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Abstract

Pregnant women are generally excluded from clinical research over safety concerns. However, demands to include them in clinical vaccine development have intensified after recent COVID-19, Ebola, and Lassa fever outbreaks given the disproportionate effect of these diseases on pregnant women and/or their foetuses. Numerous studies highlighted the scarcity of safety data for therapeutic interventions in pregnant women. Nevertheless, only a small number have assessed the number of vaccine trials including this population. Therefore, we searched for phase 3 and 4 vaccine clinical trials in healthy populations registered between 2018 and 2023 in clinicaltrials.gov and the International Clinical Trial Registry Platform. Out of 400 registered vaccine trials matching our inclusion criteria, 217 (54%) were industry-sponsored, and 222 (56%) had COVID-19 as a target. We found 22 studies (6%) that either were designed for pregnant women or included them as part of a larger population. Out of these 22 trials, 13 were designed specifically for pregnant women; seven of these were maternal vaccines aiming at protecting the foetus, namely pertussis (3), Respiratory Syncytial Virus (RSV) (3), and meningitis plus tetanus (1) vaccines, and six others targeted either flu (3), COVID-19 (2) or Ebola (1). Only the RSV and Ebola vaccine trials were industry-sponsored. We also found that nine studies targeting the general population included pregnant women. These focused

on COVID-19 (3), flu (2), COVID-19+flu (2), Ebola (1), and Hepatitis B (1). None of these studies was industry-sponsored. Our findings show that a gap still exists in terms of pregnant women's inclusion in vaccine trials. Such a gap needs to be tackled urgently to minimise the devastating effects that a future infectious disease outbreak could have on this population. This study can inform future demands for increased inclusion, especially in industry-sponsored trials, as it provides an overview of the current vaccine trials scene.

Keywords

Vaccines, Clinical trials, Pregnancy, COVID-19, Pharmacovigilance

Introduction

Pregnant women are generally excluded from clinical trials due to fears over the safety of the foetus as well as uncertainties about the effect of pregnancy-related physiological changes on the pharmaco-dynamics and -kinetics of different investigational products [1,2]. Additionally, pregnant women-related bioethical dilemmas contribute to the complexity and reluctance to include them in clinical trials [3,4]. An example of such conundrums would be the inability of foetuses to provide consent to any possible trial that recruits pregnant women. In 1977, following the incidents of Thalidomide and diethylstilbesterol (DES), which caused teratogenic effects when given to pregnant women, the US Food and Drug Administration (FDA) issued its most gender-restrictive guidance on clinical trials [5–7]. These guidelines recommended the exclusion of all women of childbearing age from early-stage clinical trials, regardless of their use of contraception methods [7]. These recommendations were later challenged by human rights activists contesting the assumption that women would not be able to take measures to avoid becoming pregnant when needed during clinical trials, and underlining that such recommendations favour the interest of the foetus over the mother’s [8]. These arguments

led the FDA to revise the 1977 recommendations and publish the 1993 guidelines, which recommend better representation and therefore inclusion of non-pregnant women in early-stage clinical research [9]. However, the FDA website still states that “In general, pregnant women are excluded from clinical research” [10].

In the last decades, the lack of pregnancy-related safety data gained increased attention. In 2011, a study demonstrated that approximately 91% of FDA-approved drugs between 2000 and 2010 had no or “very limited” safety data on human intake during pregnancy [11]. These estimates, coupled with reports on the growing use of medications during pregnancy, suggest that thousands of pregnant women are taking drugs in off-label capacities with no or scarce data on the consequences [12–14].

Besides the lack of safety data, there is limited research on the pharmacodynamics and -kinetics of medicines during pregnancy. While the physiological, immunological, and hormonal changes that the body experiences during pregnancy are well-recognised, few clinical studies have looked into how these changes affect the metabolisation and mechanisms of actions of different drugs [15,16]. Consequently, multiple reports started showing how the lack of pharmacokinetics and -dynamics data during pregnancy is becoming an alarming issue [17,18].

Within this increasing recognition of the need for more clinical research on pregnant women, multiple scientific and regulatory bodies started publishing guidelines encouraging trial organisers to include pregnant women where suitable. For example, the National Institute of Health (NIH) created the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), which issued a report (2017) and an implementation plan (2020) for working through the obstacles to include pregnant and lactating women in clinical research

[19]. Additionally, in 2018, the FDA issued recommendations on scientific and ethical considerations to factor in when conducting clinical trials on this group, especially for industry sponsors [20].

In the domain of infectious diseases, research on antiretrovirals for the Human Immune Deficiency virus (HIV) is considered to be one of the most inclusive domains for pregnant women, with many trials investigating how to stop antenatal transmission [21]. However, the majority of HIV clinical trials including pregnant women aimed to study the possibility of preventing transmission to the foetus while research is still lagging on preventive treatments for pregnant women themselves [22]. Faden et al. underlined how this selective inclusion reveals a consideration of pregnant women as simple "vessels or vectors" that carry their unborn children to term giving little attention to their own wellbeing [23]. Similar to other domains of clinical research, many projects, and working groups have issued guidance and calls to action demanding more inclusion of pregnant women in HIV clinical research. These calls aim to be able to provide pregnant women with the best evidence-based preventative and therapeutic products. Ultimately, this will help to achieve the goal of ending Acquired Immune Deficiency Syndrome (AIDS) as a public health threat by 2030 [24,25].

As for influenza vaccines, records of increased disease mortality rates in pregnant women have been available since the early 20th century, and an inactivated vaccine has been accessible since 1945 [26,27]. However, the US Centre for Disease Control and Prevention (CDC) did not endorse any recommendations regarding the administration of flu vaccines to pregnant women until 1995; even then, the vaccine was recommended only for women in their third trimester or for those who were more susceptible to experiencing influenza complications [28].

In regards to vaccine platforms, live attenuated vaccines have the stringiest exclusion criteria. Pregnant women are excluded from live vaccine trials mostly based on theoretical risks that could deny them urgently needed means of protection against a disease. According to a systematic review and meta-analysis of studies published in 2020 that looked into available evidence from the use of live attenuated vaccine during pregnancy, only first-trimester administration of the smallpox vaccine was associated with an increased risk of congenital malformations and miscarriages [36]. As for existing adult live vaccines, the CDC indicates that the yellow fever vaccine is a precaution during pregnancy but pregnant women should get vaccinated if the risk of infection is high [37]. Another example of a vaccine administered to pregnant women under specific circumstances is the rVSV replication-competent Ebola vaccine. During the 2018-2020 Ebola outbreak in North Kivu, Democratic Republic of Congo, the WHO revoked a previous recommendation and advised administering the vaccine in case of an active outbreak, as the virus showed increased mortality rates in pregnant women and/or their foetuses. In this case, the benefits of preventing the disease outweighed possible risks for pregnant women [38]. These findings highlight the importance of looking into the ethical dilemma of including pregnant women in live attenuated vaccine research through a benefit/risk ratio lens instead of a taboo one.

In the last decade, more calls for the inclusion of pregnant women in vaccine trials were made following Ebola virus disease and Lassa fever outbreaks and epidemics, since several studies of the epidemiology of both diseases demonstrated significantly high mortality rates among infected pregnant women and/or their foetuses [29,30]. Following these outbreaks, the Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies (PREVENT) Working Group issued guidelines for just and ethical inclusion of pregnant women in vaccine

clinical trials [31]. Nevertheless, the road to developing therapeutics and vaccines that have sufficient safety and efficacy data on intake during pregnancy still appears to be long. A literature review published in 2022 on UK-licensed medicines showed that around 50% of licensed drugs of interest for use in pregnancy in the UK have no pharmacokinetics data on intake during pregnancy [18].

Previous reviews of pregnant women's inclusion in clinical trials either excluded all biologics or grouped vaccines together with therapeutic antiviral medicines and different monoclonal antibodies [11,32]. However, while late-stage clinical trials for therapeutic drugs enrol sick participants, vaccine trials recruit healthy individuals, which could make the recruitment more ethically challenging. In a recently published systematic review of emergency vaccine clinical trials, Minchin et al. show that pregnant women were under-represented in emergency phase 2 and 3 vaccine clinical trials between 2009 and 2019 [33].

Our study aims to extend this evidence further towards 2023 and include the clinical development of both emergency vaccines like COVID-19 and Ebola as well as other vaccines. We plan to do this by identifying the number and nature of phase 3 and 4 clinical vaccine trials that either included pregnant women among their study participants or were designed specifically to test the safety, efficacy, or immunogenicity of a vaccine on pregnant women.

Methods

Following the guidelines proposed by Hunter et al. for performing clinical trial registries' reviews [34], we searched the two largest clinical trial databases: the US National Library of Medicine (NLM)-maintained clinicaltrials.gov (CTG) database and the WHO-supported International Clinical Trials Registry Platform (ICTRP). These databases were chosen for their

wide coverage of clinical trials around the globe, which helped provide comprehensive, geographically-inclusive results.

In CTG, we used the search terms: “vaccines OR vaccine OR vaccination OR immunization” in the intervention/treatment search field. In ICTRP, we observed that contrary to CTG, truncations yielded a higher number of results, therefore we used “Vaccin* OR Immuni*” as search terms. We aimed to make the search in both databases as broad as possible, therefore no age or pregnancy-related keywords and filters were used. We applied the advanced research filters provided by the websites to include phase 3 and phase 4 vaccine trials registered on either database between the 1st of January 2018 and the 30th of June 2023. We chose to include phases 3 and 4 given that most recommendations advise on including pregnant women in late-stage clinical research after preliminary safety data from non-pregnant populations becomes available [31,35]. Search results showing phase 2/3 trials, and trials targeting children or older adult populations were excluded manually to make sure that only late-stage vaccine trials with a target population that included women of reproductive age (15-49 years) were examined.

We opted to uniquely include vaccine trials that targeted healthy populations given that trials in the domain of autoimmune diseases or targeting organ failure patients for example are beyond our research aims. Additionally, we excluded trials with a live attenuated vaccine as an investigational product after observing that all these trials currently exclude pregnant women. Therefore, we believed that including these studies would be beyond our research aim of describing pregnant women’s involvement in trials where no precaution of (theoretical) risk could justify their exclusion.

To be included, a study had to evaluate the safety, efficacy, immunogenicity, or effectivity of a preventative non-live-attenuated vaccine in a healthy population that includes women of reproductive age against a disease that could affect pregnant women and/or their foetuses.

Data from each database was exported into an Excel file (supplementary materials 1 and 2) where the targeted disease/infection, investigational product, study sponsor type, country of trial site, and the inclusion/exclusion of pregnant women status were extracted for each study. Principal investigators PIs of studies with no mention of pregnancy in their inclusion/exclusion criteria were contacted via email for further clarification on this topic, if contact information were available. Extracted trials from the two databases were later merged in a separate file (supplementary material 3) where we conducted descriptive analysis.

Results

Our search yielded 977 records from CTG and 936 records from ICTRP; after excluding trials that were not in line with our research criteria, we had 433 studies to examine. Out of the examined studies, many did not mention whether pregnant women were included or excluded. Therefore, we contacted the (PIs) of studies where contact details were available. Out of 33 contacted persons, we received 15 replies; 4 confirmed that pregnant women were included, while 11 said they were not. Some cited the reasons for the exclusion to be the large quantities of blood drawn during the trial, or that the government of the trial site country either had no recommendations about the inclusion of pregnant women or had listed the investigated vaccine as a contraindication for pregnant women at the time of trial conduct. In 33 studies we could not verify the state of inclusion due to the absence of either contact information or reply of the PI. Therefore, these studies were excluded from the analysis and

we had 400 studies to investigate. (Figure 1) explains the process of selecting the studies included in our overview.

Sponsorship and disease target

54% of the examined studies (217 trials) were sponsored by pharmaceutical or biotech companies (referred to as “industry” in the figures and tables), while the rest were sponsored by academic or governmental institutions. As for clinical phase distribution, 117 examined studies (29%) were either a phase 4 (115 records) or a post-marketing trial (two records).

More than half (222 out of 400) of vaccine trials conducted from the start of 2018 until the end of June 2023 had a COVID-19 vaccine as the only investigational product. Out of these 222 COVID-19 trials, and during almost three years of late-stage clinical research into these vaccines, three studies included pregnant women as part of the study population and two were designed specifically to monitor a COVID-19 vaccine in pregnant women. Moreover, out of 16 studies that tested a COVID-19 vaccine as part of a vaccine combination (aimed to test co-administration of different vaccines), two trials included pregnant women as part of their larger population. Apart from COVID-19 vaccines, we found flu, pneumonia, and Human Papillomavirus (HPV) vaccines to be the most investigated vaccines in our data set. (Figure 2) demonstrates the distribution of the top five diseases/pathogens that were the sole targets of a vaccine trial, accounting for 79% of the 400 examined trials.

Diseases targeted by studies that included pregnant women:

Out of 400 examined studies, we found 22 studies (6%) that were either designed specifically for pregnant women or included them as part of a larger group of participants. We found flu and COVID-19 to have the highest number of trials including pregnant women (five trials for

each disease). Additionally, we observed that most studies designed specifically for pregnant women specified the gestational age in the inclusion criteria, while this measure was mentioned only in one of the studies including pregnant women as part of a larger population. When gestational age was addressed, all trials specified that women should be above 12 weeks pregnant or during their second or third trimester, given that the first trimester is the most critical for the foetus formation, hence the most sensitive for congenital malformations. (Figure 3) shows clinical trials including pregnant women distributed by disease.

Nature and type of the examined studies according to their inclusion/exclusion of pregnant women:

In the following subparagraphs, we describe the main types of studies analysed: those designed specifically for pregnant women, those that included pregnant women as part of a larger population, and those that excluded pregnant women.

a. Vaccine trials designed specifically for pregnant women

13 studies (3%) specifically targeted pregnant women, six of which were phase 3, while seven were phase 4 studies. Clinical trials conducted on pregnant women aimed to either study maternal vaccination, where the reason for vaccinating the pregnant mothers is to protect the foetus via placental and breast milk transfer of antibodies, or to test a vaccine that is normally given to the general population. We found seven maternal vaccine studies that examined pertussis (3) RSV (3) and meningitis plus tetanus (1) vaccines. The three RSV trials were industry-sponsored, while the rest were supported by academic research institutes. We also observed six trials that were designed specifically for pregnant women and focused on a

disease that could affect them among other populations. These studies targeted flu (3), COVID-19 (2) and Ebola (1) vaccines. Only the Ebola vaccine trial was industry-sponsored.

b. Vaccine trials including pregnant women as part of a larger population

Nine out of 400 studies (2%) included pregnant women as part of their larger pool of participants. The nine trials comprise three investigating COVID-19 vaccines, two examining the administration of both COVID-19 and flu vaccines, two for flu vaccines solely, and two studying Ebola and Hepatitis B vaccines. None of these studies was industry-sponsored.

c. Vaccine trials excluding pregnant women

378 studies of the 400 examined vaccine trials (95%) explicitly excluded pregnant women from their study populations. These studies targeted a range of infectious diseases that could affect both pregnant and non-pregnant individuals, including pneumonia, cholera, rabies, and typhoid. We also had 29 HPV studies that all excluded pregnant women. Most of the 378 trials mentioned that they aimed to monitor participants for (serious) adverse events for a period ranging from seven days to 12 months depending on the trial. The serious adverse events theoretically include any congenital defects in participants who got vaccinated around the time they became pregnant. However, out of 378 vaccine trials excluding pregnant women, 18 mentioned that they effectively monitored pregnancies that happened around the time of vaccination as a secondary objective. These were mainly phase 3 (17/18), COVID-19 (7/18) and HPV (9/18) studies, and they were mostly sponsored by industry (13/18).

Geographical distribution of examined vaccine trials:

In terms of location, trial sites were scattered between both the global north and south, with the highest number of trials taking place in China and the United States respectively. (4) shows a world map coloured according to the number of clinical trials conducted in each country. Pins show the countries that hosted clinical trials that were either conducted specifically for pregnant women or included them as part of a larger population.

COVID-19 vs. non-COVID-19-related studies:

Given the abnormal situation represented by the COVID-19 pandemic, in this section, we focus on the trials registered between 2018 and 2023 that did not include COVID-19 vaccines, as this would provide a more accurate representation of the vaccine trials' scene without an emergent pathogen of global concern. We found 162 late-stage vaccine trials that did not test COVID-19 vaccines. Out of these 162 trials, 15 involved pregnant women in different ways: four trials were specifically designed for pregnant women, four included them as part of a larger population, and seven tested maternal vaccines. If we exclude these seven maternal vaccine trials, which are inherently designed for pregnant women, we have 155 vaccine studies intended for the general population. Among these, eight (5%) included pregnant women. (Table 1) demonstrates the distribution of vaccine trials, both non-COVID-19-related and COVID-related, according to their trial phase, sponsorship, and their pregnant women's inclusion/exclusion.

Discussion:

This study presents an updated, meticulous investigation into the inclusion of pregnant women in vaccine clinical trials. Our results demonstrated that around 6% of preventative vaccine clinical trials conducted in healthy adult populations between 2018 and mid-2023 included or were designed specifically for pregnant women. In terms of trials that left out

pregnant women, trials for multiple diseases, of different investigational products and countries, completely excluded pregnant women. This criterion could be justified for HPV vaccine-related studies since the vaccine (currently) has a preventative indication only and is usually given to children before the start of sexual activity [39]. However, including pregnant women in studies against pneumococcal pneumonia, rabies, and other diseases that can affect them could have yielded important information and benefits.

In our review, the examined vaccine trials mostly targeted diseases that are nonspecific to pregnant women but that could induce higher mortality rates in this population or their foetuses, like flu, COVID-19, and Ebola. Remarkably, in a review of all phase 4 records in CTG between 2011 and 2012, Shields et al. noted that the five studies that were found to be designed specifically for pregnant women were all focused on pregnancy-related obstetric issues [32]. The number of trials targeting non-obstetric conditions observed in our results could indicate an improvement in trial organisers' readiness to conduct clinical research that includes pregnant women. However, Shields' dataset focused on industry-sponsored clinical trials conducted in the United States only, while our dataset included all phase 3 and phase 4 vaccine trials conducted worldwide and by any sponsor. Therefore, continuous screening of pregnant women's inclusion percentage is needed in both therapeutic and preventative approaches to monitor all occurring trends and continue pushing for just and ethical increased inclusion.

In our analysis, we considered trials that either included pregnant women as part of a larger population or trials that were designed specifically for pregnant women, which were the majority. Van der Graff et al. highlighted the importance of increasing the number of clinical trials designed specifically for pregnant women or purposively including subsets of pregnant

289 women instead of sampling them as part of larger trials at random [40]. The rationale behind
290 this approach is that such focused studies have the potential to have more statistical power
291 to produce safety and efficacy data, given the higher number of pregnant women involved.
292 Therefore, studies designed to include only pregnant women in a phase 2/3 or phase 3
293 stepwise design could be the way forward in terms of clinical research on this category when
294 differences are assumed -which is usually the case- in the response or safety of the
295 intervention between pregnant and non-pregnant women [40]. However, it is still essential to
296 continue asking for post-marketing specific studies as well as safety data from earlier-stage
297 studies that included even small numbers of pregnant women. This also includes studies
298 where women got pregnant even if the trial advised against it (protocol violations), as these
299 women, even in small numbers, will help detect safety signals as well both in early and late-
300 stage trials. An indication of the importance of the latter approach is the published data on
301 pregnancy outcomes from women who got pregnant around the time of the vaccine dose in
302 phase 2/3 and phase 3 clinical trials of Ebola or HPV vaccines respectively even though
303 pregnancy was an exclusion criterion [41,42]. The results of these studies could inform the
304 design of pregnancy-specific clinical trials in the future if needed, or help regulatory
305 authorities make urgent decisions in cases of emergencies. Furthermore, the information
306 generated by such studies, even if non-conclusive, could aid pregnant women and their
307 physicians in making more informed decisions about whether to take the vaccine or not in the
308 absence of larger pregnancy-specific clinical trials [41].

309 Similar to a 2019 study exploring the inclusion of pregnant women in HIV clinical research, our
310 study found that the vast majority of trials including pregnant women were sponsored by
311 universities, research centres, or government-funded institutes and not pharmaceutical

312 companies, even though the latter are more prevalent and have more extensive resources for
313 conducting trials [22,43]. The main reason for the low representation of this category in
314 industry-sponsored trials might be the fear of financial loss and reputation damage in case a
315 (related) serious adverse event occurs to pregnant women and/or their foetuses during a
316 clinical trial. To tackle this issue, entities like the PREVENT working group suggested that
317 including pregnant women in vaccine trials should be incentivised by regulatory agencies, in a
318 similar way to European Medicine Agency's (EMA) paediatric investigation plans (PIP) [31].
319 PIPs aim to encourage companies to produce data on medicine's efficacy and safety in children
320 by offering priority access to scientific advice, and extension for market exclusivity to
321 companies that provide data on drugs in children [44]. Given that pregnant women are also
322 an underrepresented group in clinical research, similar programs could encourage companies
323 to pursue studies on this group. Additionally, we believe that offering vaccine developers the
324 support of regulatory and ethics committees while drafting their protocols could facilitate this
325 process, encouraging more inclusion of pregnant women in industry-sponsored vaccine trials.
326 Moreover, further research should be conducted to identify barriers and incentives for
327 pregnant women to participate in vaccine trials in different countries, as this is a highly
328 context-dependent topic. Vaccine developers can thus mitigate the risk of designing clinical
329 trials for pregnant women and not being able to recruit enough pregnant participants. Some
330 research already tackled this issue, and we believe that this approach should be publicised
331 and replicated in other locations where trials are taking place [45,46].

332 Notably, in China, which is the country hosting the highest number of clinical trials, only one
333 out of 96 conducted trials were designed specifically for pregnant women or included them
334 as part of a larger population. In the US, five trials out of 62 included pregnant women. These

findings highlight the importance of taking global responsibility in tackling the underrepresentation of pregnant women in clinical research.

Although trials conducted in China and those sponsored by industry entities tended to exhibit less inclusivity when it came to pregnant women, it was among these two categories of trials that we identified most of the 18 studies that excluded pregnant women but mentioned effectively monitoring pregnancies around the time of vaccination. This may suggest that risk-averse organisations may be interested in gathering pregnancy-related data but are more encouraged to do it when protected from potential liabilities by their exclusion criteria.

A limitation of our study is that we searched records uploaded only on CTG and ICTRP databases, with filters on the phase and registration date. Although these databases are the largest in terms of numbers, our study may have missed trials that were not registered on these platforms, had different keywords, or could have been wrongly excluded by the filters. Nevertheless, different studies of various registries, like ICTRP and the Chinese Food and Drug Administration database, attest to the same problem of lack of inclusion of pregnant women in clinical trials [47,48]. Another limitation might be the small number of new vaccines that made it to late-stage clinical trials between 2018 and 2023, given that most known and used vaccines were developed before 2018. Nonetheless, we believe that by capturing the COVID-19 late-stage vaccine trials scene, we could provide a general idea about the nature and type of trials that included pregnant women throughout three years of a global pandemic setting, which was described in detail elsewhere [49,50]. Moreover, by looking into non-COVID-19-related trials separately, we were able to gain insight into the state of the inclusion of pregnant women in clinical trials under non-pandemic conditions. We found that 5% of trials ofnon-maternal vaccines included pregnant women, which is slightly higher than the 3% of COVID-

19-related trials that included pregnant women. This may highlight the importance of the amount of time that has passed since the development of a vaccine, which may influence trial organisers' disposition to include pregnant women in their trials after a considerable amount of real-world safety data becomes available.

Finally, it is crucial to emphasise that our findings should be regarded as a conservative estimate of the inclusion of pregnant women in trials, considering that 33 studies lacked data on this aspect. This highlights the need for researchers to share comprehensive and transparent inclusion and exclusion criteria, as doing so facilitates a more accurate retrospective assessment of trial registries. By providing detailed information, researchers can enhance the accuracy and reliability of future analyses, leading to a deeper understanding of clinical trial characteristics, outcomes, and possible reasons for including/excluding pregnant women.

Conclusion

The inclusion of pregnant women in clinical trials is a complicated topic that cannot be tackled by simply asking for universal inclusion, as there are many elements to be taken into mind. Pharmaceutical companies, which are the main sponsors of clinical trials overall, could face serious financial repercussions if a vaccine study were correlated with a serious adverse effect/event like miscarriages or congenital malformations. The result is that most developers protect themselves against liability leaving the decision about the administration of a vaccine or drug to the treating physician. This leads pregnant women and their physicians to blindly navigate the decision-making process with the help of improvised benefit-risk ratios. In this article, we reviewed over five years of clinical trial records to identify the number and type of vaccine clinical trials that included pregnant women. Out of 400 studies, we found 22 trials

that included pregnant women, even for indications and diseases that are not obstetric-specific, which is considered an improvement of clinical research on the topic. The FDA 2018 guidelines for industry on including pregnant women, together with an increasing trend in their inclusion in clinical research, seem to send an encouraging signal to this type of clinical research. However, there is still a significant gap in information available on the use of vaccines during pregnancy, which will need to be tackled urgently to minimise the devastating effects that a future infectious disease outbreak could have on this population. Therefore, it is the responsibility of all stakeholders in different countries to take measures to ensure that pregnant women's safety, autonomy, and benefits are being taken into account.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

MS performed the databases' search, data extraction, and wrote the manuscript. AP, HP, and JPVG provided expert opinions on the methods and the writing of the manuscript and comments on the final draft. All authors read and approved the final manuscript. All authors attest they meet the ICMJE criteria for authorship.

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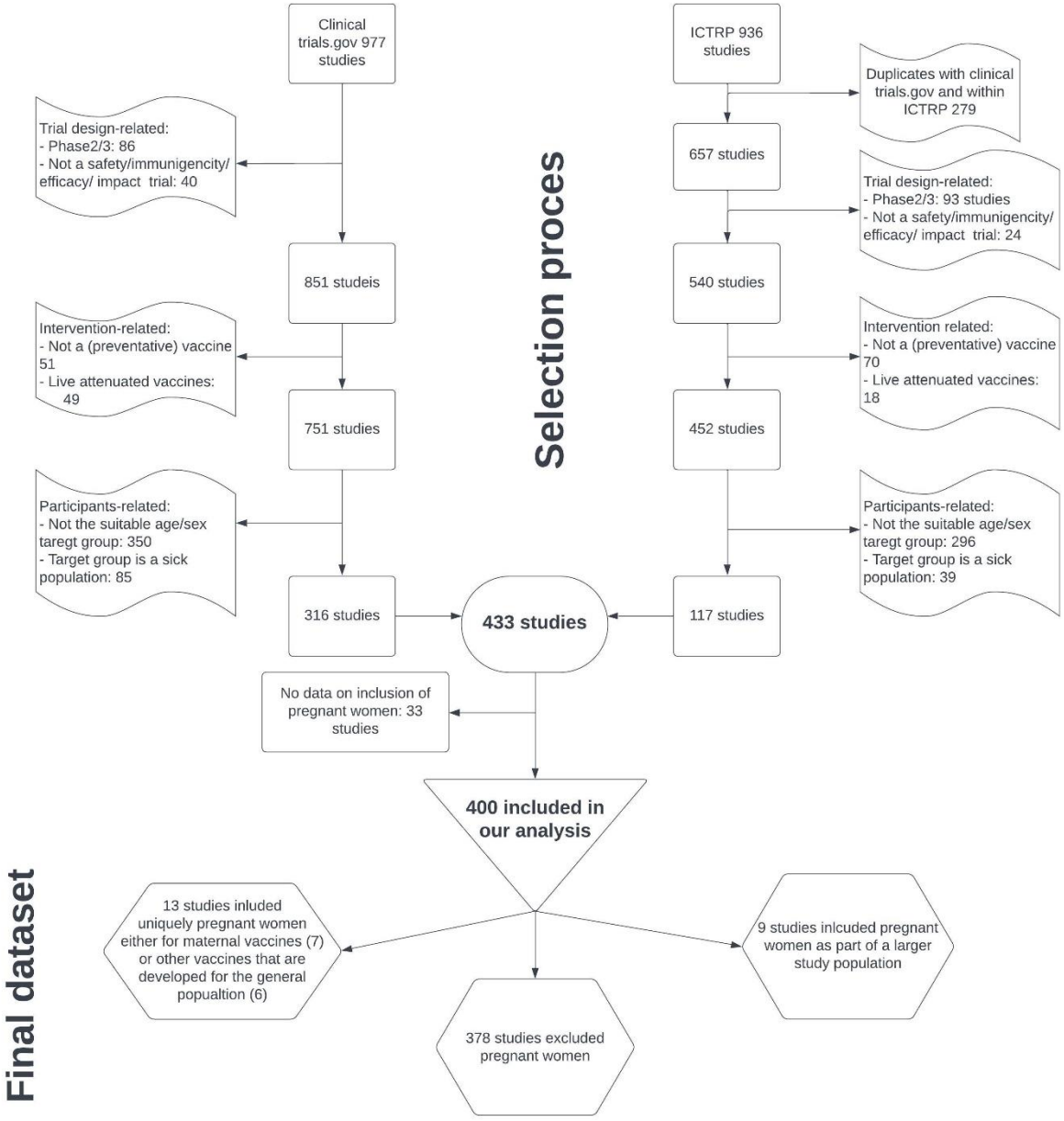
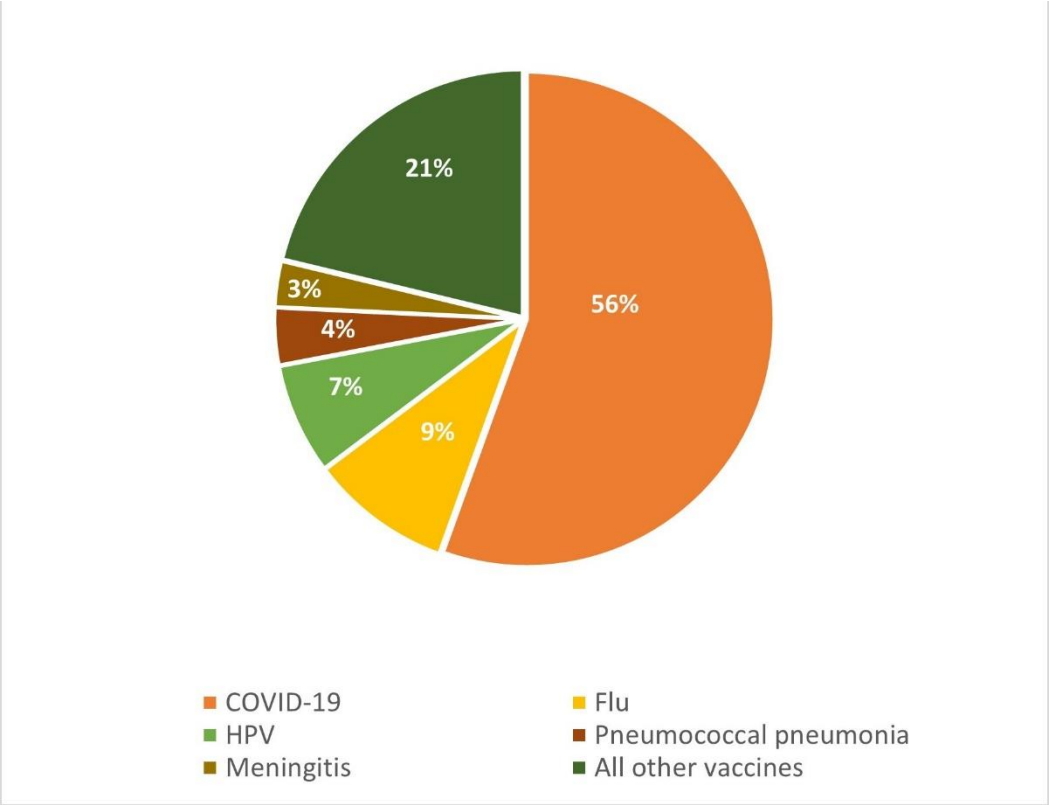
Captions of figures and pictures:



559 Figure 1: Diagram explaining the selection process and number of examined studies

560 excluding or including pregnant women from participation in vaccine clinical trials



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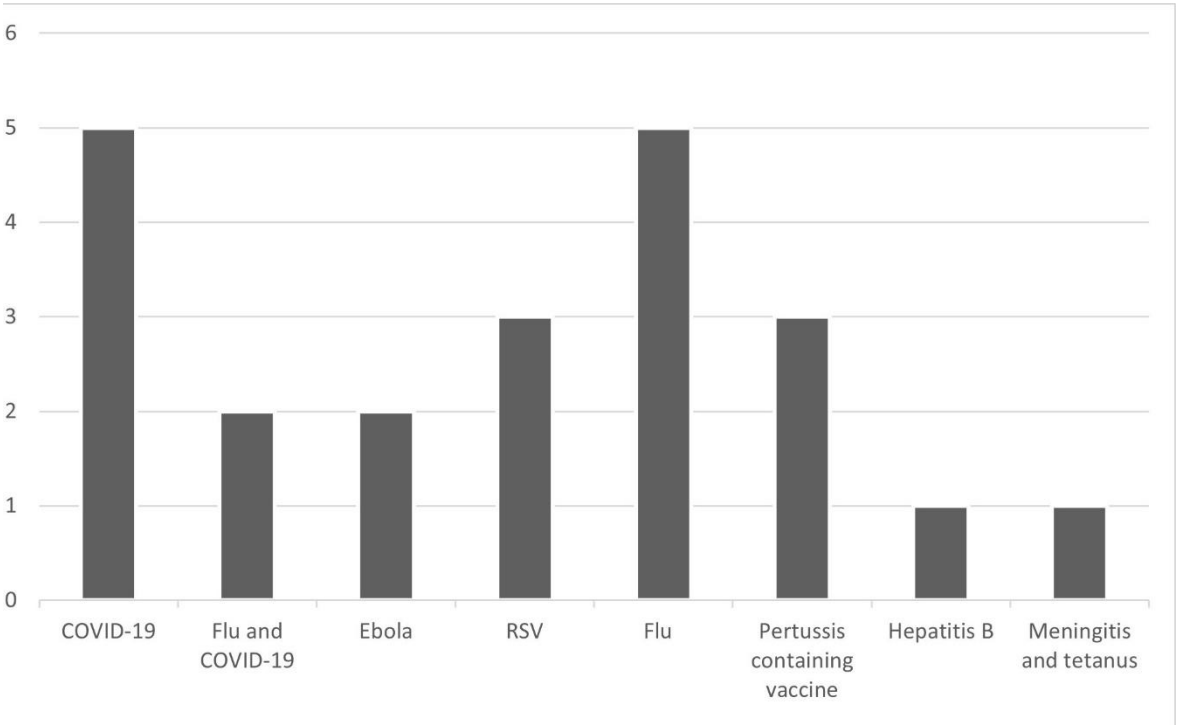
562 Figure 2: Distribution of diseases/pathogens targeted by 400 registered vaccine trials (2018-

563 2023)



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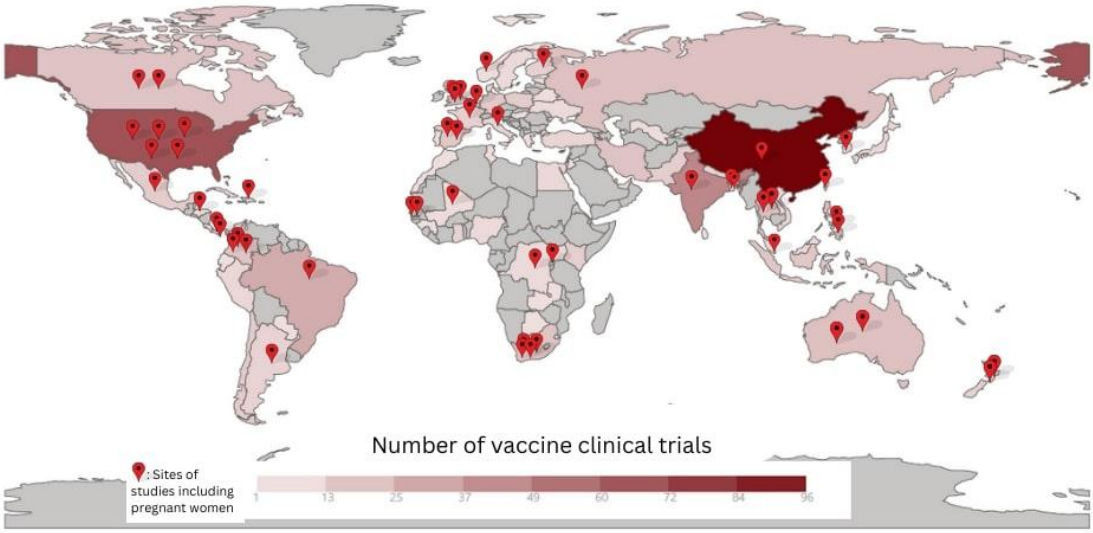
565 Figure 3: Diseases targeted by 22 (of 400) registered vaccine trials including or designed

566 specifically for pregnant women (2018-2023)



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568 Figure 4: Geographical distribution of 21 registered vaccine trials that were designed

569 specifically for pregnant or included them as part of a larger population between 2018 and

570 2023

571 * One trial that included pregnant women did not provide a location

572 ** Two of the 21 trials that included pregnant women were international multisite trials

573 which explains the presence of more than 21 pins on the map

574 Table 1: Distribution of non-COVID-19-related and COVID-related vaccine trials by trial phase

575 and sponsorship according to their inclusion of pregnant women

Distribution of non-COVID19-related vaccine trials						
		Excluded	Included	Specifically	Maternal	Total
Phase:	Phase 3	99	2	2	4	
	Phase 4	48	2	2	3	
	Total	147	4	4	7	162
	Total (%)	90,7	2,5	2,5	4,3	100%
Sponsorship	Industry	89	0	1	3	
	Academic or research institution	58	4	3	4	
	Total	147	4	4	7	162
	Total (%)	90,7	2,5	2,5	4,3	100%
Distribution of COVID-19-related vaccine trials						
Phase:	Phase 3	59	3	1	0	
	Phase 4	172	2	1	0	
	Total	231	5	2	0	238
	Total (%)	97,1	2,1	0,8	0	100%
Sponsorship	Industry	124	0	0	0	
	Academic or research institution	107	5	2	0	
	Total	231	5	2	0	238
	Total (%)	97,1	2,1	0,8	0	100%

576

577 PS. The authors do not require any figure to be coloured in print

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