the current schedule of BCG before DTP, and that mortality risk may be higher when DTP is administered with or after measles vaccine, instead of before it. These results support the hypotheses that DTP vaccine may have unfavorable effects, at least in low-income countries with high mortality from infections.

The WHO Strategic Advisory Group of Experts (SAGE)[11] commissioned two systematic reviews[12,13], to decide if there was enough evidence to consider changes in scheduling of some vaccines.

The first is a comprehensive epidemiological review[12], providing available data from RCTs, cohort and case-control studies on the impact of BCG, DPT, and MCV on non-specific and all-cause mortality in children aged under 5, excluding studies at "very high" risk of bias. Indeed, it is well known that observational studies of vaccine effects are prone to confounding, because children in poor health are less likely to be vaccinated and to misclassification bias of vaccination status. It is not clear whether these biases may have contributed to the association of DPT with all-cause mortality (RR 1.38, 95% CI 0.92–2.08). To date there are no RCTs to support this association; but, excluding a study in Papua-New Guinea at "very high" risk of bias, the overall relative risk became significant (1.36, 1.09–1.68). Therefore the authors conclude: "Although efforts should be made to ensure that all children are immunized… **RTs are needed to compare the effects of different sequences**".

The second systematic review analyzed evidence for non-specific immunological effects of the most important vaccines[13], founding a large number of different immunological outcomes, whose actual relevance to non-specific effects of vaccines remains unclear.

The WHO's expert group (SAGE) concluded that there was no need to modify current vaccination schedules or policies[11]. However, the Editorialist said[14]: "Taken together, the two systematic reviews suggest that vaccines could have non-specific effects, but the evidence remains weak. […] If RCTs are not feasible, large observational study designs incorporating innovative methods to control for confounders […] is the only alternative. […] Both epidemiological and immunological efforts need to be integrated. If we fail to come together,… we will still be in the same situation when these systematic reviews are updated in five or even 10 years".

Another interesting observational study, conducted from 1978 to 1983 on children undergoing DTP and oral polio vaccination (OPV), was subsequently published[15]. Children were part of a Guinea-Bissau urban cohort, without socio-economic difficulties and no evidence of malnutrition, in which these vaccines had been introduced in a WHO Expanded Program. The exclusion from the program was based on age, since the vaccine was only given to children aged 3–5 months. The authors compared under-5 mortality data: among the vaccinated with DTP the mortality was five times higher than in not vaccinated. The Authors conclude: "Unfortunately, DTP is the most widely used vaccine, and the proportion who receives DTP3 is used globally as an indicator of the performance of national vaccination programs. It should be of concern that the effect of routine vaccinations on all-cause mortality was not tested in RTs. All currently available evidence suggests that DTP vaccine may kill more

children from other causes than it saves from diphtheria, tetanus or pertussis. …. The recently published SAGE review called for randomized trials of DTP[12]. However, at the same time the IVIR-AC committee to which SAGE delegated the follow-up studies of the NSEs of vaccines has indicated that it will not be possible to examine the effect of DTP in an unbiased way. If that decision by IVIR-AC remains unchallenged, the present study may remain the closest we will ever come to a RCT of the NSEs of DTP[15]."

In my opinion, the huge stake and the precautionary principle should overcome the ethical arguments against the implementation of RCTs of appropriate design, dimensions and follow-up. These RCTs should recruit participants properly informed of the persistent uncertainties about this sensitive but fundamental subject.

Is it plausible that non-specific effects are absent in high-income countries?

Given the above, the focus of this manuscript is on the strategies to adopt in high-income countries.

If it in low-income countries such life-threatening effects could occur with different vaccination strategies, it is implausible that different strategies could not be associated with some non-specific, though less resounding effect, also in high-income countries. However, if these effects are not investigated with appropriate studies, and they are strongly denied by the majority of scientific world and media, they will not come to light, even if they were present and not trivial.

A recent nationwide population based cohort study in The Netherlands[16] examined whether measles, mumps and rubella (MMR) vaccine had positive non-specific effects in a high-income setting. Moreover it compared rates of hospital admissions for infections in children aged ≤2 years who received live MMR vaccine and those who received the inactivated DTP combined with inactivated polio, Hemophilus influenzae type b (DTaP-IPV-Hib) and pneumococcal vaccinations as their most recent vaccination. This study showed that the healthy vaccinee bias at least partly explains the observed lower rate of hospital admission for infection after MMR vaccination; this lower rate was indeed associated with *any* additional vaccine (also DTaP-IPV-Hib) and not specifically with MMR. MMR vaccination's non-specific effects cannot be excluded, but they cannot be distinguished from bias. The authors conclude recommending caution in the interpretation of findings from observational studies on non-specific effects of vaccination (implicitly recognizing the need for RCTs to settle the issue).

Are non-specific vaccine effects collected in a systematic way? are they detectable by the current pharmacovigilance systems?

It is unlikely. Only an *active* and accurate pharmacovigilance (with *solicited* adverse events, as it usually happens in the RCTs) allows to correctly quantify adverse events (AEs) or otherwise unexpected events. The passive pharmacovigilance based on spontaneous reporting underestimates these events in a heavy and systematical way. For example, in Italy the Veneto Region, equipped with a more advanced system of AEs reporting and collects every year 4–5 times more reports in comparison to the average of the others Italian Regions. In the 2015, when were reported also the data from an RCT on a sample of children[17], the reported AEs were over 25 times than the average of the other Regions.

The WHO manual for the causality assessment of an adverse event following Immunization (AEFI).

Case reports, case series and pharmacovigilance reports are fundamental to detect rare adverse events (and sometimes even "uncommon" ones), since size and follow-up of RCTs are often insufficient to highlight less common events (however, if one arm of an RCT should show an excess of some events, it would be essential one would not ignore them, as it often happens[18-20]).

Therefore, pharmacovigilance is essential to formulate *hypotheses*. Then, to *confirm* a causal relationship, studies with different design are needed. Indeed, with the rules of the "algorithm for the assessment of causality" proposed by the WHO[21] and adopted by the Regulatory Agencies of the various countries, it is very difficult and *almost impossible* to succeed in establishing causality in the observational context of the pharmacovigilance. Indeed, the WHO's rules for the *Causality assessment algorithm*, in such an observational context, are legitimately "guaranteed" in favor of the vaccine, similar to the principles usually applied in a criminal proceeding. Therefore, even when there would be biological plausibility and the event matches the "compatible" time window of the direct action of the vaccine, if there is a possible alternative explanation the event is classified as "undetermined". It does not matter substantially that the weight of the probabilities were shifted to a causal relationship. (Nb: one should also remember that the "compatible time window" is defined by consensus, not because there are *certain evidences* that outside that window any influence is excluded). These are restrictive criteria, understandable before admitting publicly a "suspect" against a vaccine, assumed to have preponderant social and health benefits. But it must be recognized that it is very difficult to attribute a "correlation", and it is *extremely* difficult to ascertain a "causality".

In contrast, the opposite should happen *in the RCTs setting*, since the randomization should ensure the best comparability between the study groups, the best control of the confounding factors and, consequently, the possibility of defining the causal relationship between treatment and effects observed, both for the positive effects (efficacy) and for the negative ones (risk).

The Institute of Medicine proposals

Given the many unknowns related to the long-term effects of vaccines and their ingredients, the U.S. Institute of Medicine – IOM (now National Academy of Medicine – NAM) has recommended that studies should be carried out[22]:

- to compare the health outcomes of vaccinated and unvaccinated children,
- to examine the

- long-term cumulative effects of vaccines
- timing of vaccination in relation to the age and condition of the child
- total load or number of vaccines given at one time
- effect of other vaccine ingredients in relation to health outcomes
- mechanisms of vaccine-associated injury[22].

Nevertheless, IOM stated that concerns would not be sufficient motivation to embark on costly new RCTs. Moreover, IOM supported the National Vaccine Advisory Committee Safety Working Group statement that "the strongest study design, a prospective, RCT that includes a study arm receiving no vaccine or vaccine not given according to the current recommended schedule, would be unethical and therefore cannot be done"[23].

Findings of the German health interview and examination survey for children and adolescents (KiGGS)

The KiGGS[24] evaluated data on diseases preventable by vaccination, infectious and atopic diseases, and vaccinations received, collected between 2003 and 2006 in a representative sample of 17,641 subjects aged 0 to 17 years in the framework of the German Health Interview and Examination Survey for Children and Adolescents.

Data on vaccinations were available for 13,453 subjects aged 1–17 years from non-immigrant families. 0.7% of them (95% CI: 0.5%-0.9%) were not vaccinated. The lifetime prevalence of pertussis, measles, mumps and rubella was much higher in unvaccinated subjects.

Overall, unvaccinated children aged 1–5 years had a median total number of 3.3 (2.1–4.6) infectious diseases in the previous year, compared to 4.2 (4.1–4.4) in vaccinated children. Among 6 to 10 years of age the corresponding figures were 3.0 (0.4–5.7) in unvaccinated subjects and 2.9 (2.7–3.0) in vaccinated. Among 11- to 17-year-olds were 1.9 (1.0–2.8) in unvaccinated and 2.2 (2.1–2.3) in vaccinated.

The lifetime prevalence of at least one atopic disease among 1–5-year-olds was 12.6% (5.0%-28.3%) in unvaccinated and 15.0% (13.6%-16.4%) in vaccinated children. In the elder children, atopy was more common, but its prevalence was not significantly associated with vaccination status: among 6–10-year olds, the prevalence figures were 30.1% (12.9%-55.8%) for unvaccinated vs 24.4% (22.8%-26.0%) for vaccinated children, and the corresponding figures for 11–17-year-olds were 20.3% (10.1%-36.6%) and 29.9% (28.4%-31.5%).

Although no difference reached the statistical significance, someone might note that, for atopic diseases, the lifetime (0–17 years) prevalence of at least one atopic disorder by vaccination status showed a slight disadvantage for the vaccinated children: RR 1.224 (0.810–1.860)

The tendency to a disadvantage seemed even more pronounced for the *totality* of infectious diseases (expressed as mean number in the preceding 12 months: 2.999 infections per capita in vaccinated, vs 2.789 in unvaccinated). One could have expected the opposite, since the unvaccinated children have shown a significantly greater incidence (about 3–6 times) of the infectious diseases for which a vaccination program was in place: pertussis, measles, mumps, besides a minor although non-significant incidence of rubella.

Can we conclude, from these data, a weak suggestion that vaccines might be somehow associated with an excess of atopic and infectious diseases? No, certainly, not only for the absence of any significant difference, but mostly because the unvaccinated children are probably not comparable to vaccinated children, for slight differences in socioeconomic status and likely differences in their familial environment (eg less exposure to tobacco smoke, to unhealthy foods, etc.). In an observational study like KIGGS any observed difference can be imputed to behavioral, educational and environmental factors, whose impact can obscure any eventual effect of vaccinations.

The Mawson's cross-sectional study: a step forward?

To partially overcome the systematic differences between the two different populations of vaccinated and unvaccinated, a researcher has conceived an innovative, pilot comparative study, on the health of vaccinated and unvaccinated 6–12-year-old U.S. children educated at home[25].

A major challenge in these studies is to identify an accessible pool of unvaccinated children, since the vast majority of children in the U.S. (and in other high-income countries) are vaccinated.

A higher proportion of "homeschool children" are unvaccinated compared to public school children. Homeschool families have somewhat more years of formal education and a higher average family size (just over three children) compared to the national average of just over two children. The main reasons for homeschooling was an aim to a moral environment, better family relationships, or for more contact with their children[25]. These families are more homogeneous than those compared in KIGGS[24], and this might theoretically limit the structural environmental differences that bias other similar observational comparisons.

The study design was a cross-sectional survey in four US States of homeschooling mothers on their vaccinated and unvaccinated biological children aged 6–12 (since most vaccinations are administered before age 6).

The object of this pilot study was to obtain a *convenience sample* of unvaccinated children of sufficient size to test for significant differences in outcomes between the groups. The online survey remained open for three months, with a letter to parents which began:

> "*… this study concerns a major current health question: namely, whether vaccination is linked in any way to children's long-term health. Vaccination is one of the greatest discoveries in medicine, yet little is known about its long-term impact. The objective of this study is to evaluate the effects of vaccination by comparing vaccinated and unvaccinated children in terms of a number of major health outcomes …*".

Mothers were asked to indicate, on a list of more than 40 acute and chronic illnesses, those for which their children had received a medical diagnosis. Other questions included the use of health services and procedures, "sick visits" to physicians, medications used, number of days in the hospital, hours of *vigorous* physical activity, number of siblings, family

income and/or highest level of education of parents, amount of time spent in play or other contact with children outside the household. Moreover, pregnancy-related conditions and birth history, medications during pregnancy, and exposure to a specifically defined adverse environment.

A neurodevelopmental disorder (NDD) was defined as having one or more of the following three closely related/overlapping diagnoses: a learning disability, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD).

The results on 666 homeschool children, 39% unvaccinated, were shocking. On one hand, as expected, the odds of chickenpox and whooping cough were higher in the unvaccinated children. But, for the vaccinated children, the odds of:

(1) ear infection were almost four fold higher
(2) pneumonia were significantly higher
(3) ear tube placement were eight-fold higher.

The vaccinated children were also significantly more likely to have been diagnosed with the following (% in vaccinated vs % in unvaccinated):

(1) allergic rhinitis: 10.4% vs. 0.4%
(2) other allergies: 22.2% vs. 6.9%
(3) eczema/atopic dermatitis: 9.5% vs. 3.6%
(4) any neurodevelopmental disorder: i.e., learning disability, ADHD or ASD: 10.5% vs. 3.1%
(5) any chronic illness: 44.0% vs. 25.0%.

The vaccinated children were also more likely to had: increased healthcare utilization, ear tubes placed, used antibiotics, allergy and fever medications; visited a doctor for a health issue in the previous year, and been hospitalized.

There was also an apparent "dose-response" relationship, because partially vaccinated children showed intermediate positions between the fully vaccinated and unvaccinated in several health outcomes.

In a final adjusted model with interaction, only vaccination remained significantly associated with NDD, but the interaction of preterm birth and vaccination was associated with a significant 6.6-increased odds of NDD[26].

The two studies[25,26] have generated many interesting hypotheses, but they suffer by a major weakness, that can bias the results. Indeed, the incipit of the letter to parents likely induce the response of those mothers who believe that their children have had a damage from vaccination, and not of those whose children have not had any harm. Similarly, among mothers who have chosen not to vaccinate, those same words may have selectively induced to reply those with sons without any health consequences, because they are "proud" of having no damage to complain. Therefore the incipit of the letter, accidentally selecting the respondents, probably generates two opposite bias, inflating the declaration of perceived harms associated with the vaccinations, and the relative perception of safety of having refuted to vaccine.

Again, there is need to measure the same outcomes in independent and well designed RCTs.

How to solve the ethical problems that prevent from the implementation of rcts of adequate size and follow-up in high-income countries?

If one really wants to clarify the possibility of non-specific, adverse or favorable effects, in relation to the various vaccines (at least of those effects that can occur not only in the short, but also in the medium term, as allergies, immune diseases and NDD, reported by many observational studies), the solution could consist in **large pragmatic RCTs**, with minimum exclusion criteria, **long follow up** and even longer observational extensions.

Unfortunately, the internationally dominant position would reject such RCTs for ethical reasons, because the control subjects, receiving a placebo or nothing, would be excluded from the vaccine benefits (and might involve some additional risks for contacts who cannot receive live vaccines for medical reasons).

To overcome the ethical problems of not administering vaccines, or *some* vaccines, to one of the randomized arms, the solution could be to **take advantage of the widespread *vaccine hesitancy***.

Indeed, after a provision of a complete and balanced information based on the state of knowledge, a small but not negligible percentage of parents remains definitely unable to decide to vaccine their children or to refuse the vaccination. These persistently hesitant parents should not be considered a threat, but a valuable resource for scientific research. A voluntary opportunity could be offered them: to participate in well designed RCTs, so contributing to a real advance in the scientific knowledge.

These RCTs should generally have three arms, randomized: to the vaccines in analysis, to control with placebo injections, and to control with subjects without active intervention. This third arm is important to measure also the adverse effects from injection of physiological solution, in addition to the possible "nocebo effect" (predictable, in a blinded RCT, in those who do not know if the injection contains saline solution or an active drug).

In this way, the control groups should not be afraid of the transmissible diseases prevented by the vaccines in evaluation, because the participants would not be concentrated in a confined territory, and the herd immunity effect of the vast majority of vaccinees would protect them. Probably, they will contract anyway a higher number of the infectious diseases targeted by the specific vaccines evaluated in the RCT, as it is already well documented in cross-sectional studies[25] or in population cohorts[24]. Nevertheless, having they voluntarily done the informed choice to adhere to a blinded RCT, the risk of incurring in some more vaccine-preventable infectious diseases should not be a great personal or ethical problem. The theoretical infectious risk that they might cause to some immunosuppressed subject would be negligible, if compared with the one caused by the large proportion of unvaccinated adults or by people whose antibody protective titer have vanished over the years (which is well proven in scientific literature about vaccine-preventable diseases[27-32]).

Studies like these would not present the serious selection bias that undermine the validity of conclusions in the results of observational studies.

Last but not least, these RCTs should find public-sector sponsors, because it is unlikely that private sponsors are interested in studies that could challenge part of their business. Their design should be conceived by researchers independent of commercial interests. The different schools of thought should be represented in a balanced manner among them. Finally, their management should be assigned to scientific bodies independent of conflicts of interest and financial relationships with the vast vaccine market.

Other barriers to the implementation of appropriate rcts of adequate size and duration in high-income countries

Nowadays, RCTs like those proposed above would have no chance of being financed and undertaken, and even considered.

Some preconditions could be:

- that a serious, but overt and uncensored scientific debate should take place, also at the international level
- a profound change in the orientation of the citizens: to start it, people should be favored by balanced information programs overcoming the current ideological polarizations
- a Government that wants to deepen the scientific and political issue without prejudice, in the interest of the continuous improvement of the health of the community. Governmental Institutions should be ready to review the current policies or part of them, if a serious scientific research proved they need some corrections.

Conclusions

In addition to the effects on target infectious diseases, vaccines could have also "non-specific effects". These effects, if real, could theoretically be beneficial, neutral or harmful.

They have shown potentially dramatic consequences in some low-income countries, and it is hard to believe that some non-specific effect would be absent in high-income countries.

However, the current pharmacovigilance systems do not give enough guarantees to identify them, the many observational studies implemented cannot establish causality, and the few RCTs do not have sufficient size and follow up to identify and prove causality of rare or uncommon non-specific effects, of which there is anyway a background rate.

A solution could be to take advantage of the vaccine hesitancy, that remains in some individuals even after receiving an extensive and balanced information, based on the state of knowledge. These persistently hesitant persons (for themselves or for their children), that could be tens of thousands spread wide in a country, can be offered the opportunity to participate in well designed and long-lasting RCTs, and so to contribute to a real advance in the scientific knowledge, with minimal risks for themselves, for their children and the community.

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

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