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Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs

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ABSTRACT

Evidence that influenza vaccination during pregnancy is safe and effective at preventing influenza disease in women and their children through the first months of life is increasing. Several reports of reduced risk of adverse outcomes associated with influenza vaccination have generated interest in its potential for improving pregnancy outcome. Gavi, the Vaccine Alliance, estimates maternal influenza immunization programs in low-income countries would have a relatively modest impact on mortality compared to other new or under-utilized vaccines, however the impact would be substantially greater if reported vaccine effects on improved pregnancy outcomes were accurate. Here, we examine the available evidence and methodological issues bearing on the relationship between influenza vaccination and pregnancy outcome, particularly preterm birth and fetal growth restriction, and summarize research needs. Evidence for absence of harm associated with vaccination at a point in time is not symmetric with evidence of benefit, given the scenario in which vaccination reduces risk of influenza disease and, in turn, risk of adverse pregnancy outcome. The empirical evidence for vaccination preventing influenza in pregnant women is strong, but the evidence that influenza itself causes adverse pregnancy outcomes is inconsistent and limited in quality. Studies of vaccination and pregnancy outcome have produced mixed evidence of potential benefit but are limited in terms of influenza disease assessment and control of confounding, and their analytic methods often fail to fully address the longitudinal nature of pregnancy and influenza prevalence. We recommend making full use of results of randomized trials, re-analysis of existing observational studies to account for confounding and time-related factors, and quantitative assessment of the potential benefits of vaccination in improving pregnancy outcome, all of which should be informed by the collective engagement of experts in influenza, vaccines, and perinatal health.

1. Background

The World Health Organization (WHO) has identified pregnant women and newborn children to be at high risk for seasonal influenza disease morbidity and mortality [1]. Clinical trials have shown that influenza vaccination during pregnancy can prevent influenza disease in pregnant women and their newborn children for the first 6 months of life [2,3] with no indication of harm to the recipients or their offspring [2–4]. Moreover, some studies have also found improved birth outcomes (e.g., reductions in preterm birth) associated with vaccination [5,6], raising the possibility that influenza vaccine programs may have additional benefits on newborn health beyond prevention of postnatal influenza disease. Given the potential impact of maternal influenza immunization programs on maternal and child health worldwide, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) has recommended pregnant women be prioritized for influenza vaccine receipt in countries initiating or expanding their influenza vaccine programs [1].

A major challenge to the adoption of maternal influenza immunization in low-resource countries is the paucity of data regarding the anticipated impact such programs would have on severe illness. In 2013, Gavi, the Vaccine Alliance, modeled the anticipated impact of maternal influenza immunization programs in low-income countries [7] and concluded that the impact of such

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programs on influenza disease mortality would be small compared to the impact of other Gavi vaccine investments. However, if estimates of vaccine effect on birth outcomes are accurate, the impact of such programs in the poorest of countries would be substantially greater than prior estimates and would likely influence investment and implementation decisions.

In 2013, SAGE noted that few countries had enacted maternal influenza immunization policies [7]. It encouraged WHO to quantify the risk-benefit ratio for maternal influenza immunization and in response, WHO created a taskforce of influenza experts, epidemiologists, disease modelers and health economists to synthesize and evaluate data on influenza disease incidence and risk relevant to maternal influenza immunization [8]. Taskforce members produced a report commissioned by WHO to assist in the interpretation of the relevant literature, and this manuscript summarizes the findings of this report. We sought to provide a more complete conceptual understanding of the research methods used to evaluate maternal influenza immunization, assess the empirical evidence bearing on immunization policy, and suggest additional research approaches to address the uncertainties that remain.

2. Objectives and methods

In this review of methodological and conceptual issues, we consider the evidence for a beneficial effect of influenza vaccination on pregnancy outcome, focusing primarily on preterm birth and small-for-gestational-age (SGA) birth, for which the research is most extensive. We identified comparative studies of: (i) influenza vaccination during pregnancy from two recently published reviews [5,9] and (ii) influenza disease during pregnancy from an ongoing WHO systematic evidence review [8]. We summarized the findings underlying the empirical evidence for a beneficial effect of influenza vaccination on pregnancy outcome, considering methodology and biologic plausibility that bear on a potential causal benefit from vaccination.

3. Asymmetry between studies of potential harm and potential benefit of vaccination

The interpretation of influenza vaccine studies in pregnant women has assumed that the same study design and analytic methods used to determine potential harm from immunization can be directly applied to evaluation of potential benefit (i.e., odds ratios greater than 1.0 relating vaccination to adverse pregnancy outcome would suggest harm; odds ratios less than 1.0 would therefore reflect benefit). While this seems intuitively reasonable, the underlying scenarios for harm and benefit are not symmetric.

Under a scenario assuming potential harm, exposure to immunization is viewed as a critical event at a specific point in gestation that could cause an acute adverse event such as a birth defect, miscarriage, or preterm birth, independent of the prevalence of circulating influenza. In contrast, a reduced risk of adverse pregnancy outcome is presumed to be mediated by the effectiveness of the vaccine in preventing influenza. Under this scenario, pregnant women who receive vaccine would be protected from infection, which in turn would prevent disease and any adverse effects on their pregnancy that would result from disease. The two components required for benefit are (1) reduction in risk of acquiring influenza disease as a result of vaccination, and (2) an adverse effect of influenza disease on the health of the pregnancy, reduced through receipt of vaccine.

The benefit of immunization derives from the sustained reduction in risk of acquiring disease during the influenza season, typically a period of two to three months every winter in temperate climates; immunization status outside that window would be irrelevant. Assuming the vaccine is only administered in the pre-influenza season, the period of pregnancy at reduced risk for influenza will depend on the calendar timing of the influenza season in relation to the pregnancy. For example, Fig. 1 illustrates that a woman who conceives in early fall and is immunized during the first trimester (pregnancy B) would be at reduced risk of influenza

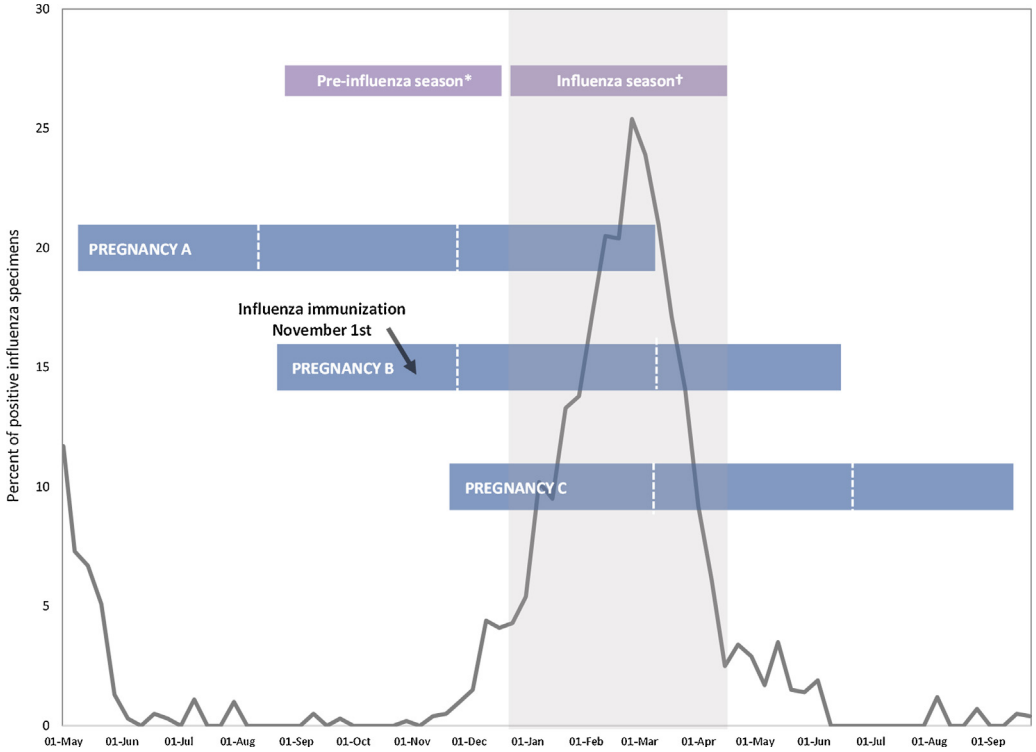

Fig. 1. Hypothetical temporal alignment of ongoing pregnancies with influenza seasonality. The pre-influenza season represents the time period in which influenza vaccines are typically administered (shown here as September to December). The dark gray line represents the proportion of positive influenza specimens and the shaded area represents a typical influenza season, defined as the first and last occurrence of two consecutive weeks with ≥5% positive influenza specimens.

during most of the second trimester and early third trimester, both of which coincide temporally with the hypothetical influenza season shown. However, she would receive no further benefit in the form of a reduced risk of influenza disease after the end of the influenza season. By extension, her developing fetus would also only stand to benefit from potentially averted maternal influenza disease during the same mid-pregnancy time period, since there would be no influenza disease to prevent during the latter part of the gestation in this example. Thus knowing whether the pregnancy is vulnerable to maternal influenza disease at particular time periods during gestation is critical to assessing potential benefits. Although there are case reports of adverse pregnancy outcomes, such as preterm birth, following early and late pregnancy influenza disease [10], the recent WHO evidence review on influenza disease during pregnancy found insufficient data from comparative studies to discern specific weeks, months, or trimesters in which influenza could produce increased risk [8].

As with all time-dependent states, pregnancies must be followed longitudinally, since a given woman is "unvaccinated" up to the time of approximately two weeks after receipt of vaccine (when it is considered fully effective), and then "vaccinated" from that point forward [11,12]. Analytically, it is insufficient to simply dichotomize a given pregnancy as vaccinated if vaccine was received at some time during the pregnancy or unvaccinated otherwise. Instead, there needs to be a week-by-week consideration of the pregnancy with regard to vaccination status and circulating influenza viruses, an approach that has been used by only a few observational studies to-date [13].

Finally, the two components required for benefit must be chained together and quantified to assess the potential effect of vaccination on pregnancy outcome. The protection from influenza is the first component: the greater the baseline attack rate for unvaccinated women and relative effectiveness of vaccination in preventing disease, the greater the absolute benefit from vaccination in preventing disease. The second component is the adverse effect of influenza disease on pregnancy outcome: the greater the harm from influenza disease on pregnancy outcome, the greater the benefit in having avoided disease. Using a counterfactual framework for assessing the causal effect of vaccination on pregnancy outcome, only those women who would have developed influenza absent vaccination but did not develop influenza with vaccination are the beneficiaries in averting influenza. Among those who averted influenza through immunization, only those who would have had a favorable outcome absent disease and an unfavorable outcome with disease realize the benefits to their pregnancy. We lack sufficient data to quantify the individual probabilities of the events in this scenario. Nevertheless, from this illustration we can see that not all pregnancies stand to benefit from vaccination, due to the sizable proportions of women whose pregnancies will have little-to-no overlap with the influenza season, who will not develop influenza disease (regardless of vaccination), or who develop influenza disease but suffer no ill effects on pregnancy outcome.

4. Evidence for a beneficial impact of vaccination on pregnancy outcome

4.1. Effect of vaccination on risk of influenza

The assessment of whether vaccination covering the period of pregnancy yields benefit starts with consideration of whether the given formulation of influenza vaccine is, in fact, effective in providing immunity against circulating influenza strains. Here, the evidence indicates clearly that influenza vaccine is as effective for pregnant women as for other populations [14]. Two randomized controlled trials of influenza immunization have demonstrated a reduction in maternal influenza during pregnancy [2,3], one of which estimated a 50% reduction in lab-confirmed influenza disease [3]. Thus, in years of moderate to high overall vaccine effectiveness, immunized women whose pregnancies pass through the influenza season will incur only half of the disease that they would have experienced absent vaccination. Observational studies provide similar indication of benefit [15,16], but indicate that the magnitude of benefit may vary from season-to-season.

4.2. Influence of influenza on pregnancy outcome

A second critical piece of information needed to assess the benefit of vaccination is the magnitude of risk of adverse pregnancy outcome among women who develop influenza. The recent WHO review assessing maternal influenza disease and adverse birth outcomes found the evidence from comparative studies to be inconsistent, in addition to being limited in both quantity and methodological quality [8]. Some studies report little or no increased risk of preterm birth among women who were hospitalized with influenza or other respiratory diseases during pregnancy [17,18], whereas others find a markedly elevated relative risk (about four-fold) of preterm birth [19,20]. While the latter studies may reflect the most severe manifestations of influenza disease, there are also concerns that the increased rates of hospitalizations are due more to clinical practice than to disease severity and may also be a nonspecific marker of concern with the health of the pregnancy. Nonetheless, there is some replicated evidence, albeit inconsistent, suggesting hospitalization with severe influenza disease during pregnancy may be associated with preterm birth, particularly for pandemic 2009 A (H1N1) disease [20,21].

Among studies that have used laboratory confirmation among women presenting with symptoms of influenza-like illness, there was evidence of a small increased risk of preterm birth in some studies [21,22], but not in others [23]. A concern in several of these studies is that other maternal-fetal problems in pregnancy motivated the testing, introducing a possible diagnostic bias [20,21]. Studies of self-reported respiratory illness during pregnancy (as opposed to laboratory-confirmed influenza) are less relevant given that in most cases only a small proportion of non-specific respiratory illnesses are in fact due to influenza virus infection [24,25]. Nevertheless, studies of confirmed influenza in pregnant women do not indicate that mild or subclinical influenza disease in mothers is associated with worse birth outcome [13,23]. Fewer studies have addressed SGA birth than preterm birth, but provide equally inconsistent results: three studies reported no increased risk associated with influenza disease during pregnancy [22,23,26] while two others found an increased risk [18,23].

4.3. Evidence that vaccination prevents adverse pregnancy outcomes

The observational epidemiologic studies that considered the potential adverse effect of influenza vaccination during pregnancy on infant health outcomes were recently summarized in systematic reviews of the evidence on preterm birth and fetal death [5,6]. Fell et al. identified 26 observational studies and one randomized clinical trial that were pertinent and found sufficient heterogeneity among the studies to preclude generating a meaningful summary estimate [5]. Among the 19 studies of preterm birth, 15 yielded adjusted odds ratios in the range of 0.6–1.0, and one suggested a markedly increased risk. While a pooled estimate was not generated, it would appear that such an estimate would fall in the range of 0.7–0.9, implying a reduced risk associated with influenza vaccination. The authors reasonably interpreted their results as providing rather strong evidence *against an adverse effect* of influenza vaccine

receipt but interpreted the *evidence of benefit* cautiously. Given lack of evidence of harm associated with vaccination [4–6,27], the concern with adverse fetal effects related to influenza vaccine received in pregnancy has largely abated.

Two studies have compared pregnancy outcomes occurring among immunized and non-immunized women within time periods defined by influenza virus circulation [28,29]. If vaccination truly prevents adverse outcomes by preventing influenza, then the benefit will be most apparent when there is a high baseline risk of influenza disease. For births during periods of intensive influenza virus activity in Georgia between 2004 and 2006, Omer et al. reported an odds ratio for preterm birth of 0.28 (0.11–0.74) and an odds ratio for SGA birth of 0.31 (0.13–0.75), more pronounced than for births during periods without circulating virus [28]. Steinhoff et al. examined the data from a randomized trial conducted in Bangladesh reported by Zaman et al. and assessed the association between influenza vaccination and preterm birth stratified into time periods defined as having limited or proven virus circulation [2,29]. When influenza was actively circulating, the adjusted odds ratio for preterm birth was 0.32 (0.05–2.29) and for SGA birth it was 0.44 (0.19–0.99), a more pronounced apparent benefit than in periods in which there was no influenza virus circulating [29].

Rather than defining the time period by when the birth occurred, the focus should be on the period of gestation during which there was risk of influenza virus exposure. The benefit is not conferred at the time of vaccination; rather, the reduced risk would be experienced over this critical period of gestation, which would be associated, but not fully aligned, with the timing of birth. In addition, when estimating the full impact of the intervention, the effect measure found in the fraction of the population experiencing the highest risk of disease should not be applied to the population as a whole.

A subtle problem, but one that may be relevant to preterm birth at least, concerns the potential for cohort truncation bias. If vaccines are administered in the pre-influenza season (for example, September to October), and the focus is on births that occur in the influenza season (November to February), then a study that selects based on timing of birth rather than timing of conception is vulnerable to selection of long or short gestations [30]. Depending on the exact timing, defining populations by "date of delivery" rather than by "date of conception" can distort results for preterm birth.

Whereas preterm birth could, in theory, be precipitated by an acute event, such as the development of influenza disease, the likelihood of vaccination having a pronounced effect on fetal growth is less plausible given that fetal growth is an ongoing physiologic process occurring over an extended period, particularly in the third trimester. Unless influenza illness were to cause significant chronic placental damage that could affect fetal growth, an effect that has not been documented, it seems implausible that this ongoing process could be disrupted so markedly by an acute event as to affect this outcome to the extent that has been reported [28,29].

Finally, there is the reported magnitude of effects, with some studies suggesting that upwards of two-thirds of all preterm births and more than half of SGA births were avoided for deliveries occurring in the influenza season [28,29]. To provide some context, it is important to note that there are no other known exogenous influences on preterm birth that come even close to this magnitude of effect (i.e., a three-fold reduction in risk) [31,32]. In scrutinizing the results for potential artifacts, it is useful to consider the types of *predictors* (not even necessarily *causes*) that are associated with marked differences in preterm birth. There are proximal predictors in the course of pregnancy that are strongly predictive of preterm birth, in part because some of these factors lead to medically indicated delivery prior to completing 37 weeks of gestation. A profile that includes a prior preterm birth, pregnancy complications, presence of underlying chronic disease, and an array of unfavorable lifestyle factors, is associated with a markedly elevated risk of preterm birth (and fetal growth restriction). It is plausible but unknown whether vaccine receipt varies in relation to these markers of risk for adverse pregnancy outcome.

Several studies suggest that influenza vaccination may not, in fact, prevent preterm birth. Three studies examined the risk of preterm birth according to the period of pregnancy in which the vaccine was administered and found no reduction for those vaccinated in the first or second trimester, despite the fact that such vaccination when administered early would protect against influenza for the greatest proportion of pregnancy [33–35]. In fact, a reported reduction in risk limited to late-pregnancy vaccination may be more consistent with the hypothesis of "selective vaccination", since the proximal predictors of adverse outcome are not identified until later in the course of pregnancy, or with "immortal time bias", since the pregnancy had to "survive" until the time of vaccination [12]. A number of methodologically strong observational studies did not report any evidence of decreased risk of preterm birth among vaccinated mothers [13,33–35]. As reflected by the evidence of heterogeneity in the systematic evidence review [5], it seems unlikely that these reflect random error only, but there are so many methodologic subtleties in cohort definitions and analytic methods that the critical features driving the results are difficult to discern.

5. Confounding by correlates of vaccine receipt

The results of the observational studies indicating improved pregnancy outcome may well be attributable to confounding rather than a causal impact of vaccination. Women with the most favorable risk profile may be more likely to receive the vaccine, a phenomenon that was found to exaggerate the apparent benefit of vaccination in preventing death among elderly influenza vaccine recipients [36,37]. In observational studies, it would be expected that the women receiving vaccine would be more highly educated, less likely to use tobacco, have a more optimal pre-pregnancy weight and diet during pregnancy, and be more likely to adhere to prenatal care guidelines. Indeed, a number of observational studies of influenza immunization during pregnancy have shown important baseline differences between vaccinated and non-vaccinated women along these lines [13,33,34,38].

Many of the observational studies of influenza vaccination and pregnancy outcome have, in fact, measured and made statistical adjustments for confounding factors, and such adjustments have tended to reduce the magnitude of reduced risk for vaccinated women [5]. However, even with careful attention to measuring and adjusting for correlated predictors of favorable pregnancy outcome, the ability to fully account for this phenomenon using statistical methods is limited. To the extent that our operational measures of "healthful lifestyle" do not fully capture the construct—and it is inevitable that they do not—there will be residual confounding, even with an attempt to remove the bias. A small reduction in the relative risk of adverse pregnancy outcome associated with vaccination may well be a product of residual confounding.

6. Conclusions and research recommendations

In 2013, SAGE recommended that WHO quantify the benefits of maternal influenza immunization in order to strengthen investment and implementation decisions [39]. The evidence for maternal immunization to prevent influenza disease in mothers and infants is strong, but the potential benefits of influenza vaccine exposure on pregnancy outcome are uncertain. Clear evidence of this additional benefit from influenza vaccination would strongly

influence maternal influenza immunization program investment decisions and vaccine use globally.

Despite a number of studies suggesting that influenza vaccination is associated with a reduced risk of adverse pregnancy outcomes, these observational studies possess important methodologic limitations. To the extent that receipt of vaccine is a discretionary activity on the part of pregnant women and their clinicians, baseline differences among vaccine recipients and non-recipients may only be avoidable through randomized trials. However, in the well-known example of hormone replacement therapy and risk of cardiovascular disease, the discrepant findings from randomized and observational studies resulted largely from the design and analytic approach of the observational studies rather than from a lack of randomization [40]. Similarly, many of the observational studies examining maternal influenza immunization fail to address the inherently longitudinal and time-varying nature of the phenomenon of interest, instead treating receipt of vaccine as a fixed attribute. Besides having the advantage of randomization, intervention trials generate analyses that follow women through time to determine their pregnancy outcome, thus explicitly accounting for the timing of vaccine administration in relation to influenza circulation and gestational age. To the extent that observational studies can do the same, and adjust rigorously for potential confounding through regression or propensity score analysis, they should be able to approximate the results of randomized trials. Several recently completed clinical trials will provide vital new insights on the question of influenza vaccine and pregnancy outcome [41], but observational studies will still be required to broaden the range of populations studied and the timing of vaccine administration. Together, randomized trials and well-designed observational studies can produce complementary evidence, providing policy-makers with the data necessary to assess full benefit.

In addition, it is important to note that all the randomized trials have been conducted in resource-constrained settings, whereas nearly all observational studies have occurred in North America and Europe. While it is theoretically possible to conduct randomized trials in Western countries and observational studies in resource-constrained settings, there are substantial logistical and ethical barriers to either approach. To the extent that we can integrate findings across the ongoing and completed trials, the inferences will come more quickly.

Given our continued reliance upon observational studies to assess the potential impact of maternal influenza immunization on pregnancy outcomes, our first recommendation is to re-analyze selected observational studies using the methods described above. This would only be possible for studies with extensive information on covariates that may act as confounders and longitudinal information on the timing of pregnancy, influenza activity in the area, and receipt of vaccine. Some studies clearly approximate this ideal [13,33], and generally show no benefit of vaccination in reducing preterm birth, although it is important to note that even when using these robust analytic approaches, Pasternak et al. found a lower risk of fetal death among women vaccinated with 2009 monovalent pandemic influenza A (H1N1) vaccine (adjusted hazard ratio: 0.44, 95% CI: 0.20–0.94) [42], while Haberg et al. did not (adjusted hazard ratio: 0.88, 0.66–1.17) [13]. These findings require further investigation given the paucity of studies on influenza disease, influenza vaccination, and fetal death [5,8].

A second recommendation is for a careful, quantitative assessment of the potential impact of vaccine on pregnancy outcome at the population level that would consider the baseline risk of influenza throughout the year, the timing of vaccination in relation to gestation, the impact of vaccination on the risk of influenza disease, and the impact of influenza disease on the outcome of pregnancy. As discussed, the only women who stand to benefit from receipt of vaccine are those whose pregnancies coincide with the part of the year when there is a risk of developing influenza, and the only ones who actually benefit are those in whom disease is prevented, resulting in a favorable outcome that would otherwise have been unfavorable. Perhaps studies in settings in which influenza occurs throughout the year would help to quantify the potential benefit. As noted above, it seems unlikely that vaccination could prevent upwards of 50% of all preterm births or instances of fetal growth restriction during the influenza season [28,29], but a more systematic analysis of these scenarios would inform research and policy.

A final recommendation is that we must engage both influenza experts and perinatal researchers to design and evaluate studies on this topic collaboratively. Much of the work to date has been done by experts in either one area or the other, and the ensuing limitations of this segregated approach are apparent in both directions. Only through the combined efforts of these disciplines can important and subtle features of both influenza and perinatal health be integrated into the design of future studies.

Studies evaluating the potential benefit of maternal influenza immunization on pregnancy outcomes will continue to be conducted, most of which will be observational. Data from these studies could prove instrumental for countries weighing the potential benefits of implementing maternal influenza immunization programs, particularly those with limited budgets and multiple competing priorities. Therefore, researchers, policy-makers, and funding agencies must ensure that such data are reliable, a goal that can only be achieved through attention to fundamental aspects of study design and interpretation.

Disclaimer

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