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REVIEW ARTICLE

The Health of Pregnant Women and Their Unborn Children– Neglected in Vaccine Development

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ABSTRACT

Background: Randomized Controlled Trials of vaccines given in pregnancy aimed at benefitting the unborn child began in 2015. Their use for licensing purposes now appears established. These trials generate data on possible benefits and harms to infants but also on maternal health impacts. The International Council on Regulations for Pharmaceutical Use in Humans has realized that current safety regulations are not adequate for clinical trials in the second half of pregnancy. They are now drawing up improved guidelines for the conduct of these trials.

Aims: To focus attention on maternal and fetal health that his new willingness to run trials in pregnancy brings into the frame.

Materials and Methods: We reviewed all recent maternal vaccine trials and their outcomes, along with potential concerns.

Results: Analysis of data from recent trials of vaccines given in pregnancy suggests that they may be associated with adverse events during the pregnancy that affect both the mother and the fetus.

Discussion: The aim of vaccine trials in pregnancy currently centres on measuring the efficacy of prevention of infectious disease, and perinatal outcome. Study of the impact of maternal vaccines on pregnancy physiology has been neglected. New, rapidly developing areas, such as epigenomics, need to be considered. It is a good time for the wider field to have an input on what might be included in the guidelines, and whether other measures are needed.

Conclusion: Insufficient attention has been given to monitoring the health of pregnant women and of their fetus during vaccine trials. The need for new guidelines offers an opportunity to require more stringent safety monitoring during pregnancy which will benefit women and their unborn children.

1 | Introduction

Vaccines have had a major impact on preventing disease. Smallpox has been eradicated; measles has become uncommon, and rubella—a hazard to the fetus—is now rare.

Starting with pertussis a decade ago, the number of vaccines recommended in pregnancy, primarily for the benefit of the fetus, has increased. Current guidance varies between nations. Women may be advised to be vaccinated routinely against up to seven different antigens—influenza and COVID-19 vaccines offer mainly maternal protection, whereas the long-established pertussis, diphtheria, tetanus, polio, and the newer respiratory syncytial virus (RSV) vaccines are primarily for the benefit of the fetus. A vaccine against Group-B streptococcus is awaiting licensing approval, and cytomegalovirus vaccines are being developed.

In the last decade, randomized clinical trials (RCTs) of vaccines in pregnancy have taken place against a regulatory background

that never envisaged such trials. There are no clear reporting requirements in place for these trials, whose focus has been on demonstrating vaccine efficacy. As outlined below, recent maternal RSV vaccine trials have shown hazards to both mother and baby, even though available safety data have not been collected systematically.

This article highlights gaps now apparent in current practices and regulations for trials that apply both to vaccines designed primarily to benefit the pregnant woman (e.g., influenza and COVID-19) and those to benefit her baby (e.g., pertussis and RSV).

Despite their undoubted benefits, all vaccines have the potential to cause adverse events in the recipient. Vaccination during pregnancy involves both the mother and the fetus. Either may be harmed by the vaccine itself, or by the effects of the vaccine, for instance, the antibodies it produces, or the treatment of any reactions with analgesics like acetaminophen. In RCTs, vaccines, compared to placebos, invariably result in an excess of "reactivity" for example injection site pain.

In addition, in multinational vaccination studies, the benefit–risk ratios of vaccines may not be straightforward. Children in Africa are more prone to fatal infections if they have received the standard triple vaccine (DPT/Tdap), and the problem is greater in girls than in boys. Clinical outcomes are better when live vaccines like measles are given to children after DPT rather than before. Furthermore, it is now clear that BCG immunization prevents diseases other than tuberculosis (Shann 2013).

These "non-specific effects" may be either harmful or beneficial. New information about non-specific effects of vaccines is now being discovered about vaccines that have been in use for decades. We know that the sequence in which these vaccines are given can shape these non-specific effects but little is known about the non-specific benefits or harms of multiple vaccines given in pregnancy.

Current vaccine trials, including those in pregnancy, do not monitor for a full range of non-specific outcomes, good and bad, especially for all-cause mortality and all infections.

2 | Regulation of Clinical Trials

The thalidomide catastrophe changed medicines' regulation worldwide. The 1962 Kefauver–Harris Amendment to the 1938 Federal Food, Drug, and Cosmetic Act in the U.S. required manufacturers to show that all new drugs were "effective and safe" prior to licensing.

The safety provisions introduced focused on detecting teratogenicity in the first trimester.

Alarmed by thalidomide and retinoids, until recently pregnant women and their healthcare professionals have increasingly aimed at a "natural pregnancy". Consuming alcohol, tobacco, soft cheeses, and pâté as well as non-essential medication was discouraged. All of these can harm the developing fetus. Despite this, in more prosperous populations there has been an increase in the taking of medication in pregnancy, particularly medication for mental health problems (Mitchell et al. 2011; Werler et al. 2023). More vaccines are being given.

These studies of medicines taken in pregnancy neglect over-the-counter medicines like acetaminophen, which is taken by up to 65% of pregnant women at some point in their pregnancy (Zafeiri et al. 2022). These medicines are recommended to be taken in response to painful vaccine reactions. Acetaminophen taken during pregnancy is increasingly linked to neurodevelopmental delay in babies (Bauer et al. 2021; Cleveland Clinic 2022). There is a suggestion that the risk may be dose-related (Woodbury et al. 2024) but the evidence is conflicting (Ahlqvist et al. 2024).

This increased use of medicines and vaccines has led to concerns about the evidence base for these changing practices. There has been a call for more RCTs in pregnancy which, it is argued, would give women the best quality evidence on which to base treatment decisions (Bayliss and Ballantyne 2017).

3 | Vaccines in Pregnancy

The first RCT of a vaccine in pregnancy was in 2015, for an RSV vaccine produced by Novavax (Muňoz et al. 2019).

Whether in trials or clinical practice, maternal vaccines may affect the fetus in four ways. (1) They can theoretically pass through the placenta into the fetal bloodstream. (2) Maternal vaccines are designed to stimulate the production of antibodies, a proportion of which will be transferred to the baby. (3) Most vaccines induce inflammatory mediators, treatments for which may enter the fetal circulation. (4) All these substances in the maternal bloodstream have the potential to affect the placenta, whether or not they enter the fetal circulation.

In addition to the active ingredient, vaccines contain preservatives, buffers, and adjuvants that come with risks. Many modern vaccines, for instance, are made using Chinese hamster ovary cells. Rabbits (although not humans) developed antibodies to hamster neogenin, a host-cell protein, when given GSK's RSVPreF3 vaccine, a stabilized form of one of the RSV proteins (Steff et al. 2020). Nobody knows the effect of even minuscule amounts of this or other proteins on the health of a pregnant woman or her unborn child.

Vaccines based on mRNA are a new concept resulting from the covid pandemic. Several mRNA COVID-19 vaccines have been approved for use in pregnancy with no RCT evidence to support them, although at least one trial took place (National Library of Medicine 2023). A trial of an mRNA RSV vaccine in pregnancy is in progress (National Library of Medicine 2024), although a trial of this product in babies was halted after an excess of vaccinated babies (naïve to RSV) developed vaccine-associated enhanced respiratory disease (VAERD) (Snape et al. 2024). All of this is taking place without any agreed guidance on best practice for trials in pregnant women.

The mRNA in these vaccines requires embedding in lipid nanoparticles (LNPs). It cannot be assumed that, when injected, these LNPS are devoid of problematic effects in their own right.

It was thought that little or none of these vaccines crossed the placenta, but a recent study has shown the presence of mRNA derived from COVID-19 vaccines in human placenta and breast milk (Lin et al. 2024). None of these issues were in the frame when the first RCTs of vaccines in pregnancy began in 2015 with Novavax's RSV vaccine.

4 | Recent Maternal RSV Vaccine Programs

4.1 | Animal Studies

Clinical trial guidelines for industry studies are produced by The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The current guideline for non- or pre-clinical safety testing of drugs in pregnancy is ICH S5 (R3)—"Detection of reproductive and developmental toxicity (DART) for human pharmaceuticals—step 5—Revision 4" which was last updated in 2020 (ICH 2020).

The requirement for developers of novel drugs is that their products are tested in two pregnant animal species, one of which is conventionally a rodent. According to the guideline however, this requirement is waived for new vaccines that need only be tested in one species.

"Selection of Species for DART Testing. The rat is generally appropriate for DART testing and is the most often used rodent species for reasons of practicality, general knowledge of pharmacology in this species, the extensive toxicology data usually available for interpretation of nonclinical observations and the large amount of historical background data...

For assessment of [embryo-fetal development] EFD only, a second mammalian non-rodent species is typically evaluated, although vaccines and biopharmaceuticals are excepted."

Historically the use of rodent or rabbit species has aimed at detecting gross organ defects in offspring and fetal loss. Although it is possible to monitor factors like the blood pressure of laboratory animals, this is at present not done.

Although rodents can be used to assess fetal development, testing in pregnant non-human primates (e.g., monkeys) seems more appropriate as fetal/pup development in primates, especially neurological development, is similar to that in humans. They can be more accurately monitored, and this appears likely to yield more pertinent information.

GSK's RSVPreF3 vaccine was tested in 24 pregnant rats and 24 pregnant rabbits. The results in both species showed "slightly higher post-implantation losses" (i.e., miscarriage) in both vaccinated groups: (rat: 9.03% vs. 6.41% for the control; rabbit: 4.27% vs. 2.02%) (Stokes et al. 2021). These were assumed to be chance findings, but other results cast doubt on this.

The almost identical Pfizer RSVPreF vaccine was similarly tested but only in pregnant rabbits as this vaccine induced antibodies in male but not female rats. "There were no indications of maternal systemic toxicity or on embryo-fetal or postnatal survival, growth, or development in the F1 offspring." There were no supporting data for this statement. (European Medicines Agency 2023).

A placebo-controlled study of maternal Group-B Streptococcus (GBS) six-valent polysaccharide conjugate vaccine (GBS6) similarly showed excess pre-and post-implantation loss in pregnant rabbits and rats. This was "not considered treatment-related because they were incidental and within the background data" for these species. Again, excess skeletal variations "were not considered test article-related because they are common findings" or "incidental". Some of the abnormalities were more common in the "vehicle control" group containing the adjuvant (0.5 mg/mL aluminum as AlPO4) than in the placebo group (Catlin et al. 2021).

The consistent detection of excess abnormalities in DART studies suggests that more research with larger samples is needed.

Animal testing also offers a chance to explore epigenomic effects of treatments. We now know that the risks of valproate would have been detected decades earlier if its effects on chromatin markers such as enzymes responsible for acetylation had been looked at—as they can be now. Fetal chromatin is more unstable than adult chromatin, and drug-induced effects on the epigenome, as with acetaminophen, can result in fetal drug levels that are many-fold higher than in postnatal life (Struhl 2024).

4.2 | Clinical Trials

Phase 1 trials set out to establish a new drug's safety and dose range; however, the numbers of participants are much too small, and the duration is too short to reliably determine safety. Pregnant women have historically been excluded from these studies.

Reports from the Pfizer and GSK Phase 1 trials of their RSV vaccines in healthy (male and non-pregnant female) volunteers do not show significant adverse events (Walsh et al. 2022; Schwarz et al. 2022). Subsequent Phase 2 and 3 trials in pregnant women were undertaken without any specific safety focus.

For example, the only blood test that was done in these Phase 2 trials was for "routine hematology and biochemistry" 1 week after the vaccination. (Simões et al. 2022; Bebia et al. 2023).

Given how little we know in this domain, pregnant women who volunteer for clinical trials arguably deserve better safety monitoring.

Although a small Phase 2 trial of Novavax's RSV F protein nanoparticle vaccine showed encouraging results (Muňoz et al. 2019), the pivotal Phase 3 study failed to achieve efficacy targets. No safety concerns were reported (Madhi et al. 2020).

4.3 | Preterm Births

The strongest signal of hazards of vaccination in pregnancy came from GSK's Phase 3 GRACE trial of RSVPreF3-Mat aimed at preventing RSV disease in babies (Dieussaert et al. 2024). This was an international RCT where over 5000 pregnant women were administered 120 μg of unadjuvanted RSVPreF3

or placebo between 24 and 34 weeks of gestation. In February 2022, the trial was terminated by its independent Data and Safety Monitoring Committee (DSMC) because of an excess of preterm births and associated neonatal deaths.

Preterm birth occurred in 6.8% of the infants in the vaccine group and in 4.9% of those in the placebo group (relative risk, 1.37; 95% CI, 1.08–1.74; $p = 0.01$). Thus, for every 54 infants (95% CI, 32–214) born to women who received RSVPreF3 rather than placebo during pregnancy, one additional preterm birth occurred. Neonatal death occurred in 0.4% of the infants (13 of 3494) in the vaccine group and in 0.2% of those (3 of 1739) in the placebo group (relative risk, 2.16; 95% CI, 0.62–7.56; $p = 0.23$). Most of the neonatal deaths were of preterm babies. There were geographical variations in the incidence of preterm births, but no cause for the excess of preterm births has been established.

An earlier Phase 2 RCT in the US of an almost identical vaccine, Pfizer's RSVPreF, had also shown an imbalance of preterm births with 14/325 in four different vaccine preparations versus 1/78 in the placebo group (OR 3.47; 95% CI, 0.45–26.77) (Simões et al. 2022). The vaccine was administered between 24 and 36 weeks of gestation.

Adverse events of "Jaundice neonatal" and other classes of jaundice were reported significantly more frequently in the babies whose mothers had received the vaccine. Although neonatal jaundice is associated with preterm births, other causes, for example high rates of maternal acetaminophen consumption, cannot be excluded.

A similar preterm imbalance was noted in the recent international Pfizer Phase 3 trial of RSVPreF in over 7000 pregnant women. An interim analysis published in 2023 showed 202/3568 babies (5.7%) were born prematurely to vaccinated mothers versus 169/3558 babies (4.7%) in the placebo group (OR 1.20 95% CI 0.98–1.48) (Kampmann et al. 2023).

Women with previous preterm births were excluded from these studies.

4.4 | Hypertensive Disorders of Pregnancy

GSK's Phase 2 trial of RSVPreF3 in pregnancy reported an excess of hypertensive disorders (gestational hypertension and pre-eclampsia) in the vaccinated groups. (Table S1, Bebia et al. 2023, see Table 1).

Although not apparent from the article, 5 of the 6 instances of pre-eclampsia in the vaccinated groups were classed as "serious" (National Library of Medicine 2021). There was a similar but smaller imbalance of pre-eclampsia in the GSK Phase 3 trial that was associated with excess preterm births.

Pfizer's Phase 3 trial of RSVPreF reports "serious" "severe" and "life-threatening" maternal adverse events in the vaccinated compared to the placebo group (Supporting Information Appendix: Table 17), (Kampmann et al. 2023).

The total number of "severe or life-threatening adverse events" is significantly greater in the vaccinated group. This difference in the System Order Class "Pregnancy, puerperium, and perinatal conditions" is 63/3682 versus 36/3675 OR 1.76 (1.1654–2.6570) $p = 0.0072$. Within that class the incidence of severe or life-threatening pre-eclampsia is 17/3682 versus 7/3675 OR = 2.43 (1.0067–5.868) $p = 0.0483$.

Hospitalization of the infant due to RSV infection in the first 12 months of life was a secondary endpoint of this Phase 3 study. There were 57 infant hospitalizations in the placebo group and 38 in the vaccinated group (Table S7, (Kampmann et al. 2023)).

These numbers (with similar denominators) seem to match the excess of "severe or life-threatening adverse events" within 1 month of vaccination in the mothers, suggesting that any benefits to the infants were offset by a similar incidence of harms to the mothers.

Cost benefit analyzes of maternal RSV vaccination policies to protect bronchiolitis in babies do not at present take into account the opportunity costs of managing these maternal conditions.

Similarly, a small RCT of BioNTech's BNT162b2 COVID-19 vaccine in pregnant women showed an excess of serious and non-serious pre-eclampsia in the vaccinated group (4 + 2)/161 versus (0 + 2)/163 in the placebo group (EU Clinical Trials Register 2024).

4.4.1 | Adverse Event Terminology

Over the last 9 years, progress has been made in making clinical trial safety data recording more precise. The Neonatal

TABLE 1 | Maternal AESIs reported until 6 weeks post-delivery.

	60 μg RSVPreF3 $N = 70$		120 μg RSVPreF3 $N = 75$		Placebo $N = 68$	
Symptom	***N***	**% (95% CI)**	***n***	**% (95% CI)**	***n***	**% (95% CI)**
At least one pregnancy-related AESI	19	27.1 (17.2–39.1)	19	25.3 (16.0–36.7)	12	17.6 (9.5–28.8)
Non-reassuring fetal status	6	8.6 (3.2–17.7)	9	12.0 (5.6–21.6)	8	11.8 (5.2–21.9)
Hypertensive disorders of pregnancy	7	10.0 (4.1–19.5)	4	5.3 (1.5–13.1)	1	1.5 (0.0–7.9)
Gestational hypertension	3	4.3 (0.9–12.0)	2	2.7 (0.3–9.3)	1	1.5 (0.0–7.9)
Pre-eclampsia	4	5.7 (1.6–14.0)	2	2.7 (0.3–9.3)	0	0.0 (0.0–5.3)

Abbreviation: AESI, adverse events of special interest.

Adverse Event Severity Scale (NAESS) was developed through international consensus (Allegaert et al. 2024) and the Maternal Fetal Adverse Event Terminology (MFAET) (Spencer et al. 2022) have both been mapped to MedDRA-the dictionary of medical terms instituted by ICH. Together, they allow the recording of the impact of conditions such as pre-eclampsia on pregnant women and neonates to be graded in severity.

4.5 | Non-Specific Effects of Maternal Vaccination

It has been known for several years that children whose mothers were not vaccinated during pregnancy subsequently have a greater antibody response to routine immunizations than those whose mothers were (Voysey et al. 2017).

In meta-analyzes of four RCTs, all conducted in low-income settings, inactivated influenza vaccine (IIV) in pregnancy had no effect on all-cause mortality of women and infants. It was, however, associated with approximately double the risk of non-influenza infectious adverse events in the women and with a 36% higher risk in their offspring up to 6 months after delivery (Hansen et al. 2021).

Pooled data from six observational studies showed maternal pertussis vaccine (mostly compared with other maternal immunizations with non-live vaccines) to be associated with an increased risk of chorioamnionitis among the pertussis vaccinated women, RR = 1.27 (95% CI: 1.14–1.42) (Andersen et al. 2022).

Children born to mothers vaccinated in pregnancy against pertussis mount a weaker response to pertussis vaccine when they themselves are immunized (Voysey et al. 2017; Barug et al. 2019).

Interference—blunting—of RSVPreF3 on the immune response to the components of dTpa when given concurrently in non-pregnant women was observed at 2 month postvaccination. The clinical significance of the lower antibody response to pertussis antigens in the study groups co-administered with RSVPreF3 remains unclear (Hermida et al. 2024).

4.6 | Monoclonal Antibodies

As the maternal vaccine trials unfolded, there were parallel studies on monoclonal antibodies (MAB) for RSV disease, of which nirsevimab is at present the best known. These MABs are given by injection to babies. Lately, these treatments have also been designated as vaccines, possibly because parents are now used to the idea of infant vaccinations. However, in addition to the standard hazards of monoclonal antibodies, in particular the development of anti-drug antibodies (ADA) (Thambi et al. 2025), we have an unknown factor in these cases, which is that infant epigenomes are much less stable than adult epigenomes through to the age of two. Although not a vaccine given in pregnancy, as outlined below, there are unknown safety factors about combining maternal RSV vaccines with monoclonal vaccines given to babies immediately after birth.

4.7 | What Do These Trials Show?

1. That current animal study testing requirements (for teratogenesis) are inadequate for a new domain where problems for women and their babies may arise in the second half of pregnancy.
2. That standard Phase 1 studies are not designed or appropriate for pregnant patients.
3. That hypertensive disorders of pregnancy, including pre-eclampsia and gestational hypertension, have been shown to be more prevalent in vaccinated mothers. Both can endanger the pregnant woman's health both in the short term and later life.
4. That several trials have shown a tendency to preterm births. Preterm babies are prone to jaundice and are susceptible to more severe infections. A rapidly growing body of research indicates that preterm birth is associated with higher risks of cardiovascular, endocrine/metabolic, respiratory, renal, neurodevelopmental, and psychiatric disorders in early to mid-adulthood. These disorders are associated with moderately increased mortality risks among men and women who were born preterm (Crump 2020). Not all of these outcomes are necessarily linked to vaccines. Some may stem from avoidable factors like medication intake and may be modified with prenatal vitamins. Controlled studies that take these issues into account may better inform us as to our options.
5. Monoclonal antibody “vaccines” introduce a further complicating factor. At present we know nothing about possible safety issues when maternal vaccines are combined with these products in immediate post-natal life. In the US, and many other countries, nirsevimab is in widespread use and there are no data on the potential hazards of combining it with a novel maternal vaccine under investigation.

A further unexpected difficulty is that there are other maternal RSV vaccines (e.g., mRNA) in development. It is difficult to see how any women could be recruited to the placebo arm of a blinded clinical trial of such a novel vaccine in countries, including the UK, where RSVPreF vaccination is officially recommended in all pregnancies.

Where any maternal vaccine, and particularly RSVpreF vaccine, is approved, an unanticipated problem is how to protect a baby born preterm, or shortly after vaccination, before adequate maternal antibodies have entered their circulation. This is a hazard given FDA guidance to restrict giving Pfizer's RSVpreF vaccine until after 32 weeks and UK guidance to consider giving it right up to labor.

5 | Harmonizing Regulations

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) was founded in 1990. This body brings together the regulatory agencies and pharmaceutical industry associations of Europe, Japan, and the U.S. Its aim is to standardize the safety, quality, and efficacy of approval processes.

A revised version of ICH Guideline E21: Inclusion of Pregnant and Breast-feeding Individuals in Clinical Trials is due to be published in 2025 (ICH 2023).

A new version is necessary because:

Effects of exposure on the fetus during pregnancy to drugs that may impact in utero and/or post-natal development need to be known to ensure the safety of the fetus, the new-born, and the child as some exposures during pregnancy may have lifelong repercussions.

A new overarching guideline that will cover principles and practices to enable the collection of a sufficiently robust set of safety, efficacy, and/or pharmacokinetic data in pregnant and breast-feeding individuals will better inform clinical decision-making in medicinal product use (e.g., improved product labeling).

This offers physicians and others in the academic community an opportunity to make recommendations about the conduct of these trials and preparatory safety measures.

5.1 | Recommendations

1. In reviewing the studies cited above, we became aware that the medical input to these trials in pregnant women came primarily from pediatricians. This is likely because the outcome of interest to pharmaceutical companies has been the occurrence of RSV in infants and young children. The results from these studies however point to impacts on a mother's health and fetal medicine issues. There is a case for ensuring that, moving forward, trials will have obstetric and gynecology, as well as fetal-medicine input to ensure the safety and future health of mothers and the best possible outcomes for infants.

2. As is policy with all other drugs, preclinical animal trials should be conducted in at least two species of pregnant animals, including non-human primates. Sufficient animals should be used to obtain robust results.

3. When vaccines are considered for use to help pregnant women or their babies, once safety has been determined in a non-pregnant population, rigorous Phase 1 trials should be performed in healthy pregnant women. In these trials, the pregnant woman's health and that of the fetus should be thoroughly monitored. This might include serial fetal ultrasound scans, tests of placental function, measurement of placental growth factor (PGF), examining for epigenome markers, and histological examination of the placenta after delivery. There should be frequent measurement of inflammatory markers. It would be appropriate to perform close monitoring of blood pressure, blood glucose, and other parameters. See (David and Spencer 2022). The use of medicines, including, for example, acetaminophen that might be taken in response to vaccine-mediated inflammatory reactions, should be recorded.

4. Participants in Phase 2 and 3 vaccine trials in pregnancy deserve to be better informed about potential adverse events and about the current limited nature of preclinical and Phase 1 studies.

5. Adverse events occurring in vaccine trials in pregnant women should be actively sought, graded, and recorded using terminology based on NAESS and/or MFAET.

6. Where vaccine trials in human pregnancy show imbalances in harms, that should be the signal to perform more animal studies.

7. Monitoring the safety of the pregnant woman is as important as measuring vaccine efficacy in her offspring.

8. Until relatively recently, many countries produced their own vaccines and could decide whether to administer them or run a study. In today's commercial world, the priorities underpinning vaccination have changed. There are ethical issues here that need further consideration.

9. Placebos in human pregnancy clinical trials should be inert in at least some trials of each treatment.

10. Given that mother and infant need to be followed for months to document vaccine efficacy against infection, the role of breast-feeding should be documented and its effects reported. In addition, lactation AEs (which have now been mapped to MedDRA) should be recorded.

11. In recent vaccine trials, antibody responses have become a surrogate marker for immunity. We do not know whether antibody responses to a vaccine, which in many instances can be many times higher than natural immunity provides, are a valid surrogate for immunity in all cases. This should be established in trials, as well as any placental and fetal effects arising from very high circulating antibody levels.

5.2 | Beyond Approval

The ICH aims at standardizing the conduct of studies done for licensing purposes. These studies are not done to inform clinical care; they are done to secure a niche in markets (Healy 2023). This gives rise to two notable points.

First, most medical statisticians deplore company uses of relative rather than absolute risks in their claims for efficacy. Nowhere is the gap between relative and absolute risk more clearcut than in the vaccine domain where Vaccine Efficacies (Relative Risks) of 80%–95% are routinely cited, which commonly translate into Absolute Benefits of 1% or less.

As an example, Pfizer's RSVpreF given during pregnancy has an 81.8% vaccine efficacy for preventing medically attended severe RSV-associated lower respiratory tract illness in babies at 90 days (Kampmann et al. 2023) but this equates to an absolute benefit for the babies of 0.7% (one in 142).

Having both metrics routinely cited would put physicians and their patients in a better position to decide on the Benefit–Risk ratio for individual women and their children.

The use of tests for statistical significance in these studies is often misguided and functions more as a Stop-Go mechanism for regulators and journal editors than to inform care (Healy 2023).

Second, companies want their studies done efficiently, and to this end, although distinguished academics may appear on the authorship line, company medical writers (ghostwriters) write these studies—as for instance with RSV and Covid vaccine trial publications. (Kampmann et al. 2023; Dieussaert et al. 2024; Polack et al. 2020; Drysdale et al. 2023).

This may be more efficient than leaving the work to medical academics, but neither the resulting authors nor medical writers have access to the data from the trials and, whereas regulators may have notional access, in practice they do not have the time or personnel to investigate issues thoroughly (Healy 2023).

Furthermore, companies cannot always be relied upon to produce and share reliable results. The pivotal Novavax trial of a RSV F Nanoparticle Vaccine was completed in July 2019. Results submitted to the National Library of Medicine are still (Nov 2024) pending Quality Control Review, despite seven iterations since July 2022 (National Library of Medicine 2020).

Given the importance of these issues to the health of future generations, and the duty of physicians to their patients, in this area should we consider holding industry to a higher standard?

If we cannot get industry to agree, they may be willing to support pregnancy registries (Healy and Mangin 2017).

Even in less complex cases than vaccine studies in pregnancy, RCTs yield convincing results much less often than is realized. As mentioned, industry studies are not designed to inform clinical practice. When they abandoned their Covid vaccine pregnancy study, Pfizer offered to analyze the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry; yet 4 years later, has not reported EU Clinical Trials Register (2024).

Good pregnancy registries have much to recommend them. They will certainly yield complex data, in part because many real-life pregnant women would not have met the inclusion criteria for company studies. The complexity of registry data will map better on the complexity of real-world decisions that physicians and pregnant women have to make. We have confidence in the abilities of women who are pregnant or contemplating pregnancy and their physicians to make good judgment calls even when the best available data are complex.

These issues are of importance to the health of future generations.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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