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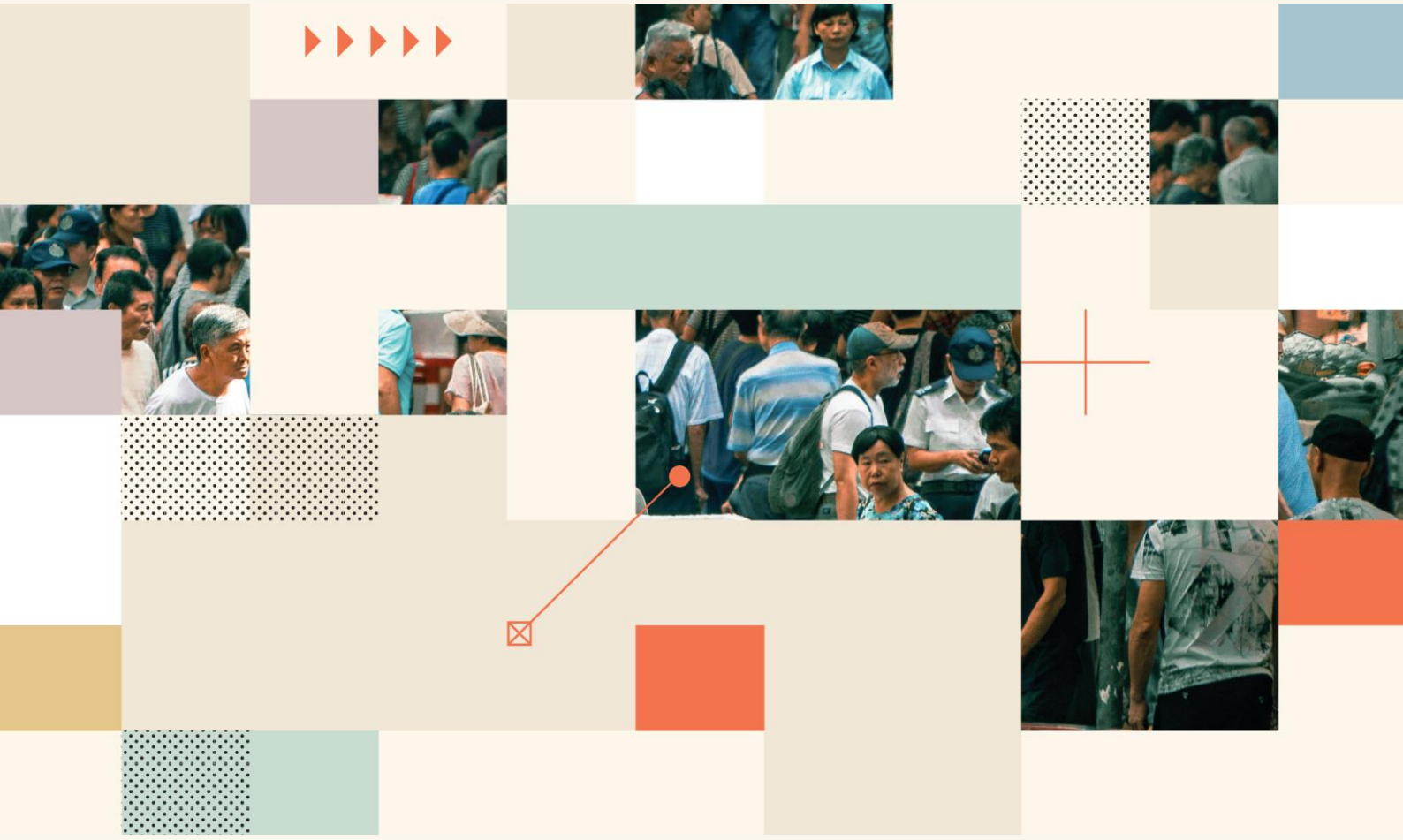
Bridging the gap

Advancing inclusive research for pregnant and lactating women in global health R&D



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A history of exclusion

Millions of women* worldwide are pregnant or lactating at any given time. Most women will take some medication during this period, with the use of medication during pregnancy increasing in the last decade.[1] Yet, there is a long-standing trend of excluding pregnant and lactating women from medical research and clinical trials. As a consequence, more than 98% of drugs have insufficient pharmacokinetic or safety data to guide dosing in women who are pregnant or breastfeeding, and less than 25% of medications available on the market present concrete information on the product label regarding risks during pregnancy.[2,3]

Without the inclusion of pregnant and lactating women in clinical trials, the data generated by clinical trials is not generalisable to this population. During pregnancy and lactation, there is a risk of infant drug exposure, and the safety of the fetus and infant needs to be considered. The body also undergoes unique physiological changes during pregnancy, which can alter drug pharmacokinetics, with dosing adjustments required to ensure effect and avoid toxicitiy.[4] Moreover, certain infectious diseases like HIV can be transmitted during pregnancy and lactation, and therefore, studying the effect of medications during this period is critical to understanding and reducing the risk of transmission.[5]

Given the lack of specific safety and efficacy data that considers pregnant and lactating women, a heavy burden is placed upon individual women and their clinicians to make decisions regarding medical intervention during pregnancy and lactation, without adequate information on the potential risks and benefits. This was exemplified during the COVID-19 pandemic. When mRNA COVID-19 vaccines first became available, safety data in pregnancy was limited because pregnant populations were excluded from pre-authorisation clinical trials.[6] Pregnant women were then confronted with the predicament of having an increased risk of severe illness and death from COVID-19, as well as an increased risk of preterm birth and stillbirth, yet not having the data required to make an informed decision about vaccine administration.[6,7]

Insufficient evidence to support clinical decision-making can result in the unsafe use of medical products for both the pregnant woman and the developing fetus. As a cautionary response to this possibility and a lack of reassurance from sparse safety data, women and clinicians can then be reluctant or refuse to prescribe or accept treatments which are necessary. Some women with chronic diseases are non-adherent to maintenance treatment during pregnancy due to a fear that their medications are unsafe for the fetus.[3]

The most common arguments against the inclusion of pregnant and lactating women are regarding fetal and infant safety. In the late 1950s and early 1960s, when the use of medications during pregnancy was not strictly controlled, thalidomide was widely used to treat

*While we acknowledge that gender identity is complex and non-binary, we use the term 'women' and 'female' to refer to biological characteristics, such as having a uterus and being capable of pregnancy, that are usually correlated with being perceived as a woman. While not all women have these sex characteristics, and not all people with uteruses are women, the overlap between female sexual and reproductive organs and the social category of 'women' is meaningful to categorise how issues specific to this biological sex have been approached culturally and institutionally.

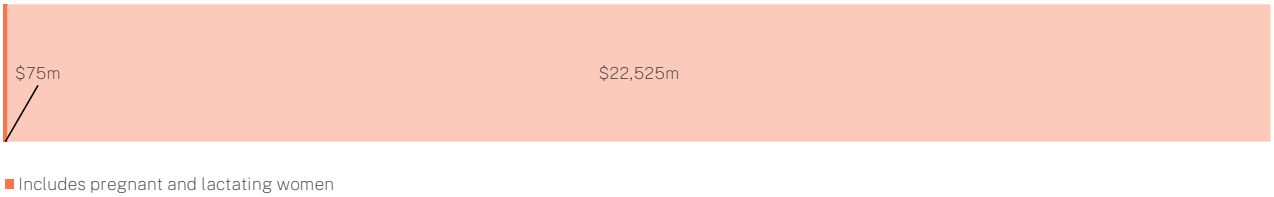
morning sickness, resulting in thousands of severe birth defects and miscarriages.[8] Beyond the devastating impact on families, this tragedy had significant ramifications on clinical research and birthed an overly cautious approach to the inclusion of women in clinical trials. In 1977, the US Food and Drug Administration (US FDA) banned all women of childbearing potential from Phase I and Phase II clinical trials.[9] This ban was retracted in the 1990s, but its legacy has remained.

While several other factors influence the inclusion of pregnant and lactating women in clinical research, many of these stem from or are related to safety concerns and a desire to avoid any risk of harm. However, failing to include pregnant and lactating women in clinical trials does not avoid risk but shifts it to individual women and clinicians. This widespread and cross-cutting issue requires innovative solutions and collaboration across sectors. Closing the evidence gap between pregnant and lactating women and the general population is a long journey ahead, and part of that step involves characterising the extent of the evidence gap.

Less than 1% of investment for neglected and emerging infectious disease clinical development involves pregnant and lactating women

Funding for the clinical development of vaccines and therapeutics targeting neglected diseases and emerging infectious diseases totalled just over $22.6bn in the fifteen years from 2007-2022. Of this, only $75m, or 0.3% of total funding, was identified as funding that included pregnant and lactating women**.** Just 8 out of the 47 neglected and emerging infectious diseases had funding that included pregnant and lactating women, despite women being affected by all conditions. Nearly three-quarters of investment ($54m, 73%) focused on malaria and HIV/AIDS. Diseases like malaria and HIV/AIDS, alongside Zika, have a unique burden on pregnant and lactating women, including the risk of transmission to fetuses and the risk of adverse birth outcomes for babies and mothers (see box-outs).

Figure 1. Proportion of funding for neglected diseases and emerging infectious diseases vaccine and therapeutics clinical development involving pregnant and lactating women (2007-2023)



Malaria R&D that included pregnant and lactating women totalled $35m across 2007-2022. Funding has fluctuated but generally trended upwards to reach a peak of $4.4m in 2022. Investment including pregnant and lactating women focused more on drug R&D ($27m, 75%) compared to vaccines ($8.7m, 25%), which differed from overall malaria clinical development investment, which was more evenly split between drugs ($1.2bn, 56%) and vaccines ($55m, 44%).

Most of the drug investment including pregnant and lactating women was focused on testing dihydroartemisinin-piperaquine (DHA-P) ($14m), which is the WHO-recommended treatment for pregnant women. This was followed by sulfadoxine-pyrimethamine studies ($8.2m). However, there was a significant overlap between the two drugs, with $6.2m of funding for trials comparing the two compounds. Little research has been funded for new anti-malarial compounds in pregnant and lactating women. This reflects the tendency for pregnant and lactating women to only be included in post-registration and label-expansion trials, which leads to severe delays in access.

Malaria

Malaria, transmitted by Plasmodium-infected mosquitoes, is a major cause of maternal and neonatal morbidity and mortality in endemic regions.[10,11] Pregnant women are particularly vulnerable due to immune changes associated with pregnancy and the additional risk of Plasmodium-infected red blood cell accumulation in the placenta.[8-10] Moreover, pregnant adults are more attractive to mosquitoes because they exhale more carbon dioxide and have a higher body temperature, putting them at greater risk of malaria.[10-12] Adverse outcomes of malaria in pregnancy include preterm delivery, intrauterine growth restriction, miscarriage, stillbirth, and neonatal and maternal death.[13] With 25 million pregnancies at risk of malaria-related complications annually in sub-Saharan Africa, effective prevention is crucial.[14] Current antimalarial treatments for pregnant and lactating women face challenges such as increasing drug resistance (e.g. artemisinin combination therapies).[15] Improved prevention of malaria in pregnant and lactating women, coupled with community-based studies on antimalarial resistance, is urgently needed to improve birth outcomes and combat drug resistance.[15]

With only small amounts of investment identified that included pregnant and lactating women in vaccine R&D, it is unsurprising that both RTS,S and R21 vaccines are not yet recommended for use in this population.[16] Trials in this domain should be funded to support malaria prevention during pregnancy and elimination efforts.[16] The EC-funded consortium running the ADVANCE-VAC4PM project, testing two vaccine candidates in pregnant women, is an exciting development as of 2022.[17]

HIV

Human immunodeficiency virus (HIV) is a virus that causes immune suppression through the targeting and continual loss of CD4+ T-lymphocyte helper cells.[18] Ongoing loss of these immune cells weakens the body's ability to fight infection and disease and predisposes those affected to acquired immunodeficiency syndrome (AIDS).[18] For pregnant and lactating women, untreated HIV poses both significant maternal and fetal risks, including transmission during pregnancy, childbirth, or breastfeeding.[19] Antiretroviral therapy (ART) can significantly reduce the risk of HIV transmission and improve maternal health. Still, current regimens for pregnant and lactating women may have suboptimal safety and efficacy profiles depending on the ART used.[20] Inconsistency in the reported efficacies of different ARTs highlights a need for improved ART options that are safe, effective, and tailored to the needs of pregnant and lactating women, particularly in resource-limited settings where treatment access and adherence remains challenging.[21]

Funding including pregnant and lactating women for HIV/AIDS totalled $19m from 2007 to 2023. This funding remained minimal between 2007-2016 ($2.9m). However, funding saw an uptick in recent years thanks to two key funders: Unitaid and the US NIH, which collectively contributed 89% of funding in this space. This has been largely driven by Unitaid's $12m investment in the University of Liverpool's DolPHin2 trial for Dolutegravir in pregnant mothers and neonates. Funding from the US NIH, totalling $5.3m, financed research into the delivery and optimisation of pre-exposure prophylaxis (PrEP) for pregnant women.

Zika

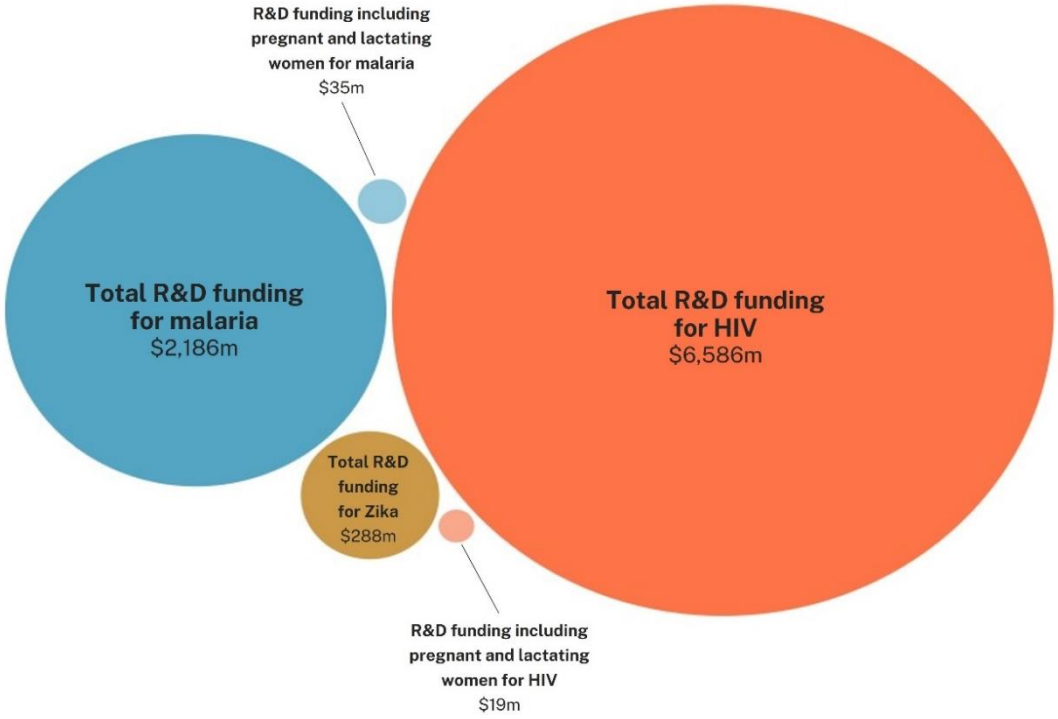
Zika virus, primarily transmitted by mosquitoes, can also be transmitted from mother to fetus during pregnancy, posing a significant threat to maternal and fetal health.[22,23] Zika often causes asymptomatic or mild illness in most people, characterised by fever, rash, and joint pain. In 5% of cases,[24] infections during pregnancy can result in severe outcomes such as Congenital Zika Syndrome (CZS), which is caused by the virus crossing the placenta.[23,25] CZS can involve fetal abnormalities such as microcephaly, hearing and vision loss and seizures in babies.[26] Currently, there are no approved vaccines or antiviral treatments for Zika. Research is intensifying to develop a vaccine that could provide crucial protection for pregnant and lactating women and their babies, preventing the devastating effects of CZS and ensuring early protection during pregnancy.[27,28] Addressing this urgent need is vital for reducing the global impact of Zika on maternal and fetal health.

Indeed, all the funding including pregnant and lactating women for HIV/AIDS was focused on drugs, largely in post-registration trials ($15m, 80%) compared to clinical trials ($3.9m, 20%). Similar to malaria, this differed from the overall split of HIV/AIDS funding, where 71% ($4.66bn) was invested in vaccine research compared to 26% ($1.68bn) in drug R&D. While there are 56 vaccines in the HIV/AIDS pipeline, the majority are in early-stage development, with just nine vaccines in Phase II trials or higher. The nascency of this pipeline explains, in part, the lack of investment that involves pregnant and lactating women.

Despite Zika's unique burden on maternal-fetal health and being declared a public health emergency of international concern (PHEIC) in 2016, no R&D funding for Zika has been identified that targets pregnant and lactating women. A $7m project funded by Innovate UK for a modified vaccinia virus Ankara (MVA) Zika vaccine acknowledged the importance of this population group, and researchers involved stated that the vaccine is expected to be safe for use in pregnant women. However, the Phase Ib/II trial excluded pregnant women.[29] While clinical trials for epidemic diseases are known to be challenging given the waxing and waning cases during outbreaks, trials in pregnant and lactating women for Zika are crucial and need to be a priority. Different ways of de-risking R&D need to be investigated, including better *in vivo* models for pregnancy to generate evidence outside of outbreaks. This is not only key to ensuring pregnant and lactating women are protected from infections, but for the whole pandemic preparedness ecosystem.

Overall, there are two key overarching trends in R&D funding including pregnant and lactating women. Firstly, R&D including pregnant and lactating women focused on drug research ($58m, 65%) compared to vaccines ($31m, 45%) and biologics ($236k, 0.3%). Secondly, there was a skew towards the inclusion of pregnant and lactating women in the later stages of development, with the largest share of funding being invested in post-registration trials ($36m, 39%), followed by Phase III ($19m, 20%), Phase II ($12m, 13%) and Phase I ($8.3m, 9.1%) trials. This demonstrates that the more experimental the R&D is, the less likely pregnant and lactating women are to be included. This is supported by the historical regulatory landscape, where pregnant and lactating women were explicitly banned from partaking in Phase I and II trials. Despite this being revoked, we are still seeing the effects of it today.

Figure 2. Proportion of funding for vaccine and therapeutics clinical development involving pregnant and lactating women, by disease (2007-2023)



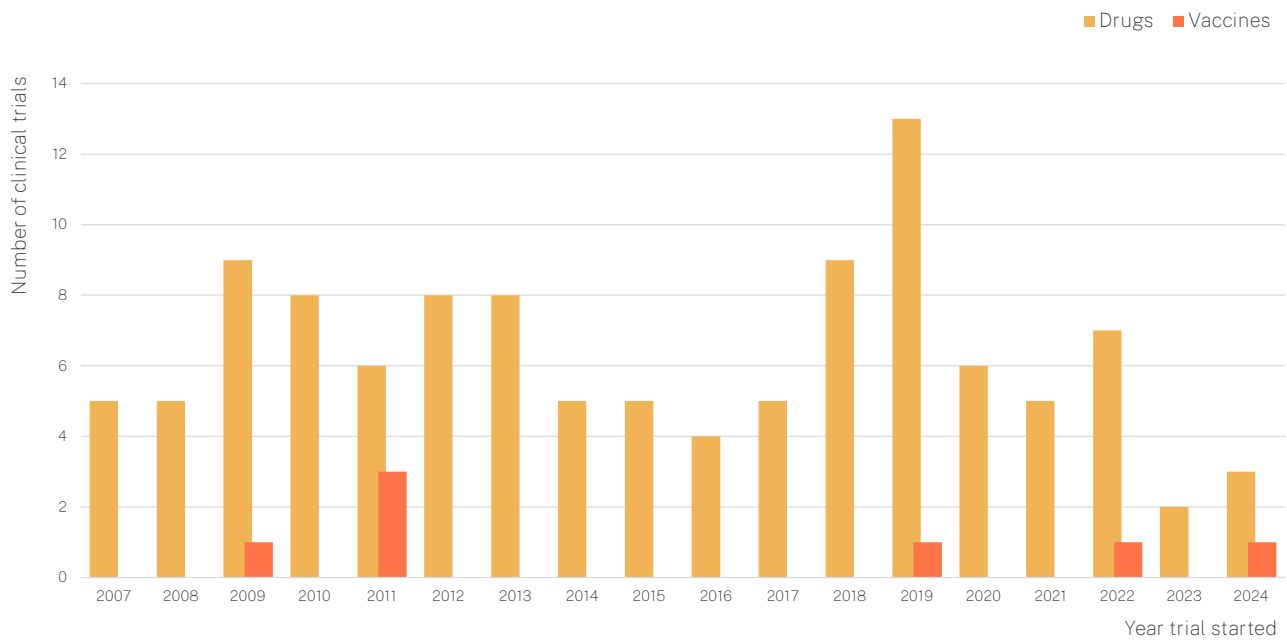
Pregnant and lactating women sparsely included in clinical trials for HIV, malaria and Zika

Between 2007 and 2024, a total of 6,176 interventional studies were conducted for HIV, malaria, and Zika, with only 120 clinical trials (2%) including pregnant and lactating women. Of the 120 studies, 64 (52%) focused on malaria, representing just 5% of the 1,325 malaria clinical trials conducted in all populations. The remaining 57 trials (48%) addressed HIV, comprising only 1% of the 4,816 identified HIV trials. None of the 35 Zika trials conducted during this period included pregnant and lactating women.

Drug-related clinical trials have dominated, with 113 studies (94%) focused on drugs and only seven trials (6%) on vaccines. The number of clinical trials involving pregnant and lactating women have steadily increased from five drug trials in 2007 to ten trials in 2009. From 2010 to

2018, the annual average number remained steady at seven, peaking in 2019 with 14 trials. However, since 2019, the number of such trials has declined, with only two initiated in 2023 and four in 2024. Across the board, more drug interventional studies have been conducted for malaria (61) than for HIV (51). Vaccine intervention studies have predominantly focused on HIV-positive pregnant and lactating women (6), though these trials have focused on vaccines for other diseases. There has only been one malaria vaccine trial involving pregnant and lactating women conducted.

Figure 3. HIV, malaria and Zika clinical trials involving pregnant and lactating women by product (2007-2024)



Most malaria clinical trials involving pregnant and lactating women have been late-stage trials. Phase III and IV trials were conducted in endemic regions of West and East Africa, Papua New Guinea, Indonesia, and Thailand. They have been aimed at evaluating the safety and efficacy of intermittent preventive treatment in pregnancy (IPTp) regimens in response to the WHO's 2004 recommendation of the use of IPTp in areas of moderate or high transmission of *P. falciparum*.

More recent trials have included the landmark Phase II PfSPZ malaria vaccine trial among Malian pregnant women, the first of its kind to target this population.[30] Although malaria in pregnancy affects all trimesters, most studies have historically focused on women in the second and third trimesters. The SAFIRE consortium plans to address this gap, with a groundbreaking Phase III trial testing antimalarial medicines, including pyronaridine-artesunate (PA) and artemether-lumefantrine (A/L) in early pregnancy.[31,32] This trial, set to begin in 2025, pioneers a new approach by including women in their first trimester, a group typically excluded from such research.

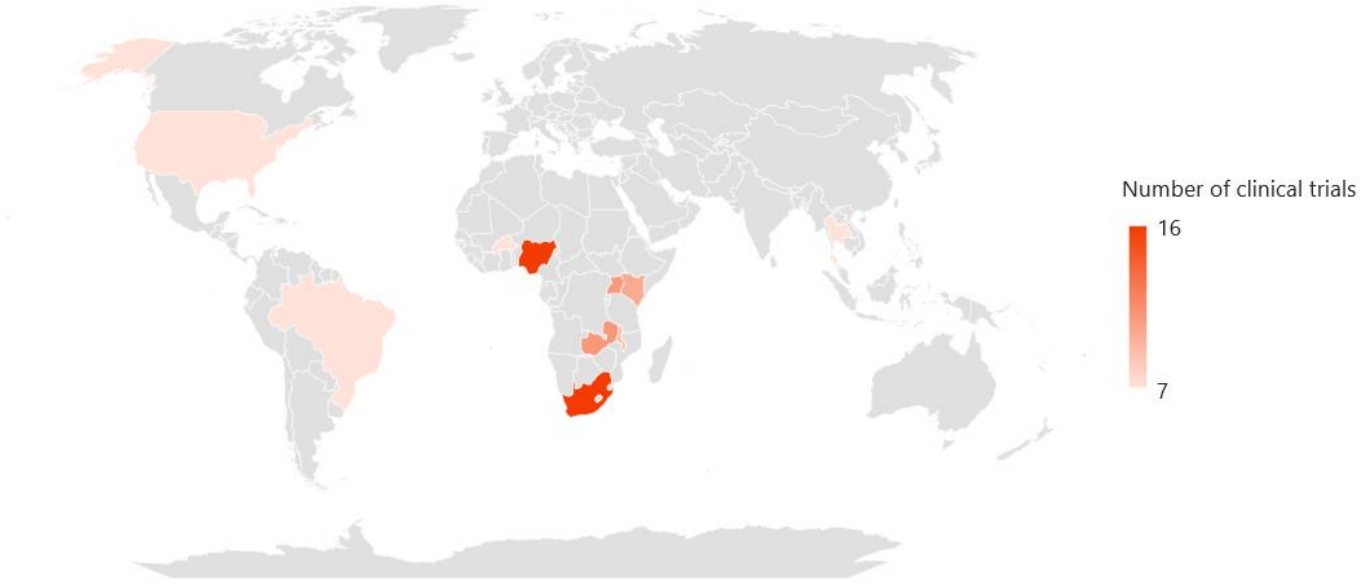
Like malaria, HIV-infected pregnant women are primarily included in late-stage trials conducted across both low- and middle-income countries (LMICs) and high-income countries (HICs). Many

of these trials focus on assessing the efficacy and safety of ART in pregnant women living with HIV infection, as well as comparing the ability of these regimens to reduce HIV mother-to-child transmission. The initial HIV trials in 2007 focused on *Kaletra’s* pharmacokinetics during pregnancy (Phase I, US) and its role in preventing mother-to-child transmission (Phase II/III, France). By 2009, seven late-stage drug trials had been initiated, evaluating several antiretroviral therapies for HIV, as well as two phase III studies on pregnancy-associated malaria treatment in HIV-infected women.

While HIV-positive pregnant and lactating women have been included in vaccine trials, these trials have focused on the safety, tolerability, and immunogenicity of vaccines for other diseases, including the Respiratory Syncytial Virus (RSV) prefusion F subunit vaccine, trivalent influenza vaccine (TIV), Group B streptococcus (GBS) trivalent vaccine, H1N1 influenza vaccine, and pertussis (Tdap) vaccine. Despite these efforts, trials of HIV-specific vaccines among pregnant and lactating women remain unexplored.

Our analysis did not identify any Zika clinical trials involving pregnant and lactating women, despite confirmed transmission in over 35 countries and the 2015-16 epidemic in South America. Currently, only prospective observational cohort studies among pregnant women are being pursued in the Americas and the Netherlands.[33-35] These studies aim to assess the virus's impact on pregnant women’s quality of life, as well as the association between Zika virus infection during pregnancy, adverse maternal/fetal outcomes and the risk of vertical transmission. Additionally, the studies look into how pregnancy may affect a woman's susceptibility to the infection.[36]

Figure 3. Top ten locations of HIV, malaria and Zika clinical trials involving pregnant and lactating women (2007-2024)



Most clinical trials (118, 98%) concentrated on pregnant rather than lactating women and primarily included those in their second and third trimesters. Two studies specifically targeted lactating women, while five trials (4%) included both groups. More than half of the trials (65, 54%) were Phase II and III interventional studies, and 90% of the total trials were conducted in LMICs, primarily in sub-Saharan Africa. Nigeria and South Africa led in trial numbers, each with 16 trials. Nearly 90% of Nigerian trials focused on malaria (14), while all South African trials addressed HIV, reflecting the significant burden of these diseases in both countries and their efforts to address its impact on high-risk populations such as pregnant and lactating women.

In the last five years, nearly all trials involving pregnant and lactating women (23, 92%) have taken place in LMICs, specifically in Africa (20), the Asia-Pacific region (2), and South America (1), signalling Africa's growing capacity for such clinical research. Only 12 early-phase interventional studies have included pregnant and lactating women, with more than one-third (5, 42%) initiated in the US between 2007 and 2022, all focusing on HIV. This is consistent with an overall trend that African clinical trials are largely Phase III and IV, with early phases done in HICs.[37]

Pregnant and lactating women should be in clinical trials as a standard, except for valid scientific and ethical reasons

Years have passed since the reversal of regulatory bans that saw pregnant and lactating women blanketly excluded from clinical trials. However, the underlying attitudes reflected in these bans remain entrenched. Even when focusing on conditions which are well-known to have a unique burden upon pregnant and lactating women, including malaria, HIV/AIDS and Zika, analysis of investment and clinical trial information demonstrates an ongoing reluctance to include and consider this population group in research efforts.

While there are valid concerns about fetal and infant safety, a broad-based exclusionary approach is not the solution. The aim should be for studies to include pregnant and lactating women in clinical trials as a default, except when scientific or ethical reasons preclude their involvement.[38] While there has been increasing attention and steps taken to promote this standard, further work needs to be done in this area if the persistent dearth of data for pregnant and lactating women is to be addressed. A multi-faceted approach will be required that addresses the issues from multiple angles, including regulatory harmonisation, financial de-risking and addressing prevailing attitudes.

Harmonising and strengthening regulatory guidance

Guidance from regulatory bodies on including pregnant and lactating women in clinical trials has evolved over the years. In 2018, the US Code of Federal Regulations for the Protection of Human Subjects was revised to no longer consider pregnant women in the list of individuals considered vulnerable in the context of clinical trials.[39,40] In 2021, the US FDA, the European Medicines Agency (EMA) and the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) published a joint article that expressed their shared intention to lead efforts to improve evidence generation for pregnant and lactating women, while describing a broad pathway for doing so.[41]

Despite ongoing efforts from regulatory bodies, however, there is a lack of global legislative harmonisation, and regulatory gaps regarding the inclusion of pregnant and lactating women in clinical trials and post-marketing surveillance still exists in various countries and regions.[3] Moreover, guidance around the inclusion of pregnant and lactating women is not mandated, and ambiguities in guidance allow researchers and industry to take a more conservative approach to inclusion.[38,42,43] Stronger regulations that require the justification of excluding pregnant and lactating women need to be developed to compel researchers and industry to include this population in clinical research.[38] International collaboration is required to address inconsistencies between national regulations to clarify expectations and promote their inclusion.[3]

Financially and legally de-risking R&D that involves pregnant and lactating women

Pharmaceutical companies and other product developers have numerous financial and legal incentives to exclude pregnant and lactating women from clinical trials. Including these populations in clinical trials exposes developers to greater risk, which can result in more expensive insurance requirements.[43] Recruitment challenges may arise if a minimum number of pregnant and lactating women are required in the trial, which may result in delays to the drug hitting the market. Including pregnant and lactating women also requires long-term follow-up to assess safety.[43,44]

Further incentives and strategies are needed alongside the strengthening of regulations to mitigate this risk and incentivise developers to include pregnant and lactating women. There are a range of approaches that could be considered, including those previously used to increase research on products for rare and tropical diseases or research involving children.[38] This may include the extension of market exclusivity for therapeutics that involve pregnant and lactating women in clinical research, tax breaks for companies that conduct research including pregnant and lactating women, and covering or subsidising clinical trial insurance costs. [43,45]

Building clinical trial capacity

Clinical trial sites need to be specifically designed or adapted to effectively include pregnant and lactating women. A systematic review demonstrated that recruitment of pregnant and lactating women in clinical trials is more likely to be successful if recruitment information is tailored to a woman's situation, communicated at a time and in a manner that considers their physical and mental state, and with sufficient time to discuss details and concerns related to the trial.[4] Recruitment of women for clinical trials therefore requires adequate infrastructure, time, finances, and sufficient staff quality are required. Further capacity is also required for risk evaluation and longer-term follow-up. Establishing large collaborative research networks may also help adequately power studies with low participation rates, promote knowledge sharing, and provide essential infrastructure to facilitate multidisciplinary research.[46]

Correcting misconceptions and reframing the conversation

Despite regulatory changes, there is a continuing misconception that including pregnant and lactating women in clinical trials is impermissible, which needs to be changed through further education and advocacy.[38] Alongside the correction of this myth, the conversation around the inclusion of pregnant and lactating women in clinical trials needs to be reframed on several levels. Firstly, pregnancy and lactation must be emphasised as a sustained state for millions of women at a population level, rather than a temporary state that affects a woman for a time-limited period. Without this reframing, the gravity and scale of the lack of evidence concerning this population are reduced, as are perceptions of the market size. Secondly, the inclusion of

pregnant and lactating women needs to be considered as essential to pandemic preparedness. In the wake of the COVID-19 pandemic, governments have sought to increase their capacity to react to and manage future pandemics. Vaccination coverage for pregnant and lactating populations will also be crucial to this. Finally, the inclusion of pregnant and lactating women in clinical trials needs to be emphasised as integral to the discourse and efforts around the elimination of infectious diseases for which there exists the risk of maternal-to-child transmission, including HIV/AIDS.

Increasing focus and advocacy for maternal health

Since the 1990s, only two marketed drugs have been developed and registered specifically for pregnancy-related conditions.[47] This neglect of the maternal health field, including the lack of funding and the low success rate of R&D, is informed by the overall stigma surrounding the inclusion of pregnant and lactating women in clinical trials across all disease areas. While addressing the latter is critical to accelerating progress in maternal health, the relationship is bi-directional: increasing focus and advocacy for maternal health will also put a spotlight on the need to include pregnant and lactating women in clinical research, which will be essential to advancing change.

A major paradigm shift is needed to support pregnant and lactating women

The current dearth of information to support clinical decision-making in pregnant and lactating women places an unreasonable burden upon individual women and clinicians to make clinical care decisions with insufficient evidence, risking inadequate or inappropriate treatment. Failing to include pregnant and lactating women in clinical trials does not equate to no risk; it simply shifts the risk to women and their clinicians. Addressing this issue will require a major paradigm shift to change underlying attitudes and beliefs related to the inclusion of pregnant and lactating women in clinical trials, alongside persistent and definitive sector-wide efforts and collaboration. These reforms should also increase targeted funding for maternal health R&D and establish specialised research networks. Education and advocacy campaigns are needed to reduce stigma and improve data collection and post-market surveillance. Finally, fostering public-private partnerships will streamline efforts and drive innovation in maternal health. These actions will create a more inclusive, evidence-based approach to clinical decision-making for this population.

Methodology

Funding analysis

The funding analysis was conducted using G-FINDER investment data from 2007-2022 for HIV/AIDS, malaria and Zika. The following scope restrictions were applied to each disease cut: vaccines, drugs and biologics only; and clinical development including Phase I, II, III and IV trials. Once the data was filtered, the following search terms were applied: 'pregnant', 'pregnancy', 'pregnancy related', 'lactation', 'lactating' and 'breastfeeding'.

All grants that returned a positive hit were included for analysis. In the case of Zika, only one study returned positive search terms, although it did not actually include pregnant and lactating women. Where possible, data was sense-checked, but given the quantum of grants, it was not possible to manually scope every grant.

Clinical trial analysis

Clinical trial data on malaria, HIV, and Zika was pulled from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) in August 2024, using the following search terms: 'malaria', 'HIV', and 'Zika'. Clinical trials were restricted to include clinical trials with a start date of 01 January 2007 onwards, interventional studies focused on vaccines, drugs, and biologics, and Phase I, II, III, or IV trials.

For the CT.gov dataset, the search terms 'pregnant', 'pregnancy', 'pregnancy-related', 'lactation', 'lactating', and 'breastfeeding' were applied to each clinical trial's 'brief summary' and 'relevant conditions' fields. For the ICTRP dataset, clinical trials sourced from CT.gov were removed, and the same search terms were applied to the 'public title', 'scientific title' and 'conditions' columns. All clinical trials that returned a positive hit were then manually scoped to determine if they included pregnant and lactating women.

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