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Sins of Omission: Model-Based Estimates of the Health Effects of Excluding Pregnant Participants From Randomized Controlled Trials

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Background: More than 90 million women in the United States have given birth. Randomized controlled trials (RCTs) of medications almost always exclude pregnant participants.

Objective: To quantify the health effects of excluding pregnant participants from RCTs.

Design: Decision analytic framework applied to case studies of thalidomide, COVID-19 vaccines, and dolutegravir.

Setting: Varied.

Participants: Pregnant people and their children.

Measurements: The authors modeled the ex post facto health effects of RCTs, comparing projected health effects of medication uptake had an RCT been conducted versus historically observed outcomes. They also modeled the a priori health effects that could have been anticipated in trial planning. They converted health effect estimates to monetary value using standard benchmarks.

Results: Across case studies, health benefits from conducting RCTs during pregnancy were projected to far exceed expected adverse effects (AEs) from RCTs. For example, had thalidomide been tested in a completed RCT with 200 treated participants, about 33 children would have experienced severe AEs, whereas knowledge from the RCT would have prevented 8000 thalidomide-related birth defects, 99.6% of all thalidomide-related birth defects from 1956 to 1962. Likewise, if RCTs for COVID-19 vaccines had included pregnant participants and if posttrial pregnant uptake were conservatively assumed to mirror that of age- and state-matched nonpregnant women, a projected 20% of COVID-19–related maternal deaths and stillbirths (8% of all maternal deaths and 1% of all stillbirths) in the United States would have been prevented from March to November 2021. Across case studies, the a priori value of RCT data would have exceeded the approximately $100 million cost of phase 1 to 3 RCTs.

Limitation: Parameter uncertainty.

Conclusion: Systematic inclusion in RCTs could benefit both pregnant people and their children by both speeding AE detection and increasing uptake of beneficial medications.

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More than 90 million people in the United States—71% of women aged 18 to 85 years—have given birth at least once (1). Although randomized controlled trials (RCTs) are required for approval of new medications, they generally exclude pregnant participants (2–5). Excluding pregnant participants is intended to protect them and their fetuses from potential adverse effects (AEs) of new medications (6–8).

Bypassing RCTs sharply contrasts with the medication review process for nonpregnant individuals, which requires RCTs before approval by the U.S. Food and Drug Administration (FDA). Once medications are FDA-approved for general use, clinicians can prescribe them, absent clear contraindications, to pregnant individuals (9). To inform recommendations, providers may draw on RCTs in nonpregnant populations, animal studies, and postmarketing observational studies in pregnant individuals (8, 9). Nevertheless, clinical guidance often emphasizes uncertainty about AEs during pregnancy due to inadequate human studies, with evidence insufficient to definitively recommend either continuing or avoiding medication (9).

Members of the medical community have advocated conducting research, including RCTs, during pregnancy for more than 30 years (10). Harms arising from the lack of research have been highlighted by policymakers and committees (11, 12), providers (3, 13–15), professional societies (16), and the press (17). Still, pregnant people remain excluded from most trials by default, and the need for better data to guide evidence-based care persists (11, 18–21). Pregnant people frequently reduce their dose of or stop taking medications because of concerns about AEs (22). Even so, 94% use medications, on average 3 to 5

See also:

Web-Only
Supplement

distinct drugs over the course of pregnancy, many of which lack rigorous safety data (11, 23–25).

This article presents a decision analytic framework developed to estimate morbidity and mortality resulting from avoiding RCTs during pregnancy. We argue that avoiding RCTs slows uptake because patients and providers are hesitant to adopt medications with limited evidence (26), which is detrimental when a medication is beneficial. Nevertheless, if a medication is harmful, more patients experience AEs before detection in observational studies than would have in RCTs. To illustrate these consequences, we apply our framework to case studies of medications with different profiles of hypothesized and true benefits and harms. Our results highlight that conducting well-powered RCTs during pregnancy would improve health outcomes compared with relying on postmarketing data.

METHODS

Analytic Overview

We compared projected health effects after RCTs versus observed clinical outcomes, quantifying 1) the ex post facto (ex post) value of RCTs that were not done, compared with health outcomes that were later observed, and 2) the a priori value that researchers could have anticipated before conducting an RCT.

We considered 3 case studies (thalidomide, COVID-19 vaccines, and dolutegravir) representing different combinations of hypothesized and actual effects. For medications with substantial AEs, an RCT would have been beneficial if it reduced total uptake; for those without AEs, an RCT would have been beneficial if it increased total uptake (Figure 1).

We describe first the calculation of ex post and a priori value and then the background and parameterization of each case study.

Ex Post RCT Value: "What If a Study Had Been Done?"

We define the ex post value of an RCT as the difference in health outcomes had an RCT been conducted—thereby altering medication uptake—compared with historically observed health outcomes absent an RCT. To estimate this, we first projected expected health outcomes after a well-powered RCT, accounting for both RCT-related adverse events and change in uptake from RCT evidence. We assumed that changes in behavior would have been driven by statistically significant benefits or AEs detected in RCTs or, for rare and severe AEs, by investigations triggered by at least 2 severe AEs in a treated group (see part A of the Supplement [available at Annals.org] for discussion of noninferiority tests for AEs). We then compared projected outcomes with observed outcomes in real-world data.

We assumed RCT sample sizes based on well-established clinical benchmarks. As a base case, we set a sample size of 200 per group, the current preregistered standard (in an observational study design) for the U.S. perinatal HIV guidelines (27). This sample size is applied in the context of high-quality alternatives and considered sufficient to indicate "a favorable risk-benefit balance compared with other [antiretroviral] options, incorporating outcomes for pregnant people, fetuses, or newborns" (27). Specifically, the Antiretroviral Pregnancy Registry derived a standard of 200 first-trimester exposures to detect a doubling of major birth defects with 80% power; an advantage of this benchmark is that it accounts for the fact that medications with teratogenic effects often cause multiple related AEs (28, 29). As a range for sensitivity analysis, we chose a lower bound of 50 people per group, assuming a smaller phase 1 safety study (30). As an upper bound, we considered 1000 people per group, a larger study, based on the Antiretroviral Pregnancy Registry's preregistered threshold for a 1.5-fold increase in major birth defects or a small to moderate phase 3 study (28, 30).

To inform whether an RCT would have merited its financial cost, we converted health effects to monetary value. These estimates were conservative, reflecting only mortality (using value of a statistical life [VSL] of $8 million as estimated willingness to pay to prevent 1 death) (31, 32) and significant disability (using disability-adjusted life-year [DALY] weights and assuming $100 000 per DALY) (33–37). On the basis of published data, we benchmarked these against combined phase 1 to 3 RCT costs of $100 million (38–40) (part B of the Supplement; all parameters are listed in Table 1).

A Priori RCT Value: "How Would Trial Planners Have Assessed the Value of Doing a Trial Before Medication Release?"

Although ex post estimates quantify potential health benefits after observing true effects of a medication, before starting a trial, researchers are uncertain about a medication's benefits and AEs (64). We therefore calculated the a priori value of a trial, viewed

Figure 1. Framework.

	True Effect: Harmful	True Effect: Beneficial
Hypothesized Effect: Beneficial	**Uptake leads to unnecessary adverse effects** ***Thalidomide***	**Limited uptake prevents treatment benefits** ***COVID-19 vaccines***
Hypothesized Effect: Harmful	–	**Limited uptake prevents treatment benefits** ***Dolutegravir (HIV)***

In each box, we describe health harms arising from individuals acting on prior assumptions or beliefs about the effect of a medication, compared with definitive evidence. For the bottom row, we assume that potential harms are sufficiently uncertain such that a randomized controlled trial would still meet standards of clinical equipoise required for ethical conduct of research.

Table 1. Model Parameters

Parameter	Value	Source
Thalidomide		
Intercalary limb deficiency (background rate), *n/N*	1/50 000	41
Rate of ILDs given thalidomide exposure, *n/N*	1/6	41
Infants exposed to thalidomide (lower bound), *n*	8000	42 (see also 43)
Individuals exposed to thalidomide who survived infancy, *n*	5000	42 (see also 44)
Disability weight for ILDs	0.237	33
Disability duration for ILDs (1960 cohort life expectancy by sex, combined with sex ratio at birth), *y*	78	45, 46
Disability weight for nausea in early pregnancy ("Moderate other gynecological disorder")	0.114	33
Disability duration for nausea in early pregnancy, *d*	45	47–49
COVID-19		
Stillbirth (background rate), *n/N*	1/200	50
Incremental stillbirth risk due to COVID-19 (wild-type, per 1000)	2.7	50, 51
Incremental stillbirth risk due to COVID-19 (delta, per 1000)	17	50, 51
Annual live births, *n (millions)*	3.7	52
Pregnant U.S. vaccine uptake	Time-varying	53
Nonpregnant U.S. vaccine uptake by age, state, and sex	Time-varying	54
Dolutegravir		
Neural tube defects (background rate)	1/1000	55
Relative risk for neural tube defects with dolutegravir in erroneous Botswana safety signal	10	56
Difference in percentage of HIV+ women aged 16–49 y receiving dolutegravir vs. percentage of HIV+ men aged 16–49 y receiving dolutegravir after safety data, *percentage points*	26.2	57
Survey sample size for women aged 16–49 y, *n*	69 578	57
Women aged 15–49 y receiving ART, *n (millions)*	14	58, 59
Reduction in mortality from dolutegravir, compared with efavirenz (risk difference)	0.00088	60
Percentage of women aged 15–49 y with HIV receiving ART	82	59
Percentage of HIV+ women aged 16–49 y who took dolutegravir before safety signal	1.9	57
Annual pregnancies among women with HIV/AIDS, *n (millions)*	1.2	59
Projected risk reduction in mortality from efavirenz over nevirapine (risk ratio)	0.97	61
Annual deaths of women aged 15–49 y receiving ART, *n*	302 700	62
Other		
Value of a statistical life, *$ (millions)*	8	31, 32
Value per disability-adjusted life-year, *$*	100 000	35, 36, 63
Cost of phase 1–3 RCTs, *$ (millions)*	100	38–40, Part B of the Supplement

ART = antiretroviral therapy; ILD = intercalary limb defect; RCT = randomized controlled trial.

from the perspective of planners before medication release. We summarized this in terms of 2 quantities, one related to the value of a trial if it produced expected health benefits and another for its value in the event of significant AEs.

For the first metric, we estimated how many additional people would need to receive the treatment due to the RCT data in order to accrue $100 million in health benefits, assuming no AEs (38–40). We calculated this number needed to treat (NNT):

$$NNT = \frac{\$100\,\text{million}}{\text{E(DALYs averted per patient)} \times \$100\,000/\text{DALY}}$$

Second, we estimated a conservative AE multiplier that researchers might reasonably have anticipated. This multiplier is a comparison of the health gains afforded by an RCT relative to observational studies. It is defined as the expected ratio of AEs that would occur before detection via postmarketing surveillance to those observed in an RCT. More AEs are identified in postmarketing studies than in RCTs both because not all individuals taking a medication are monitored outside an RCT setting and because RCTs limit medication uptake before study conclusion. We calculated this multiplier (m):

$$m = \frac{\text{E (AEs in postmarketing surveillance before detection)}}{\text{E (AEs in RCT of sample size } n\text{)}}$$

Thalidomide

We first briefly considered the canonical case of thalidomide, which was prescribed in Europe to treat morning sickness from 1956 to 1962 (44). Although animal studies did not detect teratogenic effects, thalidomide caused severe and often fatal intercalary limb defects (ILDs) (41, 43, 44). As a result, thalidomide triggered new safeguards around medication testing (65). With modern safeguards, we would expect a faster reaction from the medical community to remove medications with similar AEs from the market. Nevertheless, this case remains instructive because it looms large as an example of medication risks during pregnancy and highlights how research could have reduced tragic health harms, even in the case of severe teratogens.

Ex Post Value

To estimate the ex post value of a preapproval RCT, we assumed that if a significant increase in ILDs had been observed in a trial, there would have been no thalidomide uptake in the general population. (This is conservative because due to the rare and severe effects triggered, an RCT would likely have been discontinued early.) We projected resulting effects on 2 outcomes, deaths and ILDs (41, 43, 44). For each, we subtracted hypothetical RCT-related outcomes from observed outcomes and then converted these to monetary value. We assumed ILD disability weights of 0.237 and used German 1960 birth cohort life expectancy of 78 years (33, 45).

A Priori Value

For a priori value, we first quantified the NNT to achieve $100 million if thalidomide had eliminated nausea and vomiting without unanticipated AEs (DALY weight, 0.114; expected duration, 45 days) (33). To quantify a conservative AE multiplier in postmarketing surveillance, we first considered that ILDs were among the most rare and severe AEs possible and calculated the ratio of observed AEs to AEs expected in an RCT, noting that detection for less striking AEs would likely have been slower, with few systems available to detect AEs at the time. To make this estimate more conservative, we allowed for optimism about how quickly AEs would have been detected and reduced this multiplier by 20% (calculations in part D.1 of the **Supplement**).

COVID-19 Vaccines

We next considered COVID-19 vaccines. Pregnant participants were excluded from initial COVID-19 vaccine RCTs, despite objections (66–69). As a result, although the FDA authorized vaccines under emergency use authorization without contraindication in pregnancy in December 2020 and some medical societies (such as the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine) endorsed them thereafter, the U.S. Centers for Disease Control and Prevention (CDC) did not recommend COVID-19 vaccination during pregnancy until August 2021 based on observational data (51, 70–72). Uptake lagged accordingly among pregnant people (53, 54).

Ex Post Value

We modeled the ex post value of an RCT, assuming that if an RCT had demonstrated efficacy in pregnancy without significant safety signals, uptake among pregnant people would have increased, paralleling either women from the same age and state ("age- and state-matched") or women aged 40 to 49 years ("state-matched COVID-19 booster reference") (53, 54). These uptake assumptions are conservative because pregnant people had *higher* uptake of the 2019 influenza vaccine and COVID-19 boosters than both reference groups (**Supplement Figure 3**, available at Annals.org). We used CDC data for general population vaccine uptake; for pregnant uptake, we extrapolated from CDC's Vaccine Safety Datalink sites based on relative uptake between pregnant people and age- and state-matched women (53, 54) (data and calculations in part C.1 of the **Supplement**).

We projected effects on maternal mortality from COVID-19 (73) and stillbirths resulting from maternal SARS-CoV-2 infection (74) from March to November 2021 (before booster effects), assuming that, with vaccination, rates of maternal death and stillbirth would have matched background rates absent COVID-19. Before the delta variant, we assumed an incremental absolute increase in stillbirth risk of 2.7 per 1000 among pregnant persons with COVID-19; with the delta variant, this increased to 17 per 1000 (50, 51, 75). For both maternal mortality and stillbirths, we assumed a VSL of $8 million (31, 32). We varied stillbirth VSL in sensitivity analyses.

A Priori Value

For COVID-19 vaccines, we considered prior beliefs about the therapeutic benefit of the vaccine (in terms of impact on maternal mortality and stillbirths from COVID-19) and identified NNTs for health value exceeding $100 million. We then considered the multiplier on AEs that would have occurred if 1% to 5% of pregnant persons who planned to give birth had been vaccinated before detection. This was low in contrast to reported 2019 influenza vaccine uptake of 61% (**Supplement Figure 3**); even with gradual rollout, potential fetal AEs may not have been detectable until several months after vaccine administration (for example, at a 20-week ultrasound).

Dolutegravir

We last considered dolutegravir, an antiretroviral medication used for HIV treatment, as an example of a medication for which inconclusive observational evidence suggested potentially severe AEs but additional data proved concerns unfounded (76). Dolutegravir was approved in the United States in 2013 and recommended over other regimens because of high efficacy, low likelihood of developing medication-resistant virus, and reduced AEs (77). Botswana was one of the first countries to offer dolutegravir for all adults and adolescents with HIV, including those of childbearing potential, in 2016. In a surveillance sample of 426 infants, they observed a high rate of neural tube defects (NTDs) (0.94%, 10-fold higher than in the general population or in infants exposed to other HIV therapies) (55, 56, 78). This led the World Health Organization to caution against dolutegravir in people who might conceive, and many countries refused to offer dolutegravir to women of childbearing age (57, 79). Subsequent larger birth surveillance studies did not find increased risk for NTDs, and in 2019 the World Health Organization reversed course and recommended dolutegravir (80). Nevertheless, uptake among women of childbearing age continues to lag (57).

Table 2. RCT Value Summary

Medication and Adverse Outcome Type	Avoidable Adverse Outcomes Before Conclusive Evidence*	Adverse Outcomes During RCT ($n = 200$)†	Ex Post RCT Value		A Priori RCT Value	
			Net Health Effects	Net Value, $‡	NNT for $100 Million Health Value	AE Multiplier inPostmarketing Surveillance
Thalidomide						
From use of dangerous medication	8000	33	7967	33 104	71 150	192
Perinatal mortality	3000 deaths	12 deaths	2988 deaths	23 900	–	–
Intercalary limb defects	5000 cases	21 cases	4979 cases	9204	–	–
COVID-19 vaccines‡						
From underuse of vaccine	210	–	210	1687	62 500	35–175
Maternal mortality	71 deaths	–	71 deaths	572	–	–
Stillbirths	139 stillbirths	–	139 stillbirths	1115	–	–
Dolutegravir						
From underuse of medication	3228	–	3228	25 823	23 501	7–23
Mortality among women of childbearing age	3228 deaths	–	3228 deaths	25 823	–	–

AE = adverse effect; NNT = number needed to treat; RCT = randomized controlled trial.
* Includes the number of adverse outcomes that occurred in the real world before the true effects of the medication were understood. In the case of (truly) harmful medications, we calculate the incremental number of adverse events resulting from medication use. In the case of (truly) beneficial medications, we calculate adverse outcomes that would have been averted if uptake had paralleled that in other groups. See main text for details.
† RCT calculations are based on sample sizes of 200 per group (range in main text, 50–1000).
‡ Estimates shown use the age- and state-matched comparison group.

Ex Post Value

For our ex post analysis, we considered the events of 2018 described in the previous paragraph, in which dolutegravir was believed to be harmful but was in fact beneficial.

We assumed that if an RCT had found reassuring safety data in 2018, the rise in uptake among women aged 16 to 49 years would have paralleled the corresponding rise in uptake among men ("trend-matched reference"):

$$uptake_{women\ 16-49\ assuming\ RCT} = uptake_{women\ 50+} + (uptake_{men\ 50+} - uptake_{men\ 16-49})$$

We then quantified mortality effects over a 5-year period, first in a survey sample measuring uptake trends (57) and next in the global HIV population, assuming similar uptake patterns in both and based on previously modeled estimates of dolutegravir's mortality reduction compared with other regimens (60) (part C.2 of the Supplement).

A Priori Value

For our a priori analysis, we quantified NNT assuming that the anticipated mortality reduction of dolutegravir would be at least as large as that of efavirenz, the previous standard of care, compared with its predecessor, nevirapine (61). We calculated an AE multiplier first based on the percentage of U.S. HIV-positive pregnancies enrolled in the U.S. Antiretroviral Pregnancy Registry (81). Because the United States has a small proportion of global HIV cases and surveillance is more limited in some settings, we benchmarked this against an estimate of the number of patients exposed to dolutegravir before safety signal detection (57) (calculations in part D.3 of the Supplement).

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RESULTS

Thalidomide

About 8000 infants were affected by thalidomide-related AEs, of whom 3000 died shortly after birth. An RCT with 200 participants per group, taken to completion, would have had nearly 100% power to detect thalidomide-related birth defects. Accounting for AEs in the RCT, but assuming this information would have been sufficient to prevent medication approval, this would have prevented approximately 7967 births from being affected by thalidomide (99.6%), including an expected 2988 infant deaths and 4979 limb deficiencies (Table 2). This would have corresponded to $33 billion in health value–$24 billion from deaths averted and $9 billion from limb deficiencies averted.

If researchers had first completed a smaller safety trial with 50 participants per group, the population-level effect would have depended on response to trial information. With 94% power to detect a statistically significant ILD AE, the trial would have averted an expected 7476 ILDs if distribution stopped after a statistically significant effect. Nevertheless, the chance of at least 2 ILDs being observed in the RCT would have been greater than 99%, and if this information had been sufficient to prevent distribution, the trial would have averted an expected 7992 AEs. Even the largest RCT size we considered ($n = 1000$ per group), taken to completion, would have markedly reduced health effects, averting an expected 7833 AEs.

In terms of a priori value, if thalidomide had reduced severe nausea and vomiting during pregnancy without any AEs, and if these RCT data increased uptake by at least 71 150 women, the health value from averted DALYs would have exceeded the $100 million cost of a trial. We estimate an AE multiplier of at least 192 before detection in postmarketing surveillance compared with an RCT.

COVID-19 Vaccines

Vaccination coverage against COVID-19 among U.S. pregnant people fell below rates in both comparison groups over the study period (**Figure 2**). If RCT data had existed and had improved uptake to age-, sex-, and state-matched levels, we estimated that this would have prevented 71 maternal deaths and 139 stillbirths from March to November 2021 (**Table 2**); if uptake improved to our "state-matched COVID-19 booster reference" levels, these estimates increased to 111 maternal deaths and 213 stillbirths. This would have averted 20% to 31% of COVID-19–related AEs from March to November 2021 (8% to 12% of all maternal deaths and 1% of all stillbirths). In monetary terms, age- and state-matched uptake and COVID-19 booster uptake would have led to savings of $1.7 billion and $2.6 billion, respectively: $0.6 billion to $0.9 billion from maternal outcomes averted and $1.1 billion to $1.7 billion from fetal or infant outcomes averted. With stillbirths valued at $1 million rather than $8 million, the corresponding range was $0.7 billion to $1.1 billion.

For COVID-19 vaccines, we estimated substantial a priori RCT value across a range of assumptions (**Supplement Figure 6**, available at Annals.org). For example, even assuming a conservative maternal risk for COVID-19 mortality of 0.1% (below that found in such studies as Villar and colleagues [82] and Jering and colleagues [83]), a 5% risk for contracting COVID-19 during pregnancy, and no COVID-19–related fetal risk, the value of a prerelease RCT that included pregnant women would have exceeded $100 million with 250 000 incremental pregnant people vaccinated, 7% of annual births. We estimated an a priori AE multiplier of 37 to 185, assuming 1% to 5% of pregnant persons planning to give birth would be vaccinated before AE detection. Even these would have required relatively rapid AE detection; for reference, we estimated more than 6% vaccine coverage among pregnant people by the end of February 2021.

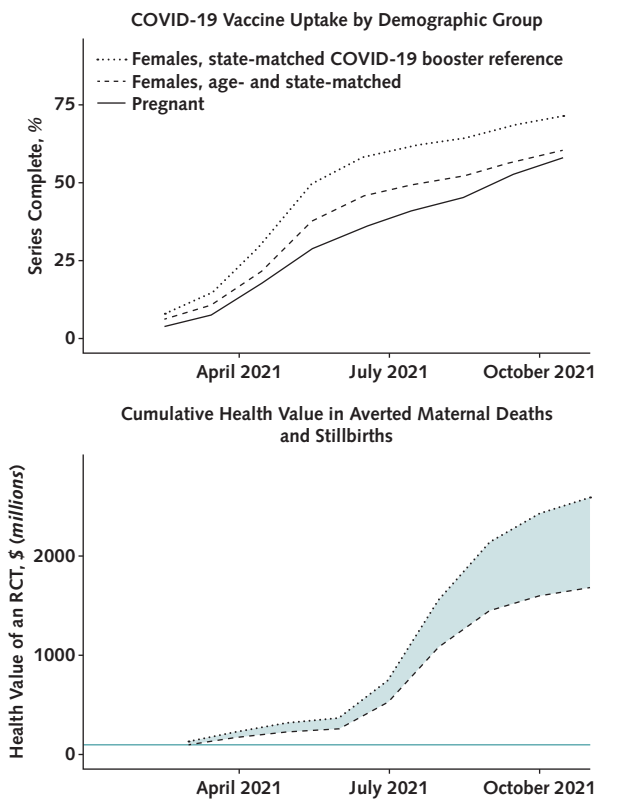
Dolutegravir

Because dolutegravir decreased mortality relative to other regimens, we estimated that low uptake among women aged 16 to 49 years after the erroneous safety signal (**Figure 3** [57]) led to 16 additional deaths in the survey sample (57) used for parameterization. Extrapolating to all women receiving antiretroviral therapy between ages 15 and 49 years, this would represent 3228 total deaths, corresponding to a $26 billion loss of life (**Table 2**).

Had a trial of 200 participants per group been conducted, it would have had minimal (<1%) power to detect the increase of NTDs to 1% in the safety signal. However, larger trial sample sizes could have detected these AEs had they existed: A study of 1000 participants per group would have 83% power to detect an effect and more than 99% to detect 2 NTDs.

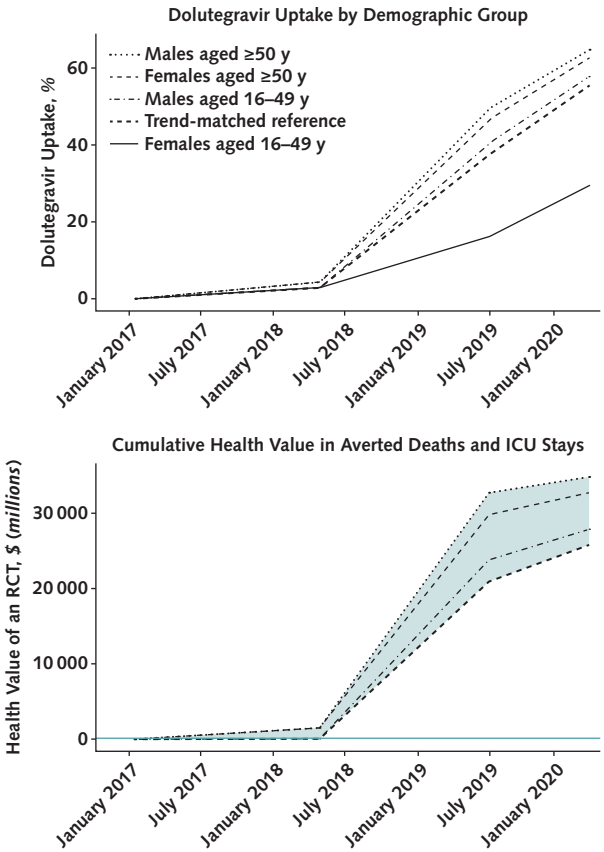
For NNT, we estimated that with posttrial incremental uptake of 23 501 women (<0.2% of women aged 15 to 49 years receiving antiretroviral therapy globally), the anticipated reduction in mortality would have been sufficient to justify a $100 million trial. For a conservative multiplier on AEs before detection, we noted that approximately 1 in 7 pregnancies were enrolled in the U.S. Antiretroviral Pregnancy Registry in 2018 to 2020 (81). However, we estimated that approximately 22 800 pregnancies were exposed to dolutegravir globally before the erroneous safety

Figure 2. COVID-19 vaccine uptake and value.



RCT = randomized controlled trial. **Top.** The cumulative percentage of the population with 2 COVID-19 vaccine doses, by age group and among pregnant persons from February–November 2021. **Bottom.** The ex post value of an RCT: the cumulative health benefit in millions of dollars that would have been achieved if pregnant uptake had matched that of the age- and state-matched females or a reference group based on COVID-19 booster uptake during pregnancy, imputed on the basis of state-matched females aged 40–49 y. The green horizontal line shows $100 million, the estimated costs of phase 1 to 3 RCTs.

Figure 3. Dolutegravir uptake and value.



ICU = intensive care unit; RCT = randomized controlled trial. **Top.** Survey-estimated dolutegravir uptake by age and sex over time. From Romo and colleagues (57). **Bottom.** The ex post value of an RCT: the cumulative health benefit in millions of dollars that would have been achieved by aligning the dolutegravir uptake trajectory among the population of females aged 16–49 y with corresponding age groups. The green horizontal line shows $100 million, the estimated costs of phase 1 to 3 RCTs.

signal, a multiplier of approximately 23 on this AE before (erroneous) detection compared with what could have been achieved in a large RCT ($n = 1000$).

Discussion

Although excluding pregnant people from RCTs is intended to prevent harm to them and their offspring, it may in fact achieve the opposite: This practice exposes more people to AEs and simultaneously allows fewer to access the benefits of medical advances than would RCTs. Even conservative estimates of morbidity and mortality associated with excluding pregnant people from RCTs in our 3 modeled case studies are substantial. When converted to monetary value, these health impacts exceed the estimated financial costs of including pregnant people in RCTs, either through general trials with sufficient pregnant participants to complete a well-powered subgroup analysis or through pregnancy-specific RCTs.

For the large number of medications that are currently permitted—but not explicitly recommended—during pregnancy, the dearth of RCT data forces stressful and uncertain decisions onto pregnant people and their providers (8, 20).

Where observational evidence is available, it requires more people to be exposed to a medication because many users are not observed by researchers, and there is a risk for biased participant samples producing misleading conclusions (84). Although RCTs would not obviate the need for observational research to detect rare effects and may be useful for studies for which a control group is not needed (for example, some pharmacokinetic studies), increased efforts to conduct RCTs on medications during pregnancy would improve the welfare of both pregnant people and their children.

Several policy interventions could support increased research on medications during pregnancy and have been endorsed by groups including the American College of Obstetricians and Gynecologists and the Task Force on Research Specific to Pregnant Women and Lactating Women (11, 16). These include reducing barriers to research in pregnant people (for example, FDA removal of pregnant women from classification as a vulnerable group following removal of this designation in U.S. Department of Health and Human Services and international guidelines) and setting stronger requirements to promptly conduct animal studies during pregnancy and, pending results, conduct trials in pregnant people (11). Funding and logistical levers likewise can support research, such as expanding grant timelines to account for slower enrollment (11) and addressing actual and perceived liability concerns, as a 2024 committee through the National Academies of Sciences, Engineering, and Medicine proposed (12). Last, investigation into AEs of greatest interest to patients and providers is needed (11), to balance powering trials adequately with the financial and logistical costs of larger sample sizes. In our analysis, we focus on aggregate end points (such as any fetal abnormality) because of shared biological pathways, the rationale underpinning the 200 exposures standard for U.S. perinatal HIV guidelines (27).

Our study has several limitations. Our case studies use selected, simplified examples of medications salient during pregnancy, and our projections have considerable uncertainty, rendering our results qualitative illustrations rather than precise quantitative estimates. In practice, patients and providers may have to weigh nuanced AE risks against significant clinical benefits rather than being able to declare a drug "safe" or "unsafe," and there are complex interplays between evidence, clinical guidelines, and patient behavior. Nevertheless, we highlight that across a broad range of circumstances, it would remain beneficial to conduct well-powered RCTs. Further work could assess the sensitivity of these results to circumstances and

nuances (for example, variation across pregnancy trimesters and AE types) to prioritize efforts to fill gaps in evidence (11).

Despite these, our results suggest a need to reconsider the current default of excluding pregnant participants from RCTs and in doing so causing larger passive harms to avoid the lesser harms of AEs incurred by research. There would be substantial value—to both pregnant people and their offspring—from systematically enrolling pregnant participants in RCTs.

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Supplemental Material*

Bilinski A, Emanuel N, Ciaranello A. Sins of omission: model-based estimates of the health effects of excluding pregnant participants from randomized controlled trials. Ann Intern Med. 29 April 2025. [Epub ahead of print]. doi:10.7326/ANNALS-24-00689

Supplement. **Supplemental Material**

* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

CONTENTS

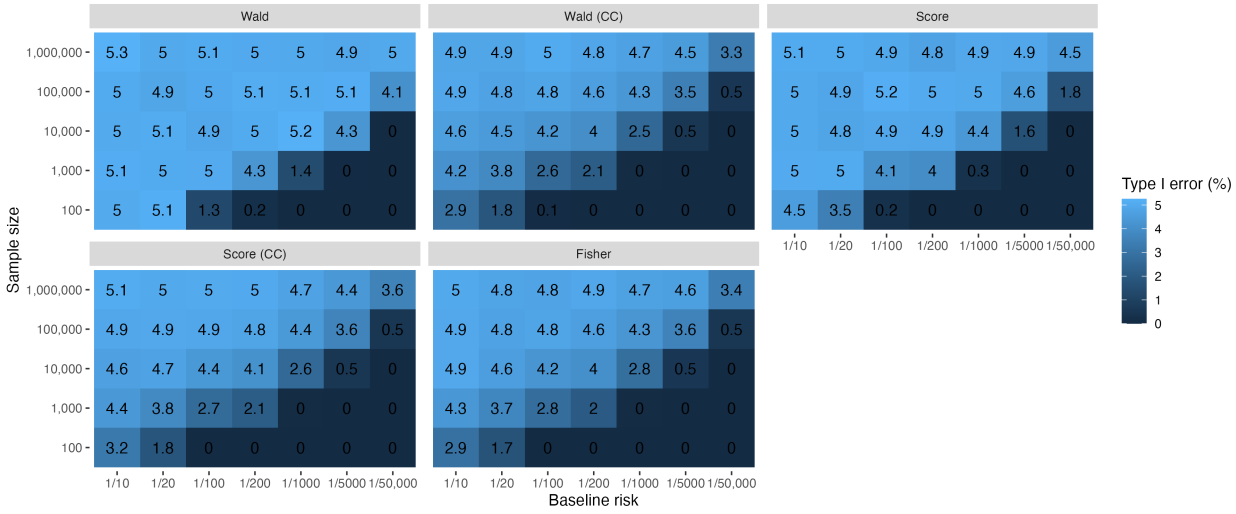
I METHODS

A Statistical tests

We considered two statistical approaches to detecting effects. In the main text, we assume null hypothesis of no effect ("standard power"). The choice of the best method for constructing a confidence interval for a test of proportions has been the subject of considerable debate [1, 2, 3]. We compared the type I error associated with five methods over our base rates of interest: Wald (simple asymptotic estimate), Wald with a continuity correction, score, score with a continuity correction, and exact (Fisher) [2]. We drew independent binomial proportions with equal baseline and treated risk over our range of base rates of interest and tested for a statistically significant difference, evaluating type I error over 50,000. We found that all methods performed well; based on prior work (e.g., [4]) and to guard against known concerns about Wald intervals [2], we chose the score interval as our main specification.

Second, we note that non-inferiority approach may be used to estimate power required to rule out AEs of a given magnitude ("non-inferiority power"). While, in practice, many studies use the first approach to identify and report AEs, non-inferiority tests have the advantage of directly addressing evidence against AEs (in contrast to a lack of evidence of AEs, which may also be a result of low power). A non-inferiority test sets a null hypothesis that $p_1 - p_0 > \delta$, that an AE exceeds some margin δ, and evaluates the strength of the evidence that $p_1 - p_0 < \delta$ at a chosen level of statistical significance. However, due to common practice in the literature, we leave further discussion of this approach to future work.

Supplemental Figure 1: Type I error by inference method



Note: The x-axis varies baseline risk and the y-axis varies sample size. We ran 50,000 simulations, drawing independent binomial proportions with the corresponding per-arm sample size and equal baseline and treated risk over our range of base rates of interest, testing for a statistically significant difference with different methods [2], and summarizing results as type I error rates.

B RCT costs

There is considerable variation in the cost of RCTs for drug approval, and there are limited data on the cost of trials specifically including pregnant participants (e.g., [5, 6, 7]). We use $100m as a conservative estimate of trial costs, assuming increased costs associated with pregnancy-related monitoring and liability [8]. In published studies, upper ranges of combined Phase I-III trial costs were approximately $79m [5] in one study and $110m in another [6]. Another found that 75% of pivotal trials cost less than $33m, with a long upper tail [7] including approximately 5-6% exceeding $100m.

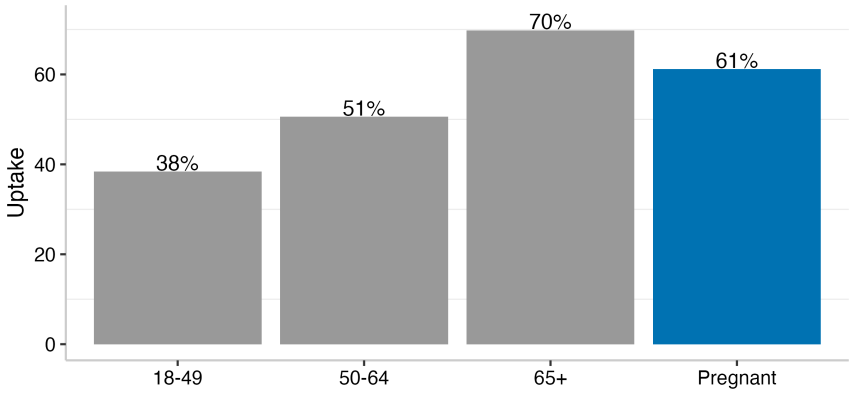
II *Ex post* VALUE OF INFORMATION

A COVID-19 Vaccines

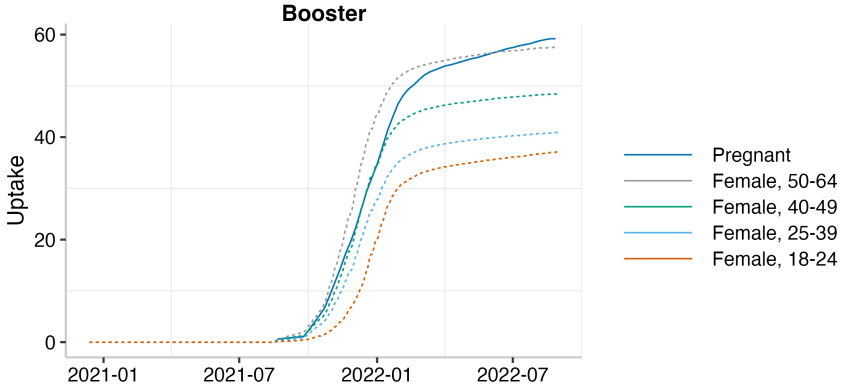
Vaccine uptake counterfactuals. We obtained data on COVID-19 vaccine uptake in the general population by state, sex, and age group as well as among pregnant people from a subset of states in the Vaccine Safety Datalink from the Centers for Disease Control and Prevention [9, 10]. We constructed two potential counterfactuals for COVID-19 vaccine: paralleling either: 1) women from the same age and state ("age- and state-matched") or 2) women aged 40-49 the same state ("state-matched COVID-19 booster reference"). Figure 2 highlights that even the latter counterfactual is conservative relative to uptake of the 2019 flu vaccine and COVID-19 booster uptake in VSD states, which was strongly recommended during pregnancy.

Supplemental Figure 2: Uptake of pregnant vs. counterfactual uptake of other vaccines

Panel A: 2019 influenza vaccine [11, 12]



Panel B: COVID-19 booster [9, 10]



We first estimated the relative rates of vaccination between pregnant women and the counterfactual group in VSD states (Table 1). For each month (m), we estimated population vaccine series completion in the counterfactual group:

$$r_m^{CF} = \sum_s \sum_a w_{as} r_{asm},$$

where s indicates state, a indicates age groups in a chosen counterfactual, w_{as} indicates the weight given to a particular age group a in state s and r_{asm} is the proportion of individuals in age group a and state s that had completed primary COVID-19 vaccination series by month m.

We considered 3 values for w_{as}. For primary analysis, we obtained data on fertility rate by maternal age from National Vital Statistics [13] and combined this with female age-specific population estimates [14] to construct weights to represent proportion of births in state s and age group a. As sensitivity analyses, we considered weights representing the proportion of births in age group a and location s, setting state population to enrollment population in VSD per Table 1, the proportion of the population, rather than births, in age group a and state s, and for the 40-49 counterfactual, total births and total population in state s.

We then estimated the relative vaccination rate as:

$$RR_m^{CF} = \frac{r_m^{CF}}{r_m^{preg,VSD}},$$

where $r_m^{preg,VSD}$ represents the proportion of the pregnant VSD sample vaccinated at month m.

Extrapolation. We used these relative rates to estimate pregnant vaccination in states outside of the VSD.

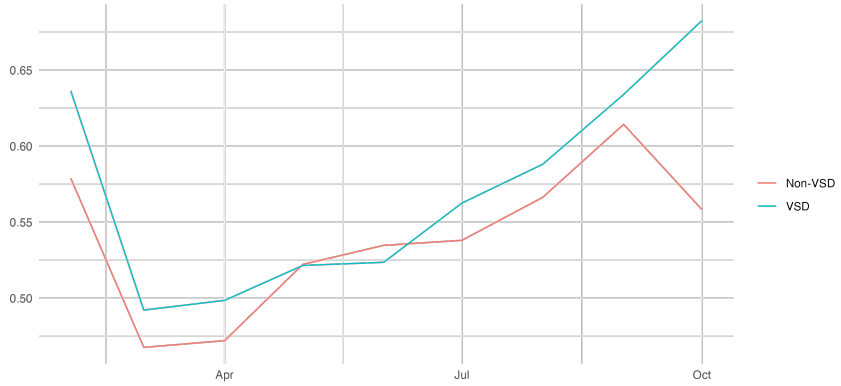
Supplemental Table 1: VSD Enrollment by Site. Sites were extracted from [15]. Enrollment figure sources are included in replication data (Table_S2_Sources).

Site	Enrollment	State
Kaiser Permanente Southern California	4,800,000	CA
Kaiser Permanente Northern California	4,600,000	CA
HealthPartners	1,200,000	MN
Kaiser Permanente Washington	670,000	WA
Kaiser Permanente Northwest	639,302	OR
Kaiser Permanente Colorado	512,906	CO
Marshfield Clinic	310,000	WI
Denver Health	100,000	CO

To assess robustness of the assumption underlying extrapolation of the relative risk of vaccination from the VSD population to non-VSD states, we compared the relative uptake of vaccination among pregnant versus non-pregnant individuals in and outside of VSD states with data the COVID-19 Trends and Impact Survey (CTIS). CTIS was a cross-sectional internet survey that operated daily throughout the pandemic with over 20 million responses [16]. It included questions about both vaccine and pregnancy status; we calculated relative risks by month and these in VSD and

non-VSD states. Although survey respondents are not fully representative of the US, even with weighting [17], the result suggested that our assumption was reasonable, and potentially conservative in terms of reduced relative uptake in non-VSD states. (Data analysis was deemed exempt human subjects research by the Brown University IRB, STUDY00000186.)

Supplemental Figure 3: Relative vaccine uptake of pregnant vs non-pregnant individuals in CTIS



Health outcomes and valuation. Because vaccination took approximately 1-2 weeks to take full effect [18, 19, 20] and the time from infection to death was 2-3 weeks during the study period [21, 22, 23], we aligned vaccination rates at the midpoint of one month with health outcomes for the following month (i.e., 4 weeks before the midpoint of the month corresponding to health outcomes). In sensitivity analyses, we varied this by 2 weeks in either direction.

1. *Maternal mortality from COVID-19 during pregnancy:* We obtained data on COVID-19 deaths during pregnancy from the CDC [24]; we denoted deaths in month m as d_m.

2. *Stillbirth:* Stillbirth is defined as death after 20 weeks of gestation but before or during birth [25]. Prior to the delta variant, we assumed an incremental absolute increase in stillbirth risk of 2.7 per 1000 among pregnant individuals; with the delta variant, this increased to 17 per 1000 [26, 27]. We multiplied this by the number of diagnosed COVID-19 cases in pregnant people (c_m in month m) to estimate monthly stillbirths due to COVID-19 (s_m) [24].

Estimation. We calculated the observed value of information, assuming that given trial data, pregnant individuals would have had the uptake trajectory of the counterfactual group. We omitted transmission effects because pregnant individuals are

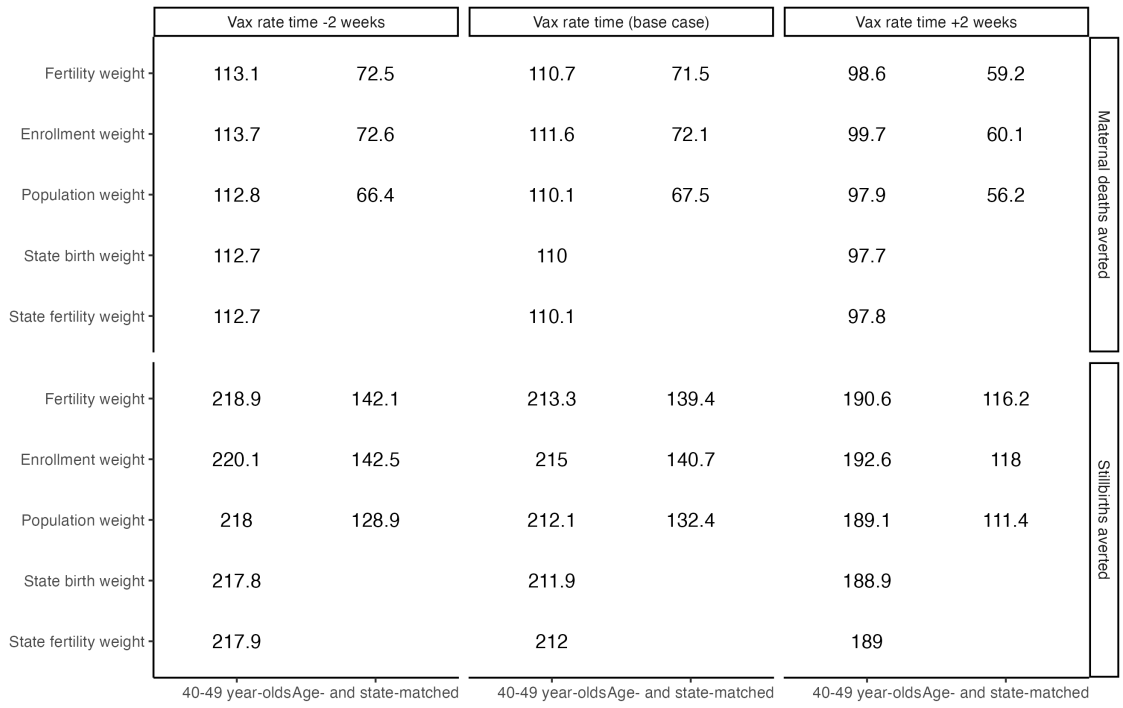
a sufficiently small and diffuse group that we expect these to be minimal; resulting bias would be conservatively. (See also replication code.)

We estimated health effects and morbidity and mortality costs avertable with RCT data under that counterfactual as:

$$d^{CF} = \sum_m RR_m^{CF} * d_m$$
$$s^{CF} = \sum_m RR_m^{CF} * s_m$$
$$h^{CF} = \sum_m RR_m^{CF} * VSL(d_m + s_m)$$

Sensitivity analyses.

Supplemental Figure 4: Sensitivity analysis



Note: We present results by weight type and vaccination rate timing. Results were not sensitive to these assumptions.

B Dolutegravir

We estimated expected mortality reduction from dolutegravir over alternative regimens based on Table 2 (row 3) of previous work [28]:

$$\frac{276,500 \text{ deaths from EFV } - 262,800 \text{ deaths from DTG}}{3.1 \text{ million women } \times 5 \text{ years}}$$
$$= 0.00088 \text{ decrease in maternal deaths/year,}$$

where EFV refers to efavirenz (the alternative studied in comparison to dolutegravir) and DTG refers to dolutegravir. These estimates used a 5-year time horizon [28]. Our calculation assumed mortality risk was constant over that horizon, an approximation selected based on the short time horizon and generally low risk profile of the target population. Main results were not sensitive to small deviations of this parameter.

Another estimate, which used a 20-year time horizon, projected a greater difference in mortality [29] (Table 3, "AIDS death rate in people on ART (per 100 person-years)"). While the base case death rate for non-dolutegravir regimens was similar at 1.7 deaths per 100 person-years (equivalent to 264,000 deaths for a cohort of 3.1 million over 5 years), they projected a decrease in mortality to 0.72 deaths per 100 person-years from dolutegravir-based regimens, which would correspond to 111,600 deaths per 100 person-years for a cohort of 3.1 million over 5 years. We attributed this difference to non-linear effects on mortality over a longer time horizon, and used the lower estimate to be conservative, with the assumption that individuals on non-dolutegravir based regimens may switch to higher efficacy regimens over a longer time horizon.

Last, we compared our risk difference estimate to the corresponding risk ratio from [28] at 0.95. This study assumed a base mortality rate of 8.9% over 5 years among a cohort of HIV positive individuals on or initiating treatment, approximately 1.8% per year. This mortality rate was similar to one estimate of overall HIV mortality among women 15-49 of childbearing age [30, 31, 32], which would make risk ratio and risk difference estimates similar, but did not account for deaths among individuals unexposed to ART. A lower base mortality rate among HIV positive individuals who have started ART may reduce the corresponding risk difference, but given limited data and the conservative estimate in [28] compared to [29], we deferred to the risk difference estimate.

III *A Priori* VALUE OF INFORMATION

A Thalidomide

We obtained NNT to obtain $100m health value:

$$\frac{\$100m}{0.114 \text{ DALYs} * 45 \text{ days}/365 \text{ days/year} * \$100,000 \text{ WTP per QALY}} = 71,150$$

Our AE multiplier was generated:

$$\frac{8000 \text{ affected individuals with ILDs}}{200 \text{ treated individuals in RCT} \times 1/6 \text{ affected by ILDs}} * 0.8 \text{ for optimism down-weighting} = 192$$

All parameters are sourced in Table 2 (main text).

B COVID-19

At the start the pandemic, it was unknown how the pandemic would progress. Researchers in the spring and summer of 2020 when COVID-19 trials began would not have known, for example, about the larger impacts that the delta variant had relative to wildtype and alpha variants [26, 27].

Because there were substantial uncertainties, we explored the range of beliefs about vaccine risks and benefits to pregnant people and their offspring that could have substantially reduced the *a priori* value of a vaccine trial.

1. *Risks to pregnant people from COVID-19:* Pregnant people are typically at a higher risk of severe complications from viral infections like influenza [33]. Early in the pandemic, although maternal deaths were observed, most commonly during the second or third trimester, complications were less extreme than those observed in other novel coronaviruses, SARS-CoV-1 and MERS [34, 35, 36]. Over the course of 2020 and early 2021, a substantial body of literature came to support the finding of increased adverse outcomes in pregnant people due to COVID-19 [e.g., 37, 38]. Based on these, we varied prior belief about COVID-19 mortality during pregnancy from 0.05% to 1%.

2. *Expected pandemic intensity post-vaccine availability:* With a high rate of circulating SARS-CoV-2, all people are at a higher risk of catching the virus; if vaccines had driven down COVID-19 to minimal levels in the population, achieving herd immunity, this risk would have been lower. At the time of vaccine rollout, the alpha variant had arisen, demonstrating evolutionary potential of the virus, but it was not yet known whether the virus would evolve to evade transmission benefits of the vaccine (even as protection against severe disease and

death remained high). To address the possibility of low incidence diminishing the value of a vaccine or a new variant, we varied the expected probability of contracting COVID-19 during pregnancy from 0.5%-10%.

3. *Risks to fetuses from COVID-19:* Perhaps the largest source of uncertainty was the risk of negative outcomes on fetuses. This uncertainty is significant both because there was weaker evidence about vaccines' fetal impacts and because the main conclusions above depend considerably on the fetal impacts of the vaccine. Early, small studies did not find significant effects on fetal outcomes, though these estimates often lacked power to detect rare events [e.g., 39]. Findings of an increased risk of pre-term labor from COVID-19 exposure, as well as documented poor outcomes in pregnant people, were consistent with increased risks to the fetus [37, 38]. We varied the risk difference in stillbirths with and without COVID-19 vaccines from 0 to 2%.

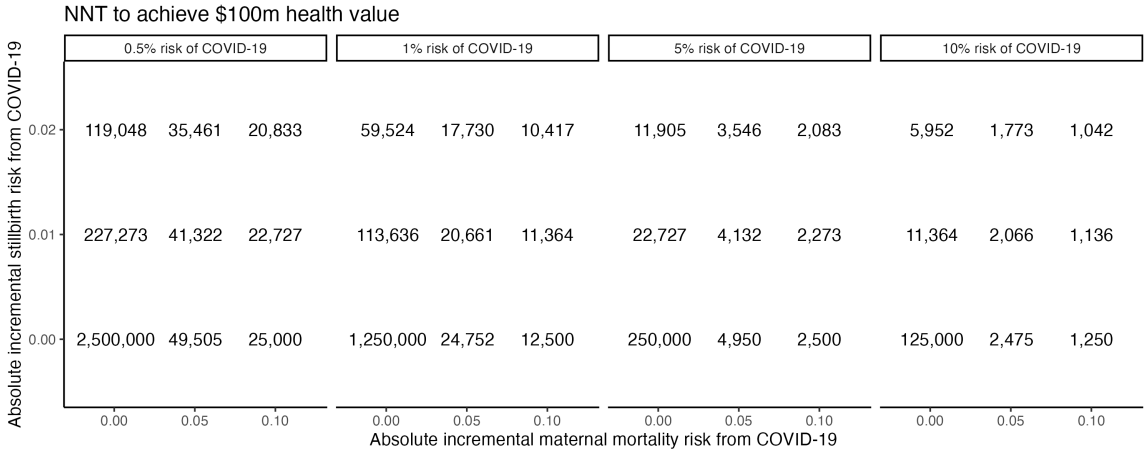
We begin with a simple calculation, assuming an infection fatality similar to influenza and more conservative than [37, 38].

$$\frac{\$100m}{0.001 \text{ IFR} \times 0.05 \text{ probability of contracting COVID-19} * \$8m \text{ VSL}} = 250,000$$

For AE multiplier, we multiplied 2019 live births (3.7 million) by 1-5% [40] and divided by 1000 assumed in a large RCT.

For a more complex analysis, we compared the costs of an RCT to the total health benefits varying the 3 types of uncertainty (above) and calculating NNT.

Supplemental Figure 5: NNT across assumptions



C Dolutegravir

We obtained NNT to obtain $100m health value:

$$\frac{\$100m}{1.773\% \text{ mortality rate} \times 0.03 \text{ risk reduction} \times \$8m \text{ VSL}} \approx 23,501$$

For our second AE multiplier benchmark, we multiplied the proportion of women exposed to dolutegravir prior to the erroneous Botswana safety signal (1.9%) by annual pregnancies among women on ART (1.2 million) to obtain 22,800.

All parameters are sourced in Table 2 (main text).

IV Other Statistics

A Population That Has Given Birth

For the statistic that 71% of women aged 18-50 have given birth at least once, we estimated the total population in the US that has given birth using the 2014, 2016, 2018, and 2020 waves of the Current Population Survey (CPS) June Fertility Supplement [41]. The CPS asks all women aged 15-50 surveyed in each fertility supplement how many live births they have ever had. For those over age 50, for whom this question is not asked, we used the age 50 ever-given-birth rate. We pooled the four survey years and estimate for each single year of age 18 through 50 a weighted, all-waves female birthing rate and an average-across-waves adult female population size, using the person-level weights given by CPS. We multiplied birth rates and population sizes for each year of age, summed these ever-given-birth populations, and divided by the total adult female population.

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