Health systems determinants of delivery and uptake of maternal vaccines in low and middle-income countries: A qualitative systematic review

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Preamble

Plagiarism declaration

I, Bronte Davies (DVSBRO006), hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abstract

Maternal vaccination has been widely recognised as a key component of the comprehensive package of antenatal care aimed at improving maternal and child health. Low- and middle-income countries (LMICs) are currently falling short of maternal and neonatal mortality targets, with gaps in quality health coverage and a high burden of vaccine-preventable diseases that affect both maternal and child health (MCH). There is a variety and increase of grey and published literature in recent years from LMICs on maternal vaccination programmes and their importance in addressing these gaps in MCH. However, there is a gap in the available literature for research on the role of health systems in the functioning of maternal vaccination programmes, particularly in LMICs. Based on available evidence, understanding health systems determinants of maternal vaccine uptake and delivery requires qualitative insight to inform maternal vaccine programming. A qualitative systematic review was conducted in two phases: a rapid scoping review exploring maternal vaccination and health systems was followed by a systematic review to identify health systems determinants of maternal vaccine delivery and uptake in LMICs. The systematic review was conducted following the Preferred Reporting Items for Systematic Review and Meta-analyses guidelines. Six electronic databases were searched for primary research from LMICs published in English between 2009 and 2021. A qualitative approach to data extraction and evidence synthesis was guided by conceptual health systems framing developed through the scoping review. Thematic analysis identified key descriptive and analytical themes to explore the health systems barriers and enablers of maternal vaccine delivery and uptake in LMICs. Of the 1 242 records identified through database searches, 47 studies were included in the systematic review from 28 LMICs. The majority of included studies were from the South America region (28/47) and included pregnant women as the primary population study group (38/47). Included literature explored mainly Influenza (25/47) and Tetanus toxoid (18/47) maternal vaccine uptake and delivery. Health systems enablers of maternal vaccine uptake included high level of maternal trust in healthcare providers and policy-makers. Barriers to uptake include out-of-pocket spending for vaccination services. Poor communication of policy and guidelines between policy-makers and public/private healthcare providers was identified as a barrier to vaccine delivery, in addition to reliance on external donor funding for vaccine programme implementation and reliance on paper-based antenatal and vaccination records. Urban residence and shorter travelling times to facilities enabled vaccine uptake during pregnancy, while influence of family and influential community members serves as a barrier to vaccine uptake. Limited healthcare worker capacity and subsequent decreased time spent educating patients is a barrier to both vaccine uptake and delivery for pregnant women. Health systems determinants of maternal vaccine delivery and uptake identified and explored in this review study highlight the need for improved communication of vaccine policy guidelines and safety between healthcare providers, policy-makers, pregnant women and the broader community. Monitoring and reporting systems for vaccine delivery in MCH need to be strengthened to inform service delivery policies. This review study provides a health systems approach to maternal vaccination and contributes to the increasing body of work in MCH that can inform future introduction of new maternal vaccines in LMICs.

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Acronyms and abbreviations

AEFI	Adverse Events Following Immunisation
AMI	Advancing Maternal Immunisation
ANC	Antenatal care
BMGF	Bill & Melinda Gates Foundation
COVID-19	Coronavirus Disease 2019
EPI	Expanded Programme on Immunisation
GAVI	Gavi, the Vaccine Alliance
GBS	Group B Streptococcus
HIC	High-income country
IgA	Immunoglobulin A
IgG	Immunoglobulin G
LMIC	low- and middle-income country
MCH	Maternal and child health
MDG	Millennial Development Goal
MIACSA	Maternal Immunization and Situational Care Analysis
MNTE	Maternal and Neonatal Tetanus Elimination
NITAG	National Immunisation Technical Advisory Group
PRIMSA-ScR	PRISMA extension for Scoping Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RSV	Respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts on Immunization
SDG	Sustainable Development Goal
Tdap	Tetanus, diphtheria and acellular pertussis (adult)
VPD	Vaccine-preventable diseases
WHO	World Health Organization

Glossary of terms

Antenatal care	A host of healthcare services offered to pregnant women from conception to birth.
Expanded Programme on Immunisation	Launched by the World Health Organization in 1974, this programme aims to deliver vaccines to children and women of child-bearing age to protect against a range of vaccine-preventable diseases[1].
Health system	Organizations, people and actions that aim to improve health and health equity, provide responsive, efficient healthcare and protect individuals from social and financial risk[2].
Health system determinants	Factors relating directly to health systems, including dimensions such as service delivery, human resources, information systems, medical products, financing and/or leadership and governance[2].
Health system hardware	Tangible systems building blocks such as resources, financing, and medical products[3].
Health system software	People, processes, networks and behaviours that drive health systems[3].
Vaccine coverage	Proportion of people in the entire target population who have received a recommended vaccine[4,6].
Vaccine delivery	Delivery of health care services directly relating to vaccines, not to be confused with *vaccine delivery system*[5].
Vaccine uptake	Proportion of target population that receive a vaccine during a specified time period[6].

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[1] World Health Organization. (2009). State of the World's Vaccines and Immunization.Geneva: World Health Organization.
[2] World Health Organization. (2007). Everybody's business--strengthening health systems to improve health outcomes: WHO's framework for action. Geneva: World Health Organization.
[3] van Olmen, J., Criel, B., Van Damme, W., Marchal, B., Van Belle, S., Van Dormael, M., & Kegels, G. (2010*).* Analysing health systems to make them stronger. *Studies in Health Services Organization & Policy, 27.*
[4] Global vaccine action plan: monitoring, evaluation and accountability. (2020). Secretariat annual report 2020. Geneva: World Health Organization.
[5] United Nations Children's Fund. (2018). UNICEF Immunization Roadmap 2018-2030. New York: UNICEF.
[6] Crocker-Buque, T., Edelstein, M., & Mounier-Jack, S. (2017). Interventions to reduce inequalities in vaccine uptake in children and adolescents aged< 19 years: a systematic review. *J Epidemiol Community Health*, *71*(1), 87-97.

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Introduction

Following the Millennial Development Goal to improve maternal health and reduce maternal mortality by 2015, the third Sustainable Development Goal (SDG) – to ensure healthy lives and promote well-being at all ages - emphasises the need for maternal health beyond just survival. Specifically, Goal 3.1, which outlines the aim to reduce global maternal mortality by less than 70 per 100 000 live births by 2030 [1].

Interventions to achieve these goals in maternal health have been implemented at antenatal, intrapartum and postnatal levels of care that range from disease screening, prevention and treatment and health promotion to birth attendance, respectful care, communication and family planning [2]. Recommended antenatal services provide a range of interventions for early detection and treatment for complications and diseases, disease prevention and health promotion. Increased frequency of antenatal visits has been associated with decreased perinatal mortality [2]. A key intervention for disease prevention during pregnancy is the administration of tetanus, pertussis and influenza vaccines. There is a growing consensus that vaccination during pregnancy is a key intervention for improving maternal and child health (MCH) and contributes to achieving SDGs, given that sepsis due to maternal infection with vaccine-preventable diseases (VPDs) accounts for 9% of maternal deaths [3,4]. Pregnant women are more susceptible to vaccine-preventable diseases with more severe adverse outcomes and mortality rates compared to the general population [2]. For these reasons, maternal vaccination has been widely recognised as a key component of the comprehensive package of antenatal care aimed at improving MCH.

Implementation of these maternal, and specifically antenatal, interventions and attainment of SDG 3 varies by country and region, due to socio-economic, geopolitical and environmental factors. Globally, we are falling short of SDG targets, and the maternal mortality ratio in low and middle-income country (LMIC) contexts is up to 60 times higher than in high-income countries (HICs) [1]. Additionally, over the past decade, neonatal mortality has declined the least in LMICs, despite increased access to healthcare and programmatic interventions. Vaccine-preventable diseases like pneumonia, diarrhoea, and malaria, as well as pre-term birth and intrapartum complications remain the leading cause of death in children under five years of age [5,6]. Globally, failure to seek and access care during pregnancy is the culmination of various sociocultural, geographic, and financial factors. In LMICs, some pregnant women face barriers in accessing maternal care due to catastrophic payments for services, limited service provision in rural areas, and access to basic information about maternal and reproductive health [3].

A major barrier to achieving SDG targets are systems factors which inhibit the implementation of evidence-based maternal health interventions shared across LMICs. For example, the lack of human resources for health, including persistent staff shortages, lack of integration and collaboration between different levels and types of providers, that overburden healthcare workers who typically have limited capacity and/or access to training, skill development, and knowledge of evolving evidence [7]. This is compounded by a lack of material resources commonly experienced in LMICs, a result of inadequate health system funding and infrastructure [7]. Additionally, LMICs continuously experience a mismatch between policy and practice guidelines that impedes on effective service delivery through conflict over prescribed roles and responsibilities [7–9]. Lastly, there is a shared barrier across LMICs in the limited ability to routinely collect data and monitor interventions [9].

The current gap in quality maternal health services in addressing the burden of maternal death is highlighted by the delayed, inadequate and sometimes harmful care, indicating continuous missed opportunities for health improvements for women and their children [10]. The additional burden of HIV, Tuberculosis and malaria and programme prioritisation for these diseases compounds this issue of lack of quality maternal care in LMICs that results in fragmented approaches [3,7]. Addressing this fragmentation and deficits in maternal health implementation in LMICs require sustained commitment from researchers, donors, national government as well as collaboration with other sectors including private health providers [3].

Health systems also need to be capacitated to deliver services that address the specific needs of pregnant women and their children, even during system shocks like conflict or disease outbreak [3]. The need for strong health systems that are resilient to changing demographics, financial stability and epidemiology has been exemplified by the current Coronavirus Disease 2019 (COVID-19) pandemic. More recently, rollout of COVID-19 vaccines has further highlighted health access and equity issues for certain populations in LMICs including pregnant women [11].

Maternal vaccination efforts fall at the intersection of maternal healthcare and routine immunisation programmes in the context of broader health systems, and Shen et al. [12] highlight that 'any vaccine… is only as effective as the health system that delivers it.' (p.397). Despite the successes of the global Expanded Programme on Immunisation (EPI), key public health challenges ranging from the programmatic level to the health systems level remain [12]. An enabling environment that advocates for sustainable and effective routine immunisation programmes is crucial [12,13]. Health systems challenges that maternal health interventions are mirrored in immunisation programmes in LMICs, with the addition of specific vaccine cold-chain and logistics management [12]. Vertical disease programmes have the potential to weaken health systems through resource reorientation and burden on healthcare workers [14]. For these reasons, building linkages between MCH and integrating service delivery platforms has been proposed to aid health system strengthening, thereby enhancing immunisation programme performance [12,14]. Considering the shared barriers to healthcare in LMICs, understanding the complexities of delivery and uptake of maternal vaccines in LMICs can guide the implementation of new and under-utilised vaccines as a strategy towards strengthening MCH.

Literature review

A scoping review was conducted with the following aims: to map the existing evidence-base and current research agendas in the field of maternal vaccination; to identify key literature and themes in the literature; to understand current gaps in knowledge; and to identify and characterize the body of literature at the intersection of health systems research and maternal vaccination. A detailed description of the scoping review methods used is provided in the Methods section.

The World Health Organization (WHO) currently recommends a total of eight antenatal visits for pregnant women, up from four in previous guidelines [15,16]. This current guideline could incentivise antenatal care expansion and strengthening, ensuring access to extensive antenatal interventions, including vaccination [17]. In LMICs, the number of antenatal visits varies greatly across countries. It has been reported that even though contact with health facilities is particularly constrained in rural or conflict-affected areas, pregnant women in LMICs will attend antenatal care at least once during their pregnancy [18–20]. In an analysis of 69 LMICs, attendance of the first antenatal visit within an appropriate vaccination window ranged between 55% to almost 100% of pregnant women [21]. The median attendance of a fourth antenatal visit was measured to be

66.4%. Also worth noting from this same study was the fact that LMICs with a higher proportion of pregnant women attending the first antenatal care visit had higher maternal vaccination coverage rates [20].

In Ghana, it has been demonstrated that better access to quality of antenatal care correlates with increased socioeconomic status [18]. It was also shown that geographical setting played a key role in access to quality maternal care, where women in urban areas received better quality care compared to their counterparts in rural and hard-to-reach areas. Increased quality of care during pregnancy in this setting was also shown to correlate with attendance of least four antenatal visits [18]. In Nigeria, it was found that utilisation of antenatal care was high compared to post-natal care [19]. This makes the case for maternal vaccination as an upstream intervention that protects both mother and child during pregnancy at a time when contact with the health system is most frequent. Accordingly, in Ethiopia, it has been found that successful maternal tetanus immunisation and full dose coverage was more dependent on the number of contacts with the health system during pregnancy, than the quality of those contacts [22].

On the supply-side, the quality of maternal health service delivery in LMICs has faced several challenges. An analysis of health systems in five LMICs (namely, Kosovo, Myanmar, Uganda, Malawi and Tanzania) found that barriers to implementation of maternal health interventions were shared across contexts and included limited health workforce, shortage of health resources, inability to collect high-quality data due to staff shortage, inadequate funding and infrastructure, and policy implementation issues [7]. Additional barriers identified as being unique to certain political, cultural and Organizational contexts included accountability issues in implementation, and mistrust and miscommunication between patients and providers [7]. Taken together, it can be deduced that health systems barriers to accessing and delivering effective maternal health services could potentially affect the quality of maternal vaccination programmes in LMICs. This also highlights the necessity for consideration of the context in which health systems, and the people within them, function: be it sociocultural, economic, geographical, religious, historical and/or political [23].

Overview of maternal vaccination

A timeline of the history of maternal vaccination is provided in Figure 1, guided by key literature identified from this scoping review in Tables 1-3. This timeline includes the official introduction of maternal vaccination strategies globally. Inclusion of pregnant women in vaccine trials has followed a varied trajectory over time: from initial research policies that excluded them from clinical trials to a more recent inclusive approach for selected VPDs. This is based on a shift in the perception of pregnant women as a highly vulnerable population to a valuable target population for reducing the burden of VPDs and associated mortality [6].

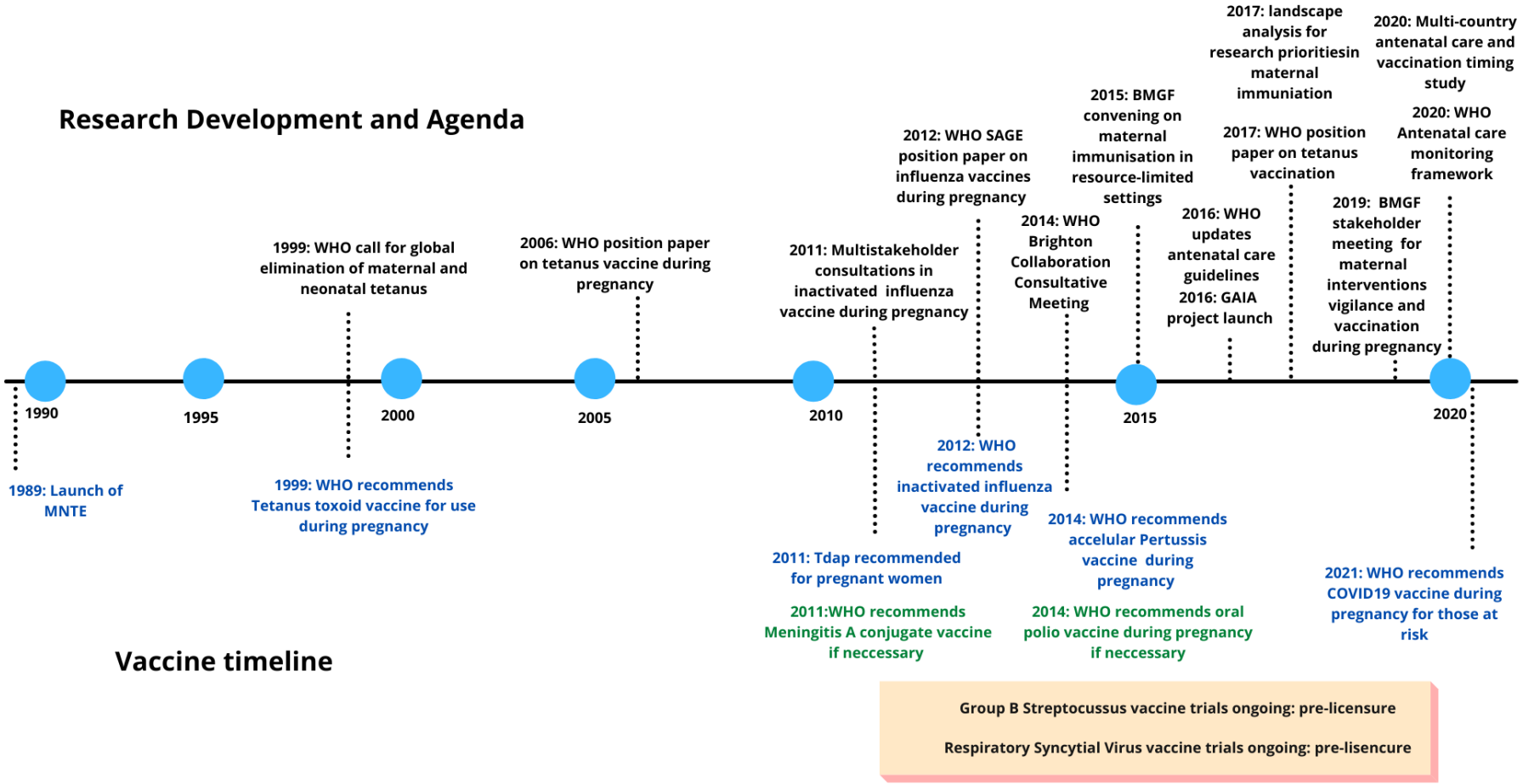

Figure 1 Timeline of the development of maternal vaccination research and maternal vaccine recommendations by the World Health Organization**.** Note: MNTE: Maternal and Neonatal Tetanus Elimination, BGMF: Bill & Melinda Gates Foundation, SAGE: Strategic Advisory Group of Experts on Immunization *[Source, author]*.

Table 1 Summary of key literature on current and future maternal vaccines.

Author, Year	Title	Geographic area	Study design	Vaccine	Key Findings
Aranda et al., 2019 [24]	Prevention of paediatric respiratory syncytial virus lower respiratory tract illness: perspectives for the next decade	Global	Review	RSV vaccine	Maternal immunisation offers most effective approach to RSV disease burden in neonates and children, with specific vaccination timing windows. Context and cultural factors affect vaccine acceptance in pregnant women.
Bardaji 2016 [25]	The burden of vaccine-preventable diseases in low-resource settings	Global	Commentary	Maternal vaccines	Still need to understand the true burden of disease of vaccine-preventable diseases in low-resource settings to accelerate maternal vaccination progress.
Bardaji et al., 2019 [26]	Maternal immunization: a call to accelerate progress	Global	Commentary	Maternal vaccines	Vaccination during pregnancy remains under-utilised due to lack of disease burden data, limited uptake by pregnant women due to poor communication strategies, highlighting need for more tailored context-specific vaccine implementation strategies.
Cutland et al., 2015 [27]	Lessons learnt from enrolment and follow up of pregnant women and their infants in clinical trials in South Africa, a low-middle income country	South Africa	Quantitative observational & RCT	GBS vaccine	Low uptake of vaccines due to health provider ignorance and patient hesitancy. Lack of measurable AEFI definitions and reporting.
Engmann et al., 2020 [28]	Closer and closer? Maternal immunization: current promise, future horizons	Global	Review	RMNCH health interventions	Maternal vaccines are safe and effective. Acceleration of vaccine programmes will rely on ANC and EPI integration at service delivery level.
Giorgakoudi et al., 2018 [29]	Cost-effectiveness analysis of maternal immunisation against group B streptococcus disease: a modelling study	UK	Quantitative model	GBS vaccine	Maternal GBS vaccines administered during pregnancy would be cost effective
Greenwood, 2003 [30]	Maternal immunisation in developing countries	LMICs	Review	Maternal vaccines	Immunogenicity and effectiveness of maternal vaccines could be affected by high HIV and TB burden in Sub-Saharan Africa. Developing country settings favour maternal vaccination programmes due to high infant death rates, infant disease burden, universal breastfeeding and already existing platform of ANC.
Hartley et al., 2019 [31]	The burden of infant group B streptococcal infections in Ontario: Analysis of administrative data to estimate the potential benefits of new vaccines	Canada	Quantitative	GBS vaccine	GBS incidence is under-reported. With 60% coverage in pregnant population, over half of GBS disease cases can be prevented.
Kachikis et al., 2020 [6]	The history of maternal immunization	Global	Review	Maternal vaccines	Timelines and vaccine development
Kim et al., 2014 [32]	Cost-effectiveness of a potential group B streptococcal vaccine for pregnant women in South Africa	South Africa	Quantitative model	GBS vaccine	Vaccination with combination of intrapartum GBS prophylactic treatment is more cost-effective than a vaccine only during pregnancy.
Kim et al., 2017 [33]	Cost-effectiveness of a potential group B streptococcal vaccine for pregnant women in the United States.	USA	Quantitative model	GBS vaccine	The vaccine is cost-effective if it is over 90% effective and has high coverage in pregnant populations. Effectiveness of the vaccine affects total cost in comparison with intrapartum GBS prophylactic treatment.

Larson, 2015 [34]	Maternal immunization: The new "normal" (or it should be).	Global	Commentary	Maternal vaccines	Building confidence in healthcare providers and pregnant women through effective communication strategies around vaccine safety and effectiveness is crucial for uptake
Li et al., 2020 [35]	Health and economic burden of [RSV] disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries	72 LMICs	Quantitative model	RSV vaccine	Protection through RSV vaccination could aid in avoiding treatment costs by avoiding hospitalisation and death. Duration of RSV immunisation by vaccination is yet to be confirmed.
Modjarrad et al., 2015 [36]	WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23–24 March 2015.	Global	Conference report	RSV vaccine	Infants in LMICs are disproportionately affected by RSV disease burden and mortality and key LMIC need to be included in phase 3 clinical RSV trials, with assurance of vaccine availability post-trial.
Pecenka et al., 2017 [37]	Maternal immunisation in Malawi: piloting a maternal influenza immunisation program costing tool by examining a prospective program	Malawi	Quantitative model	Influenza vaccine	Incremental costs of introducing the vaccine are low, but current available price would mean some LMICs rely on vaccine donation.
Regan, 2016 [38]	The safety of maternal immunization	Global	Commentary	Maternal vaccines	Routine safety data systems need to be developed for new maternal vaccines in addition to the robust safety profiles of tetanus and influenza vaccines for use during pregnancy.
Russel et al., 2016 [39]	What Pertussis Mortality Rates Make Maternal Acellular Pertussis Immunization Cost-Effective in Low- and Middle-Income Countries? A Decision Analysis	Bangladesh, Nigeria, Brazil	Quantitative	Acellular pertussis vaccine	Vaccination is cost-effective is vaccine is cheapy available and in countries without very nigh infant mortality rates.
Russel et al., 2017 [40]	Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan Africa	Guinea-Bissau, Uganda, Nigeria, Ghana	Quantitative model	GBS vaccine	A maternal GBS vaccine would prevent between 30-70% of deaths, provided pregnant women attend 4 or more ANC visits. The vaccine is cost-effective, and dependent on vaccine coverage and effectiveness.
Rasmussen et al., 2014 [41]	Vaccines during pregnancy: past and present	USA	Review	Maternal vaccines	Influenza vaccines should be administered at any time during pregnancy, while Tdap vaccines have a specified gestational age administration window. Barriers to receiving recommended vaccines need to be explored, and vaccine safety data to be expanded.
Saso and Kampmann, 2016 [42]	Vaccination against respiratory syncytial virus in pregnancy: a suitable tool to combat global infant morbidity and mortality?	Global	Review	RSV vaccine	Research and implementation need to be further researched in low-resource settings
Sato and Takasaki, 2019 [43]	Psychic vs. Economic Barriers to Vaccine Take-Up:Evidence from a Field Experiment in Nigeria	Nigeria	Quantitative	Tetanus vaccine	Monetary costs affect vaccine take up in rural women in Nigeria.
Swamy and Beigi, 2015 [44]	Maternal benefits of immunisation during pregnancy	Global	Review	Maternal vaccines	Maternal vaccines are an effective strategy to address heightened vulnerabilities to infectious diseases during pregnancy

Sobanjo-ter Meulen et al., 2016 [45]	Assessing the Evidence for Maternal Pertussis Immunization: A Report From the Bill & Melinda Gates Foundation Symposium on Pertussis Infant Disease Burden in Low- and Lower-Middle-Income Countries	LMICs	Conference report	Pertussis vaccine	Highlights dearth of data: LMICs need disease burden, epidemiological data and cost-benefit analyses before maternal pertussis interventions can be prioritised.
Van Bellinghen et al., 2018 [46]	Is adding maternal vaccination to prevent whooping cough cost-effective in Australia?	Australia	Quantitative model-based	Diphtheria and acellular pertussis vaccine	The vaccine is cost-effective when administered in the third trimester of pregnancy, dependent on vaccine coverage and effectiveness.
Vizzotti et al., 2016 [47]	Impact of maternal immunisation program against pertussis in a developing country	Argentina	Quantitative time-series analysis	Acellular pertussis vaccine	Effect of maternal pertussis vaccine is protective in infants younger than 6 months, reducing disease burden by 50% in vulnerable populations

[Source, author]

Since the initiation of the global Maternal and Neonatal Tetanus Elimination (MNTE) programme in 1989, neonatal tetanus has been reduced by 96% in targeted countries [15,21,22]. It is not surprising then that globally, maternal tetanus vaccination programmes have been considered a major public health success in reducing the devastating burden of maternal and neonatal tetanus, and therefore have emerged as a platform for introduction of new and underutilized maternal vaccines [30,38]. Despite this, 18 other LMICs have yet to eliminate neonatal tetanus [23].

In recent years, vaccination of pregnant women has gained momentum as a key strategy to alleviate maternal and neonatal morbidity and mortality due to VPDs, particularly in LMICs where the disease burden is greatest. A summary of the health benefits of maternal vaccination conferred to the pregnant woman and the infant is provided in Figure 2 (Panel a). While providing protection to the pregnant woman by inducing robust immune responses against VPDs, infants are also protected against VPDs in vulnerable stages of early life both while a foetus and post-birth, because of placental antibody (IgG) transfer during pregnancy and antibody (IgA) transfer in breastmilk [48]. Thus, maternal vaccination plays a significant role in improving early childhood survival and achieving the third SDG of reducing maternal, neonatal and under-5 mortality [6,49].

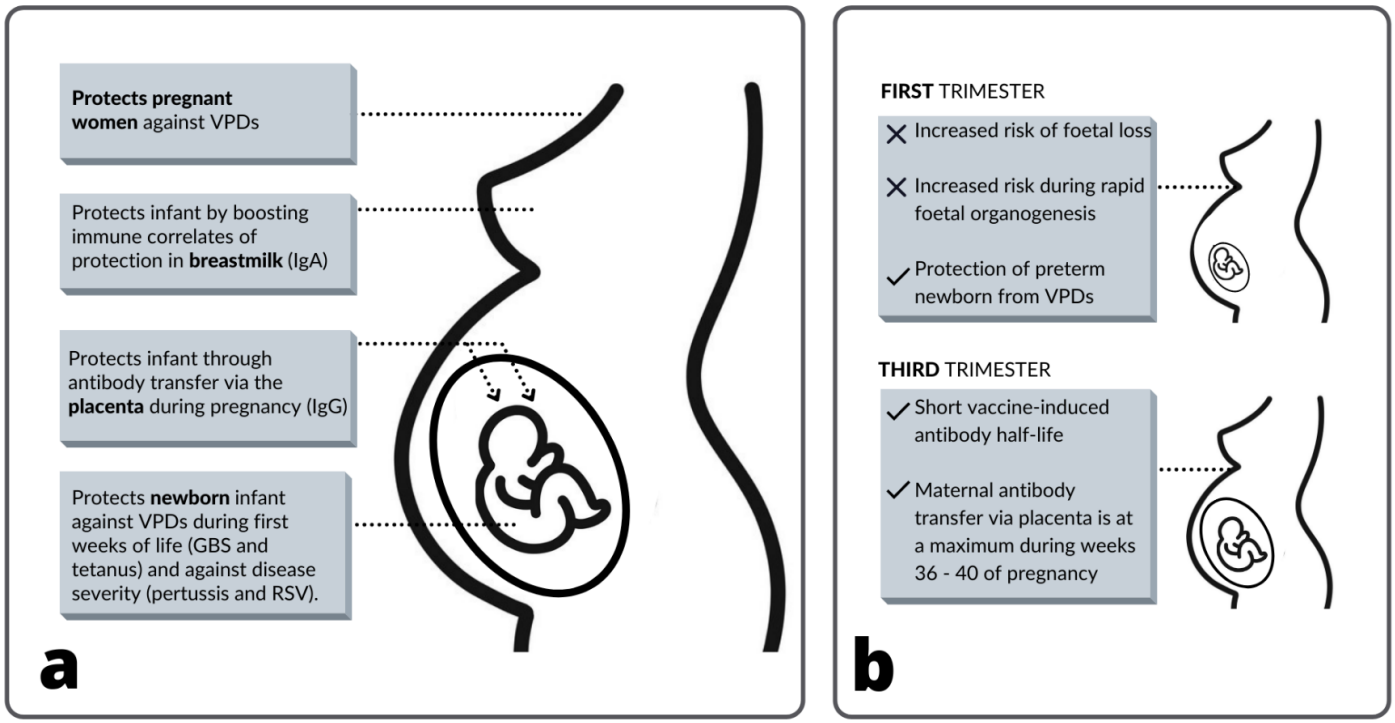

Figure 2 Summary of the benefits of maternal vaccination (a) and maternal-infant factors affecting optimal timing of vaccination (b). Note: VPDs: vaccine-preventable diseases, IgA: immunoglobulin A, IgG: immunoglobulin G, GBS: Group B Streptococcus, RSV: Respiratory Syncytial Virus *[Source, author]*.

Current vaccines for pregnant women

Seasonal maternal influenza vaccination has been recommended by the WHO since 2005 [9]. After the 2009 H1N1 pandemic, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) further recommended that pregnant women be prioritized for seasonal influenza vaccination as a high-risk group in 2012 [9,50]. Following this recommendation, wide acceptance of maternal flu vaccinations has contributed to a shift in acceptance of other maternal vaccines in many countries [50].

The diphtheria, tetanus and pertussis combination vaccine (Tdap) was first recommended for pregnant women by WHO in 2015 [8,9]. This Tdap vaccination programme has been successfully implemented through public funding in many South American countries. A notable success was in Argentina, where maternal Tdap administration decreased neonatal pertussis incidence by 51% [51]. Maternal Tdap vaccination is recommended at the gestational age of 18-32 weeks, when efficiency of placental antibody transfer is at a maximum [48]. This very narrow window introduces vaccine uptake issues which need to be further explored in LMICs where antenatal visits are limited [8,39]. Vaccination prior to the third trimester is not ideal as the immune protection has been shown to wane over time, as is shown in Figure 2 (Panel b) [48]. Vaccinating pregnant women with the Tdap vaccine protects neonates against infection in their first weeks of life, providing protection during the most vulnerable period. Additional vaccines recommended for administration during pregnancy in endemic countries or during outbreaks include the meningococcal A, yellow fever, cholera, Ebola, Hepatitis E, rabies and tick-borne encephalitis vaccines [6,48].

Future vaccines for pregnant women

Vaccines against Group B streptococcal disease (GBS) and respiratory syncytial virus (RSV) are currently in late-stage clinical trials and have yet to be licensed for use in pregnant women [42,52]. Whereas screening for GBS during pregnancy is common practice in HICs [33], this is not the case in resource-constrained LMICs. Maternal GBS vaccination serves to fill a gap in primary prevention in both HICs and LMICs, in addition to prevention measures such as antibiotic prophylaxis where available [8,31,53]. Such an intervention would be ideal in LMICs given that the incremental costs of introducing new vaccines are less than those associated with screening and treating the disease [46].

Respiratory syncytial virus or RSV is a leading cause of severe respiratory infection and subsequent hospitalisation of neonates worldwide [54,55]. It is estimated that over 92% of global incidence of the disease and 99% of RSV-associated mortality occurs in LMICs. In these settings, almost half of all associated hospitalisations and mortalities occur in infants under six months of age [54]. Future RSV vaccines have the potential to decrease this substantial burden on health systems through disease and hospital resource alleviation. For maximum protection of mother and child, these vaccines require narrow immunisation windows and could be programmatically difficult to introduce in LMICs [24,55]. While several clinical trials undergo phase 3 RSV maternal vaccine development [42], there is still limited understanding of the true burden of the disease. This is because a substantial proportion of RSV cases are not seen in health facilities. To support vaccine development and introduction efforts, there is increasing need for strengthening disease surveillance and global consensus on the characterization of the disease [36]. Current trial designs and policy-makers rely on hospital-based studies from LMICs that may not accurately estimate the true RSV burden. This requires model parameter estimates to carry high uncertainty when estimating maternal vaccination impact [20].

In addition to vaccines against GBS and RSV, recent COVID-19 vaccines have also been targeted for pregnant women. Preliminary data from the United States indicates that COVID-19 vaccines such as the Moderna and Pfizer-BioNTech mRNA vaccines are safe and effective in pregnant women, although robust longitudinal data are still required as vaccination rollout progresses [56].

Box 1. Summary of evidence for current and future maternal vaccines

Overall, the body of literature on maternal vaccination, and current and future maternal vaccines consists predominantly of reviews, quantitative model-based studies and commentary pieces (see Table 1). Most of these review studies did not include rigorous and transparent methodology, but do serve to outline key developments, including successes and challenges in the field [6,24,28,30,41]. The heavy focus on quantitative literature on the cost-effectiveness of maternal GBS and RSV vaccines is expected [29,32,33,35,46], considering these are candidate vaccines in trial phase and will be crucial for low-resource settings where the disease burden is oftentimes the greatest [40]. Notably, such model-based investigations for cost-effectiveness rely on many assumptions for model inputs, although all studies do include an element of sensitivity analyses that identify vaccine coverage and effectiveness [yet to be determined for GBS and RSV] as the most sensitive variables. Also worth noting, is the fact that such analyses are mostly based on data from HICs [29,31,33,46]. Limited inclusion of studies conducted in LMICs during model-based investigations has been attributed to the persistent lack of disease surveillance data from these settings where ANC services are routinely used as a proxy for vaccine delivery and coverage [40]. Finally, commentary pieces do not follow reproducible methods but are useful as they provide an indication of key researchers, actors, initiatives, Organizations and research priorities contributing to the field of study [34,36,45] .

Characterising maternal vaccine delivery and uptake in LMICs

In order to optimise maternal and neonatal outcomes through maternal vaccination efforts, barriers to implementation globally and in areas of high VPD endemicity must be understood before the intervention can be applied as a 'cure-all' approach [57]. Current maternal vaccination programmes in LMICs are characterised by various factors that affect delivery (on the vaccine supply side) and uptake (on the vaccine demand side).

In terms of delivery, given their significant resource constraints (see above), some LMICs are not likely to achieve the WHO's antenatal care model, which could have significant implications for scaling-up maternal vaccination programmes. However, if achieved, increased number and quality of antenatal contacts will enhance opportunities for vaccine delivery and advocacy during pregnancy [34,41]. Successful integration of maternal vaccination programmes with antenatal care ensures that health care services throughout the continuum of care are of acceptable quality, ensuring effective, safe and people-centered services [58]. This is because integration is intended to address system delivery and fragmentation issues through person-focused, population-based care and inter-sectorial partnerships [5,49,51]. Historically, delivery of integrated health care interventions have been shown to improve continuity of care and service delivery co-ordination [15,60].

The substantial cost associated with developing new maternal vaccine delivery platforms creates an additional barrier to vaccine programme implementation in LMICs where several health programmes compete for limited budgets and health infrastructure [61] . Thus, using existing infrastructure – rather than developing a new delivery system – is ideal for expanding the continuum of care and reducing costs associated with maternal vaccination [58,61]. This approach would also be useful in reducing healthcare provider burden, as a key barrier to effective implementation and subsequent delivery of maternal vaccination programmes [57,62]. In contexts where antenatal visits are suboptimal, maternal vaccines have been delivered through community health systems for women in rural or hard-to-reach areas as a complement to antenatal platforms, demonstrating a mixed vaccine delivery

approach as an alternative method of achieving optimal vaccine coverage in place of complete reliance on the antenatal platform [17]. Such an approach was utilized in areas of high risk for infection during the maternal and neonatal tetanus elimination initiative in El Salvador [1]. It has been proposed that further research needed to support implementation of maternal vaccination programmes should consider the lessons drawn from integration of antenatal care with HIV testing, nutritional supplementation or Malaria screening and treatment, to optimise service delivery models for health service co-ordination [21].

When considering whether to introduce a new vaccine as part of evidence-based national service delivery packages [either through antenatal care or national programmes on immunisation], decision-making bodies rely on regional epidemiological data to understand disease burden and regional needs [26,63]. This is a consistent programmatic challenge in LMICs because of a dearth in baseline epidemiological data, including disease burden and neonatal health outcomes [25,62,64]. Oftentimes, lack of reliable epidemiological data is a barrier to sound vaccine policy formulation by actors like National Immunisation Technical Advisory Groups, resulting in delays in vaccine recommendations and programme rollout [63]. This is because decision-makers rely on robust data collection and evidence synthesis to inform vaccination programme frameworks [63]. Compounding this issue is the limited diagnostic capacity for VPDs in many LMICs, where diseases like RSV, GBS, pertussis and influenza require formal laboratory testing which may not be readily available or accessible in health facilities in some LMICs [65]. In contrast, tetanus is clinically diagnosable without laboratory confirmation and this is considered as one of the determinants of the success of maternal tetanus vaccination programmes in most LMICs [64]. The diagnostic requirements also inform assessments such as cost-benefit analyses, whose estimated parameters for studies conducted in LMICs carry high uncertainty in predicting epidemiological, social and financial needs and burden of disease due to lack of reliable data [13,20,35]. In Malawi, for example, policy-makers rely heavily on health and epidemiological data from neighbouring countries with similar health, economic and geographical profiles [13]. A study in Kenya relied on pregnant women's antenatal books, which are kept personally and not in clinic records, to estimate antenatal care attendance for implementation of the future RSV vaccine; demonstrating a need for harmonization of health information systems [26,55].

Consideration of local context is also key to successful implementation of maternal vaccines and health service delivery in general [66]. Contextual factors, such as disease burden and political will, that affect vaccine delivery may stem from national prioritisation of certain disease-specific programmes over others [66]. To garner additional support for maternal vaccines and secure its place in national public agenda, it has been recommended that more women need to be included in policy formulation and in decision-making around vaccine implementation [8]. Increased empowerment enhances agency and creates informed policy-decision models that have the potential to enhance advocacy strategies and improve prioritisation issues in the implementation and delivery of maternal vaccines [67].

It is well understood that existing antenatal care services are an optimal platform for delivering maternal vaccines. As it stands, national immunisation programmes co-ordinate vaccine delivery, procurement, storage, cold chain management and reporting at a national level in most LMICs [30]. There is a great need to harmonise the various policy processes and ethical frameworks that govern these delivery systems effectively (such as coordination between national immunisation programmes and maternal, neonatal and child health services), given that suboptimal integration and collaboration at health facility level often leads to health resource scarcity which is a barrier to implementation of maternal health interventions in LMICs [7,8]. Efforts to address these co-ordination issues have been

initiated by expert groups and public-private partnerships to generate roadmaps (in the case of PATH, WHO and the Advancement of Maternal Immunization agenda[7]) towards improving maternal vaccination programmes in LMICs. In this regard, the focus-point has been the maternal RSV vaccine [68], and the maternal tetanus vaccine which formed part of the recently completed Maternal Immunisation and Antenatal Care Situation Analysis (MIACSA) study [69]. These efforts emphasised the need for (i) strengthening record-keeping systems in antenatal care across LMICs, (ii) introducing consistent disease surveillance systems, (iii) promoting eight antenatal contacts, and (iv) increasing global and national funding mechanisms for advancement of maternal vaccination [69].

Another dimension to effective delivery of maternal vaccines in LMICs is the role of public-private partnerships. There is very limited exploration in the current literature of how public-private collaborations in LMICs might influence maternal vaccine delivery. Such partnerships are important to consider in the context of vaccine policy, planning and implementation, especially in LMIC contexts that often rely on such partnerships to deliver effective health services. In El Salvador for example, it has been reported that private providers refer pregnant women to state facilities for maternal vaccinations because of the zero-cost involved [17]. This highlights the need for research that investigates integration of different maternal health service delivery platforms, be it through harmonisation of services or collaboration across health sectors and among service providers [58].

Unlike delivery, which is most heavily influenced by health systems constraints, it has been noted that the *uptake* of maternal vaccines is heavily dependent on robust communication strategies that address maternal knowledge, perceptions and attitudes towards vaccination during pregnancy [13]. Uptake is also strongly positively associated with healthcare worker communication with pregnant women, and thus their responsibilities extend to advocacy, risk communication and vaccine administration in addition to standard antenatal services [69,70]. In many LMICs, these tasks increase an already-heavy burden on human resources for health, especially when considering the limitation in the capacity of the health workforce, an issue also highlighted with vaccine delivery [8,64,70]. Communication strategies cannot adopt a 'one-size-fits all' approach, but rather need to be contextually appropriate to be effective in the varied LMIC settings [67,71]. An example that necessitates this approach is the reliance of male-partner permission by pregnant women in some LMICs to access certain healthcare services [71]. This requires vaccine communication strategies to take into account the content, audience and approach to promote public trust of key stakeholders in maternal vaccination, including policy and decision-makers, pregnant women and their partners/family, and healthcare providers [67]. Pregnant women in LMICs need to be encouraged to attend all recommended antenatal visits, where implemented, to access the full complement of health services offered [55]. To develop effective communication and advocacy strategies, decision-makers rely on reliable data, as mentioned above, to promote governmental buy-in and vaccine uptake among the target population.

A systematic review of global vaccine hesitancy during pregnancy applied the SAGE Working Group 'Model of determinants of vaccine hesitancy' to describe the concept, which views vaccine hesitancy as a product of interacting contextual, individual and specific vaccine-related factors [72]. The concept of vaccine hesitancy among pregnant women is multifaceted but has been found to mainly stem from a lack of knowledge around the benefits of maternal vaccination, unaddressed risk and safety

[7] The Advancement of Maternal Immunization is a collaboration of partnerships and experts coordinated by PATH and WHO since 2017. The collaboration coordinates maternal, newborn and child health programmes that inform maternal vaccination decision-making around vaccine introduction.

concerns, and various contextual factors (such as endorsement by a partner or close friends) [73,74]. Vaccine hesitancy is not limited to LMICs, but has also been qualitatively recorded in HICs, although extensive maternal vaccination knowledge appears to be associated with higher income status [75]. It is crucial that vaccine communication efforts include widely accessible and comprehensive information [as is well understood from clinical trial and immunological profile data] on the lifesaving benefits to both mother *and* child, while clarifying potential vaccination risks and side-effects [64]. For optimal uptake and coverage, confidence and trust in maternal vaccination is crucial, especially as new vaccines become licensed and introduced [34,70]. Providing transparent and timely information for pregnant women (and healthcare providers) is also key to programmatic success [62,70]. These issues around vaccine communication and trust highlight the importance of vaccination programmes that are responsive to contexts in which they are delivered, to provide appropriate care. Many of the deficits in vaccine communication and advocacy can be addressed through strengthened pharmacovigilance monitoring and reporting of adverse events following immunisation [AEFI][8], that promotes trust in healthcare providers and maternal vaccines [67].

In summary, key determinants of maternal vaccine uptake include acceptance and level of maternal knowledge, as well as healthcare provider capacity and communication. These key factors overlap with those related to vaccine delivery, namely healthcare provider and systems capacity, and demonstrate the complexity and interaction of various health system elements to produce outcomes in maternal vaccination coverage. Improved understanding of how the determinants of both vaccine delivery and uptake interact and influence the performance and outcomes of maternal vaccination programmes in LMICs requires deeper analysis.

Box 2. Summary of evidence on maternal vaccine delivery in LMICs

The literature identified on maternal vaccination programmes (Table 2) indicates a variety of quantitative, mixed-methods and qualitative studies that have been conducted in LMICs. This is indicative of the breadth of the field, giving insight into the complexity of interacting determinants of vaccination programmes in LMICs. Understanding the determinants of vaccine uptake like vaccine hesitancy and trust cannot only be quantified and call for qualitative insight. With the exception of one qualitative investigation and inclusion of HICs in some reviews, all vaccination programme experiences described in these studies include LMIC-specific contexts. Primarily, literature from African and South American contexts dominates the field, as seen in Table 3, with some representation of Asian countries like Bangladesh included as part of multi-country studies. Although some studies focus on maternal pertussis, influenza, and RSV vaccines only, the majority focus on maternal vaccines in general. This does not disregard the nuances of individual vaccines, like the importance of windows of administration for gestational age, which emerges as a saturated theme in the evidence-base.

[8] Adverse events following immunisation or AEFI refers to a medical occurrence post-vaccination that may not necessarily depend on vaccine use, and may include unfavourable laboratory results, symptom or disease.

Table 2 Summary of key literature on maternal vaccination programmes in relation to maternal healthcare and other interventions [Source, author]

Author, Year	Title	Geographic Area	Study design	Vaccine/Intervention	Key Findings
Afulani et al., 2015 [18]	Rural/urban and socioeconomic differentials in quality of antenatal care in Ghana	Ghana	Cross-sectional Quantitative	Antenatal care	Pregnant women attended attend at least one ANC visit throughout pregnancy Socioeconomic disparities [e.g., Education] linked to quality of ANC received Some disparities are accounted for by health system factors, where quality of care varies by health facility and by groups of women
Allen et al., 2018 [76]	Associations between increased intervention coverage for mothers and newborns and the number and quality of contacts between families and health workers: An analysis of cluster level repeat cross sectional survey data in Ethiopia	Ethiopia	Cross-sectional quantitative	Antenatal, intrapartum and postpartum.	Higher coverage of interventions [like tetanus] is linked to better quality of care is during pregnancy. Tetanus toxoid protection coverage increased with more ANC visits. Practice of health workers is as much of a priority as health services supplies and commodities.
Alvarez et al., 2020 [70]	Enablers and barriers of maternal and neonatal immunization [MNI] programs in Latin America	Latin America: Argentina, Brazil, Honduras, Mexico, Peru.	Mixed methods	Maternal influenza, tetanus and tetanus-diphtheria vaccines	Acceptability of vaccines, political will, existence of NITAGs, free access to vaccines, facility incentives and pooled funding mechanisms cited as enablers to MNI programmes Lack of user information, issues to healthcare access, inadequate infrastructure, lack of training, little communication and weak information systems cited as barriers.
Baral et al., 2020 [20]	The impact of maternal RSV vaccine to protect infants in Gavi-supported countries: Estimates from two models.	69 LMICs	Quantitative	RSV maternal vaccine	Attendance of first ANC visit in over 93% of women]; reduced to 64% by 4th ANC visit. Late presentation at ANC visits compromises opportunity for uptake of vaccines with limited gestational window
Fleming et al., 2018 [17]	Implementation of maternal influenza immunization in El Salvador: Experiences and lessons learned from a mixed-methods study	El Salvador	Mixed-methods	Maternal influenza vaccine	Communication, advocacy and education for vaccine amongst healthcare workers is crucial to acceptance Contextual violence huge barrier to access of vaccines
Fleming et al., 2019 [77]	Maternal immunization in Malawi: a mixed methods study of community perceptions, programmatic considerations, and recommendations for future planning.	Malawi	Mixed-methods	Maternal tetanus vaccine	Community trust and health worker acceptance and positive perception of vaccines Limited awareness and education around disease itself lead to low prioritisation Need for strengthened disease surveillance High trust of healthcare workers by pregnant women
Gauld et al., 2020 [78]	A qualitative study of views and experiences of women and health care professionals about free maternal vaccinations administered at community pharmacies	New Zealand	Qualitative	Maternal pertussis and influenza vaccines	Provision of vaccines in a pharmacy setting could overcome barrier to uptake and gaps in vaccine awareness by pregnant women Increasing awareness of availability of vaccines depends on communication methods and education of and by healthcare providers
Giles et al., 2020 [69]	Antenatal care service delivery and factors affecting effective tetanus vaccine coverage in low-and middle-income countries: Results of the Maternal Immunisation and Antenatal Care Situational analysis [MIACSA] project	137 LMICs	Mixed-methods	Maternal tetanus vaccine	Most countries have not implemented updated WHO guidelines for 8 ANC visits
Groman et al., 2019 [79]	Lessons learned from the Advancing Maternal Immunization collaboration: identifying evidence gaps for informed	Global	Qualitative gap analysis	RSV maternal vaccine	The AMI collaboration provides a framework from which other countries and Organizations can work in advancing maternal vaccination, emphasising the need for cross-programme collaboration with diverse expertise and perspectives to contribute to decision-making.

	respiratory syncytial virus maternal immunization decision-making				
Hardt et al., 2016 [61]	Vaccine strategies: Optimising outcomes	Brazil, South Africa, UK, USA, Japan, Spain, Australia,	Review	Immunisation programmes	Range of communication strategies from policy-makers to providers is crucial for implementation. Cost of immunisation programmes and feasibility varies by country/context. Capacity building ogranisations [like universities or non-profit sector] contribute to programme success
Kochhar et al., 2019 [62]	Introduction of new vaccines for immunization in pregnancy–programmatic, regulatory, safety and ethical considerations.	LMICs, non-specific	Review	Maternal vaccines	Programmatic challenges for maternal vaccine introduction in LMICs include lack of disease data and reporting; vaccine availability; poor logistics; lack of integrated care approaches; low number of trained providers; ineffective communication of risks.
Larson Williams et al., 2019 [71]	Maternal vaccine knowledge in low-and middle-income countries—and why it matters	LMICs	Commentary	Maternal vaccines	Knowledge, attitude and perception of vaccines by pregnant women is key to vaccine uptake, and heavily influenced by health care provider perception and awareness. Cost, availability and accessibility are known global barriers to vaccine programme implementation
Mehanna et al., 2020 [80]	Knowledge and health beliefs of reproductive-age women in Alexandria about tetanus toxoid immunization	Egypt	Quantitative	Maternal tetanus vaccine	Healthcare provider awareness and education of maternal vaccines is crucial to acceptance and uptake in pregnancy.
Nyiro et al., 2020 [55]	Implications of gestational age at antenatal care attendance on the successful implementation of a maternal respiratory syncytial virus [RSV] vaccine program in coastal Kenya	Kenya	Quantitative, cross-sectional	Maternal tetanus and RSV vaccines	Just over 50% coverage for RSV vaccines could be reached in Kilifi, using tetanus vaccines as a proxy and within gestational age window for RSV. Access to health facilities and health provider strikes are major barriers to uptake
Olaitan et al., 2017 [19]	Ending preventable maternal and child deaths in western Nigeria: Do women utilize the lifelines?	Nigeria	Quantitative	Maternal and child health services	Utilisation of ANC is high, majority at public health facilities [74%], but barriers include: Financial constraints; distance to health facility; partner restriction and health provider attitude are barriers to utilisation. Pregnant women's education predictive of ANC utilisation. Trust in significant family members exceeds that of health care providers
Otieno et al., 2020 [73]	Drivers and barriers of vaccine acceptance among pregnant women in Kenya	Kenya	Mixed-methods	Maternal vaccines	Tetanus vaccine most commonly received; of 71% of sample receiving a vaccine during pregnancy. Reasons cited for uptake were disease prevention, benefit to baby, and following provider recommendations. Refusal was linked to possible side effects and vaccine safety, stemming from lack of information. Identified majority willing to take vaccines during pregnancy
PATH, 2018 [68]	Advancing RSV maternal immunization: a gap analysis report.	14 LMICs	Mixed-methods report and roadmap	Maternal RSV vaccine	RSV vaccines require specific gestational age windows for delivery, thus the MNTW model is not ideal. Improved surveillance data required in LMICs. Delivering RSV in LMICs will require modification and expansion of EPI and current ANC
Pathirana et al., 2015 [74]	Determinants of maternal immunization in developing countries	Cambodia, Pakistan, Ethiopia, Bangladesh, India, Angola, Malawi	Mixed-methods	Maternal tetanus vaccine	Major health system barriers are financial and human resources, including service delivery for EPI. Consideration of health system aspects is key for maternal vaccination.

Saso et al., 2020 [48]	Maternal Immunization: Nature Meets Nurture	Global	Review	Maternal vaccines	Maternal immunological factors highlight the issue of gestational windows for vaccination. Vaccines are safe and effective ways to prevent maternal and infant disease
Sobanjo-ter Meulen et al., 2020 [8]	Preparing to introduce new maternal immunizations in low-and lower-middle-income countries: A report from the Bill & Melinda Gates Foundation convening "Allies in Maternal and Newborn Care"; May 3–4, 2018	LMICs	Conference report	Maternal vaccines	ANC platforms crucial for expansion of vaccine delivery, in coordination with EPI. List of potential research areas listed.
Sobanjo-ter Meulen et al., 2019 [67]	Maternal interventions vigilance harmonization in low-and middle-income countries: Stakeholder meeting report; Amsterdam, May 1–2, 2018	LMICs	Conference report	Maternal health interventions	Key elements of vaccine risk communication plan outlined by content, target audience and recommended approach. Community engagement improves trust and emphasises the importance of contextual consideration in implementing maternal vaccine programmes
Vizzotti et al., 2015 [51]	Maternal immunization in Argentina: a storyline from the prospective of a middle income country.	Argentina	Review	Influenza and pertussis maternal vaccines	Disease prevention strategies made successful through political will, prioritisation, media communication and community awareness,
Wilson et al., 2015 [72]	Understanding factors influencing vaccine acceptance during pregnancy globally: a literature review	Global	Systematic review	Maternal vaccines	Majority of vaccine hesitancy studies are based in North America, mostly focused on tetanus vaccine during pregnancy. Results interpreted according to SAGE Working Group 'Model of determinants of vaccine hesitancy', according to individual, vaccine and contextual factors.

[Source, author]

Intersection of vaccination, maternal healthcare and health systems

Exploring health systems determinants of optimal maternal health outcomes, including reduction in maternal morbidity and mortality due to VPDs, requires a better understanding of the interaction among broader maternal healthcare services, maternal vaccination programmes, and the health systems that deliver them.

Various conceptual frameworks for health systems research exist and have evolved over time, ranging from descriptive and analytical to deterministic and predictive [81]. These frameworks share the health systems principles of equity, quality, coverage, access and safety [82]. Shared critical functions, sometimes described as health system 'building blocks', include: services, health workforce, health information, technologies and commodities, demand generation, financing and governance [81]. A useful conceptual framework of 'health systems as a shelter' for exploration of maternal, new born and child health outcomes through a systems lens has been applied in research in West Africa, and offers a useful basis for unpacking systems complexities in terms of health systems hardware, software and values [83]. While systems hardware refers to tangible systems building blocks such as resources and financing, software refers to the people, processes, networks and behaviours that drive systems [23,82]. The WHO's Strategies Toward Ending Preventable Maternal Mortality agenda necessitates a systems hard- and software approach to respond to women's health in order to improve the state of MCH in LMICs [84]. Complementing the 'health system as a shelter' framework is a previously published logic model that integrates health systems critical functions with core immunisation programme components of: (i) policy, standards, and guidelines, (ii) governance, Organization, and management, (iii) human resources for health, (iv) vaccine cold-chain and logistics, (v) service delivery, (vi) communication and community partnerships, (vii) data generation and (viii) sustainable financing [12,85]. It is worth noting that both frameworks assess the context in which health systems exist and function.

Box 3. Summary of the evidence at the intersection of maternal health, vaccination and health systems

Literature identified as falling within the intersection of health systems and maternal vaccination consisted predominantly of review studies, with the exception of one mixed-methods study [83] and one conference report [50]. This small subset of studies indicates a dearth in the field of research on the role of health systems in the functioning of maternal vaccination programmes, especially in LMICs. Most of the studies reviewed tend to assess selected health systems determinants in isolation. This implies that in most cases, the capacity of health systems to support maternal vaccination programmes in LMICs is not comprehensively captured in the published literature. However, these studies, particularly those identified in Table 3, provide methodological guidance for this scoping review.

Table 3 Summary of key literature on maternal vaccination programmes and health systems in LMICs *[Source, author]*

Author, Year	Title	Geographic Area	Study design	Key Findings
Amponsah-Dacosta et al., 2020 [85]	Health systems constraints and facilitators of human papillomavirus immunization programmes in sub-Saharan Africa: a systematic review.	Sub-Saharan Africa	Systematic Review	Framework for the interface between National Immunisation Programmes and health systems
Agyepong et al., 2017 [83]	Spanning maternal, newborn and child health [MNCH] and health systems research boundaries: conducive and limiting health systems factors to improving MNCH outcomes in West Africa	Burkina Faso, Benin, Mali, Senegal, Nigeria, Ghana	Mixed-methods	'Health system as a shelter' framework is applied qualitative review of maternal, newborn and child health policies. Context, health systems factors and interventions interact in a complex way with decision making, policy and implementation to produce maternal and child health outcomes.
De Jongh et al., 2016 [58]	Integration of antenatal care services with health programmes in low–and middle–income countries: systematic review	18 LMICs	Systematic review	Integration of ANC and health programmes is challenged by limited health system capacity for management, financing and programme monitoring, in addition to contextual complexity of each LMIC setting. Implementation requires strong coordination of all health actors, ranging from policy makers to non-profit providers.
Krishnaswamy et al., 2019 [13]	Key considerations for successful implementation of maternal immunization programs in low and middle income countries	LMICs	Review	Vaccine hesitancy is multifaceted and dependent on trust in healthcare providers. Global maternal and neonatal tetanus elimination serves as a platform from which to strengthen and expand maternal vaccine efforts in LMICs. Integration of data systems and service delivery is a step towards this.
Ortiz et al., 2011 [9]	Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions	"Resource-limited settings"	Review	Limited evidence in resource-constrained settings on disease burden in pregnant women and neonates; vaccine safety, effectiveness, knowledge, attitudes, perceptions, feasibility and cost-effectiveness. These gaps need to be addressed in order to prioritise maternal vaccination policies.
Ortiz et al., 2012 [50]	Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings	"Resource-limited settings"	Conference report	Need a whole-systems approach to vac programmes: from costing, communication, to uptake and acceptability, safety monitoring. need to strengthen NITAG capacity in LMICS; vac programmes should not be disruptive to MNCH initiatives currently ongoing. LMICs have no AEFI compensation programmes atm. Therefore, a need to strengthen reporting systems; and vaccine safety communication.
Shen et al., 2014 [12]	The future of routine immunization in the developing world: challenges and opportunities	"Developing countries"	Review	Schematic and framework for critical elements of routine immunisation programmes

[Source, author]

Drawing on the abovementioned frameworks, a new conceptual framing is proposed in Figure 3, which takes into consideration the interaction between vaccination programmes and maternal health systems. This framing takes into account key considerations for maternal vaccine introduction such as disease burden, vaccine availability, capacity of the health system and optimal timing for vaccine administration during pregnancy [28]. Here, health systems are framed by the context in which they exist, as they have been framed in the 'health system as a shelter' model for MCH [83], indicating how delivery of maternal vaccines falls at the intersection of vaccination programmes and maternal healthcare. Health systems functions are classified into hardware and software which are not mutually exclusive [82], but rather interact with each other, the broader health system and the prevailing context to produce optimal MCH outcomes. Hard-and software descriptors have been adapted from a logic framework developed for analysis of health systems and national immunisation programmes in Sub-Saharan Africa [85].

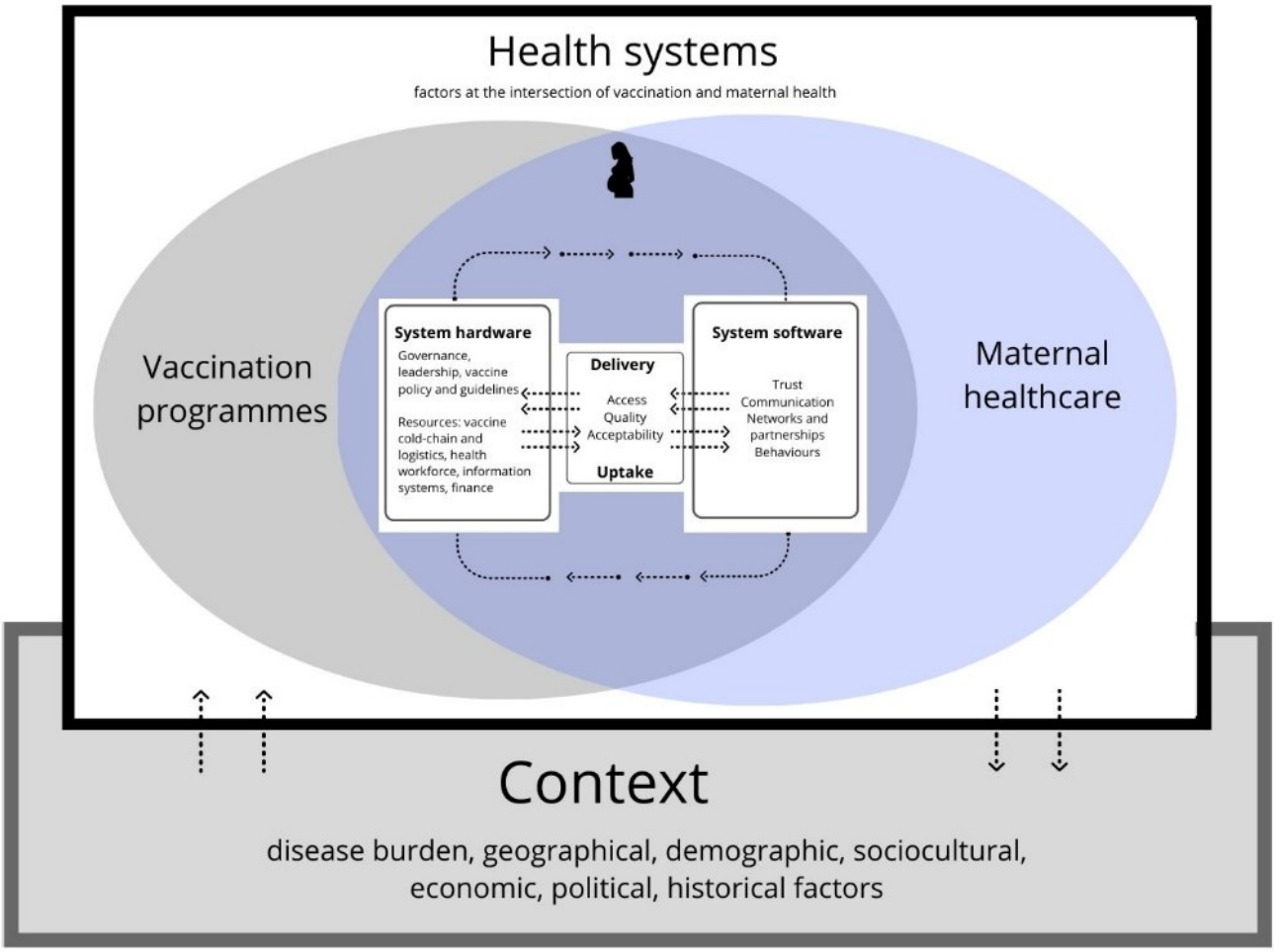

Figure 3 Framework for conceptualisation of health systems factors [82] at the intersection of vaccination programmes and maternal health *[Source, author]*.

Study Rationale and Research Question

The available literature in the field of maternal vaccination has increased significantly over the past decade – and there has also been a parallel increase in multi-stakeholder meetings to identify challenges and successes in current maternal vaccination programmes, and identify evidence gaps (Figure 1, [6]). However, as shown in the above review, most of the literature relates to cost-benefit analyses of maternal vaccination programmes and investigation of financial incentives in antenatal care, qualitative studies on maternal vaccine acceptance and uptake, multi-stakeholder analyses of integration of care systems, and multi-stakeholder analyses for development of a roadmap for future maternal vaccines.

Considering global interests in better understanding and addressing the barriers to effective maternal vaccination programmes in LMICs, as well as the urgency to expand the reach of new and under-utilised vaccines among pregnant women, there is a need to strengthen the evidence-base within this terrain, and to synthesise more effectively across varied forms of evidence. A qualitative approach to evidence synthesis is appropriate to the body of literature identified in this scoping review, and has been applied to reviews in the terrain of health systems and vaccine programmes previously [85,86]. For this purpose, a qualitative systematic review study is proposed to address the following research question; ***what are the health systems determinants of maternal vaccine delivery and uptake in LMICs?***

Review Objectives

1. To describe the health systems determinants of the delivery and uptake of maternal vaccines in LMICs
2. To describe how health systems determinants may serve as barriers or enablers to effective maternal vaccination programmes in LMICs
3. To draw policy- and practice- relevant recommendations to support current and future maternal vaccination programmes in LMICs

Methods

To address the research question and objectives, a qualitative systematic review study will be conducted in two phases: a scoping review in Phase 1 (reported above), followed by a qualitative systematic review in Phase 2.

Phase 1: Scoping review

A scoping review was to map the existing evidence-base of maternal vaccination and its intersection with health systems and policy research. The scoping review methodology, as outlined by Arksey and O'Malley [87] and revised by Peters *et al.* [88], was applied to identify key themes at the intersection of maternal vaccination and health systems to inform a further systematic review. We aligned our approach with the scoping review method developed by the Joanna Briggs Institute with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [89], which has also been applied in other scoping reviews on similar topics [90–92].

This scoping review exercise served to provide a broad overview of the literature, with room to explore various complexities and methodologies in the fields of focus [93]. In this review phase, peer-reviewed and grey literature was identified through library-accessed electronic health databases namely: PubMed, Scopus [Medline and Embase], Web of Science, and EBSCOHost (Academic Premier, Africa

Wide information, CINAHL, Health source nursing academic, Medline, APApsych, and Apa psychinfo). Additionally, search terms were applied to available vaccine resource libraries (GAVI, The Vaccine Alliance; PATH Vaccine Resource Library and the WHO library). Supplementary searches were also conducted in Google Scholar. Search terms relating to maternal vaccination, health systems and maternal healthcare were developed and refined to optimise the yield and scope of relevant literature (Table 4). The scope was limited to any antenatal or prenatal healthcare services and maternal vaccination literature, but not limited by publication date, to gain an understanding of a timeline in the field's development.

The scoping review was designed to inform the second more systematized phase, in particular the formulation of the systematic review question and objectives and the conceptual health systems framing to be applied during the data analysis process of the systematic review. The eligibility criteria for inclusion of studies in this scoping review was as follows: (i) studies involving pregnant women only or pregnant women and other populations (such as neonates or children), and (ii) studies published in English. The literature search was not limited by publication date in order to gain a better understanding of the timeline in the field's development (Figure 1). The scoping review was conducted between January and March 2021. In the development of this protocol, new relevant literature published after March 2021 was included if it met the criteria described above. In addition, some literature that was missed by the search strategy was retrieved through bibliographic searches. Although terms related to LMICs were specified in the search strategy, some studies from HICs were also retrieved and reviewed for comparison. For critical appraisal, the quality of empirical quantitative, qualitative and mixed-methods studies were appraised using the Critical Appraisal Skills Programme tools [94], which contain checklists for appraising qualitative, quantitative and mixed-methods empirical research. Studies considered to be 'low quality' by these checklists were not automatically excluded from the review, particularly if findings were relevant, unless study design and/or results were considered unreliable. Broad variables were used for extraction of data from the identified literature. A limitation of this scoping review is that publication bias could not be avoided, due to reliance on internet-based databases and published literature sources.

Common findings and themes of interest were identified and grouped by narrative synthesis, in accordance with the objectives of the scoping review, allowing for mapping and characterisation of the literature as reported in the subsequent sections. This method of synthesis has also been applied by a previous scoping review in the field [83,85,86] and was conducted through consultation with the research supervisors in this study.

Table 4 Search strategy for scoping review *[Source, author]*

Query	Terms
#1	"Maternal immunisation" OR "maternal immunization" OR "maternal vaccination" OR "antenatal vaccination" OR "antenatal immunisation" OR "antenatal immunization" OR "maternal vaccine" OR "antenatal vaccine""
#2	"Health system" OR "global health" [Mesh] OR "service delivery" OR "delivery of health care" [Mesh] OR "health information systems" [Mesh] OR "healthcare financing" [Mesh] OR "governance" OR "policy" [Mesh] OR "health workforce" [Mesh] OR "healthcare personnel" [Mesh] OR "medical technology" OR "vaccines" [Mesh] OR "vertical health program" OR "health systems strengthening" OR "health systems performance" OR "integrated health service" OR "Delivery of Health Care, Integrated" [Mesh] OR "integrated health systems" OR "antenatal care" OR "prenatal care" [Mesh] OR "maternal health" [Mesh] OR "maternal health services" [Mesh] OR "primary health care" [Mesh] OR "primary health service"
#3	"deprived countries" OR "developing countries" [Mesh] OR "less developed country" OR "low gross national" OR "low income countries" OR "middle income country" OR "middle income economies" OR "poor economy" OR "third world" OR "transitional country" OR "under developed economies"
#4	#1 AND #2 AND #3
FILTER	ENGLISH

Phase 2: qualitative systematic review

In the second phase a qualitative systematic review will be conducted. This methodological approach has been used previously in assessing health systems barriers, facilitators and social determinants of vaccination programmes for adolescents and adults [85,86,95], as well as integration of maternal healthcare interventions into service delivery platforms [58].

To identify relevant published literature for this systematic review, search terms defined in Phase 1 of this study will be indexed and optimised for each electronic database; namely, PubMed, Scopus [Medline + Embase], Web of Science, and EBSCOHost (Academic Premier, Africa Wide information, CINAHL, Health source nursing academic, Medline, APApsych, and Apa psychinfo). A supplementary search in Google scholar will be conducted (Appendix A).

Literature from search yields will be exported to the Zotero (v.61) reference manager, with duplicates removed and titles, abstracts and full texts screened for inclusion using the Rayyaan systematic review management online platform [96]. Evidence sources will only be included in this review if they involve human participants in quantitative, qualitative and mixed-methods empirical studies, conducted in LMICs and published in English between 2010 and 2021. This period was identified in Phase 1 as a crucial stage in the development of research within the field of maternal vaccination programmes in LMICs. The review will only include literature sources published in languages English. Published literature reporting on studies conducted in HICs, reporting on health interventions or programmes that do not include maternal vaccination, and are not primary research publications will not be included in this review. Conference reports, commentaries and reviews will not be included.

The quality of empirical quantitative, qualitative and mixed-methods studies will be appraised using the Joanna Briggs Institute Critical Appraisal Checklists and the Mixed-methods Appraisal Tool [88,97] which, as mentioned above, contains checklists for appraising qualitative, quantitative and mixed-methods empirical research and have been utilised in other qualitative systematic reviews [85,86,98,99]. Studies considered to be 'low quality' by these checklists will not automatically be excluded from the research, particularly if findings are relevant, unless study design and/or results are considered unreliable.

Data will be extracted from the findings of included studies according to variables defined in a data extraction table designed for this study. A complete data extraction table is provided in Appendix B. This table will be used to extract data on study characteristics (author, year article was published, year of study, title, journal, country/countries, study design, study aim, vaccine type/s) as well as variables informed by the conceptual framing developed during the scoping review. Data extraction variables have been adapted from Alvarez et al.'s [70] summary of main components for maternal and neonatal immunization programmes, in line with findings and key themes from the scoping review conducted in Phase 1 of this study:

- *Context* refers to the specific socioeconomic, geopolitical, geographic, epidemiological or historical context in which the study was conducted.
- *Vaccine decision-making* refers to decision-making processes that include governance; National Immunisation Advisory committees; criteria that inform decisions to introduce new vaccines; and the policy and health policy frameworks within which an immunisation programme is introduced.
- *Planning and implementation* refer to where the responsibility for programme planning lies; vaccine distribution; vaccination implementation; funding mechanisms; cold-chain procurement mechanisms; health workforce capacity training, performance incentives.
- *Delivery* refers to the timing of vaccine administration [gestational age]; platform for delivery (EPI, ANC or other models); access to vaccines.
- *Monitoring and reporting systems* refer to vaccine coverage; AEFI surveillance; individual reporting of AEFI; and systems-level reporting in terms of vaccine coverage.

With regards to the data analysis approach adopted for this review, descriptive or analytical data will be extracted from quantitative studies, understanding relationships and/or associations between variables, regardless of significance. Qualitative studies and data may help contextualise quantitative data through identification of concepts using thematic analysis [100].

Extracted data will be grouped thematically. Thematic inductive analysis will be applied to elicit meaning of the data extracted, as has been applied in previous reviews on vaccine uptake and delivery [86,95,101]. The conceptual framework (Figure 3) will be applied to the data analysis to identify possible relationships between data and/or themes. The emergent themes will be described through rich and complex interpretation of the extracted data, in an effort to identify underlying complexities at the intersection of health systems and maternal vaccination programmes. Thematic analysis allows room for rich description as well as interpretation of which context(s) play a crucial role in influencing maternal vaccination programmes in LMICs [100]. This level of analysis will contribute to improving our limited understanding of the contextual complexities of maternal vaccination programmes in LMICs while informing recommendations which may be transferrable to similar settings, although not necessarily generalisable.

In terms of rigour, literature selection, screening and data extraction will be conducted by one reviewer (the student) with oversight and consensus (where needed) provided by the supervisors of this thesis, ensuring reflexivity and corroboration of findings [102]. Dependability of the study will be ensured through detailed, transparent reporting of systematic review search, extraction, and analysis strategies, and through detailed description of all tools and appraisal guidelines used to assess the quality of the selected literature sources. This will be further enhanced through researcher collaboration with supervisors who will oversee the literature screening and appraisal process and

reduce selection bias. To minimise publication bias, a diverse range of evidence will be explored through peer-reviewed literature. Validation of themes through multiple sources of data (quantitative, qualitative or mixed-methods) will ensure greater confirmability and credibility of the study [103]. Trustworthiness of findings from extraction and thematic analysis will be ensured through student and supervisor reviewer triangulation, to validate themes in accordance with the conceptual framework applied and the research question posed. Researcher reflexivity will be accounted for through checking of the coherence between the identified themes and their implications for maternal vaccination programmes and health systems decision-making, practice and policy [101,104].

Ethical Considerations

This systematic review study will not require the direct involvement of human participants. As such, this study does not pose direct risks to humans and will therefore not require formal ethics approval. All data sources used in this study will be retrieved from publicly available electronic databases.

COVID-19 considerations

This research is not dependent on COVID-19 restrictions or protocol due to the desk-based nature of the study. Conducting this study does not put anyone at risk of contracting or transmitting COVID-19.

Dissemination of Findings

For dissemination, findings and themes will be translated into thematic statements, which has been suggested to enhance a study's value for utilisation in health practice. This requires summarising key themes for readers in such a way that the complexity of the themes is preserved [104]. These thematic statements will be submitted in the form of an original review manuscript for publishing in a peer-reviewed journal. The findings of this review will also be presented at local and international meetings including the Annual African Vaccinology Course hosted by the Vaccines for Africa Initiative, based at the University of Cape Town.

Study Budget

Given that this systematic review study will be a desk-based study, it is anticipated that the main costs incurred will be data for internet access to electronic databases which will be covered by the University of Cape Town data allocation for students during the transition to remote learning due to the COVID-19 pandemic. Other additional costs have been provided in the study budget in Table 5.

Table 5 Estimated budget for the systematic review study *[Source, author]*

Item description	Unit cost [R]	Total units	Total cost [R]
Data for electronic database searches and use of Rayyan	39.00	25	975.00
Data for consultation with UCT Libraries	39.00	5	195.00
Data for supervisor consultations	39.00	10	390.00
Printing protocol [one copy]	1.15	30	34.50
Printing thesis [one copy]	1.15	100	115.00
Total			1 709.50

Proposed Timeline

Table 6 Anticipated study timeline. Note: Q= quarter *[Source, author]*

	2020	2021				2022	
	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Scoping review							
Protocol development							
Protocol submission							
Data extraction and analysis							
Manuscript write up							
Thesis submission							
Journal manuscript submission							

References

1. World Health Organization. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2019 [cited 2021 Sep 15]. 104 p. Available from: https://apps.who.int/iris/handle/10665/327595
2. Miller S, Abalos E, Chamillard M, Ciapponi A, Colaci D, Comandé D, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. The Lancet. 2016 Oct;388[10056]:2176–92.
3. Koblinsky DM. Quality maternity care for every woman, everywhere: a call to action. 2016;388:14.
4. Pellegrini C, McCabe ERB. Maternal immunization at the crossroads. Vaccine. 2015 Nov;33[47]:6501–2.
5. You D, Jones G, Wardlaw T. United Nations Inter-agency Group for Child Mortality Estimation. Levels & trends in child mortality: estimated developed by the UN Inter-agency Group for Child Mortality Estimation. New York: UNICEF. 2010. 2011.
6. Kachikis A, Eckert LO, Englund JA. Chapter 1 - The history of maternal immunization. In: Leuridan EE, Nunes MC, Jones CE, editors. Maternal Immunization. Academic Press; 2020]. p. 3–24. Available from: https://www.sciencedirect.com/science/article/pii/B9780128145821000012
7. Ritchie LMP, Khan S, Moore JE, Timmings C, van Lettow M, Vogel JP, et al. Low-and middle-income countries face many common barriers to implementation of maternal health evidence products. J Clin Epidemiol. 2016;76:229–37.
8. Sobanjo-ter Meulen A, Liljestrand J, Lawn JE, Hombach J, Smith J, Dickson KE, et al. Preparing to introduce new maternal immunizations in low-and lower-middle-income countries: A report from the Bill & Melinda Gates Foundation convening "Allies in Maternal and Newborn Care"; May 3–4, 2018. Vaccine. 2020;38[28]:4355–61.
9. Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. Vaccine. 2011 Jun 15;29[27]:4439–52.
10. Koblinsky M, Moyer CA, Calvert C, Campbell J, Campbell OMR, Feigl AB, et al. Quality maternity care for every woman, everywhere: a call to action. The Lancet. 2016 Nov;388[10057]:2307–20.
11. Figueroa JP, Bottazzi ME, Hotez P, Batista C, Ergonul O, Gilbert S, et al. Urgent needs of low-income and middle-income countries for COVID-19 vaccines and therapeutics. The Lancet. 2021 Feb;397[10274]:562–4.
12. Shen AK, Fields R, McQuestion M. The future of routine immunization in the developing world: challenges and opportunities. Glob Health Sci Pract. 2014 Dec 1;2[4]:381–94.
13. Krishnaswamy S, Lambach P, Giles ML. Key considerations for successful implementation of maternal immunization programs in low and middle income countries. Hum Vaccines Immunother. 2019;15[4]:942–50.

14. Rodriguez DC, Neel AH, Mahendradhata Y, Deressa W, Owoaje E, Akinyemi O, et al. The effects of polio eradication efforts on health systems: a cross-country analysis using the Develop–Distort Dilemma. Health Policy Plan. 2021 Jun 3;36[5]:707–19.
15. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience: summary: highlights and key messages from the World Health Organization's 2016 global recommendations for routine antenatal care. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/handle/10665/259947
16. World Health Organization. recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
17. Fleming JA, Baltrons R, Rowley E, Quintanilla I, Crespin E, Ropero A-M, et al. Implementation of maternal influenza immunization in El Salvador: Experiences and lessons learned from a mixed-methods study. Vaccine. 2018;36[28]:4054–61.
18. Afulani PA. Rural/urban and socioeconomic differentials in quality of antenatal care in Ghana. PloS One. 2015;10[2]:e0117996.
19. Olaitan T, Okafor IP, Onajole AT, Abosede OA. Ending preventable maternal and child deaths in western Nigeria: Do women utilize the life lines? PloS One. 2017;12[5]:e0176195.
20. Baral R, Li X, Willem L, Antillon M, Vilajeliu A, Jit M, et al. The impact of maternal RSV vaccine to protect infants in Gavi-supported countries: Estimates from two models. Vaccine. 2020;38[33]:5139–47.
21. Baral R, Fleming J, Khan S, Higgins D, Hendrix N, Pecenka C. Inferring antenatal care visit timing in low- and middle-income countries: Methods to inform potential maternal vaccine coverage. PloS One. 2020;15[8]:e0237718.
22. Allen E, Schellenberg J, Berhanu D, Cousens S, Marchant T. Associations between increased intervention coverage for mothers and newborns and the number and quality of contacts between families and health workers: An analysis of cluster level repeat cross sectional survey data in Ethiopia. PloS One. 2018;13[8]:e0199937.
23. Sheikh K, Ranson MK, Gilson L. Explorations on people centredness in health systems. Health Policy Plan. 2014 Sep 1;29[suppl_2]:ii1–5.
24. Aranda SS, Polack FP. Prevention of pediatric respiratory syncytial virus lower respiratory tract illness: perspectives for the next decade. Front Immunol. 2019;10:1006.
25. Bardají A, Steinhoff M, Macete E, Aguado T, Menéndez C. The burden of vaccine-preventable diseases in pregnancy in low-resource settings. Lancet Glob Health. 2016;4[3]:e152–3.
26. Bardají A, MacDonald NE, Omer SB, Aguado T. Maternal immunization: a call to accelerate progress. Vaccine. 2019;37[22]:2882–3.
27. Cutland CL, Cunnington M, Olugbosi M, Jones SA, Hugo A, Maharaj K, et al. Lessons learnt from enrolment and follow up of pregnant women and their infants in clinical trials in South Africa, a low-middle income country. Vaccine. 2015;33[47]:6406–12.
28. Engmann C, Fleming JA, Khan S, Innis BL, Smith JM, Hombach J, et al. Closer and closer? Maternal immunization: current promise, future horizons. J Perinatol. 2020;40[6]:844–57.
29. Giorgakoudi K, O'Sullivan C, Heath PT, Ladhani S, Lamagni T, Ramsay M, et al. Cost-effectiveness analysis of maternal immunisation against group B Streptococcus [GBS] disease: A modelling study. Vaccine. 2018 Nov 12;36[46]:7033–42.
30. Greenwood B. Maternal immunisation in developing countries. Vaccine. 2003;21[24]:3436–41.
31. Hartley J, Li Y, Kunkel L, Crowcroft NS. The burden of infant group B streptococcal infections in Ontario: Analysis of administrative data to estimate the potential benefits of new vaccines. Hum Vaccines Immunother. 2019;15[1]:193–202.
32. Kim S-Y, Russell LB, Park J, Verani JR, Madhi SA, Cutland CL, et al. Cost-effectiveness of a potential group B streptococcal vaccine program for pregnant women in South Africa. Vaccine. 2014;32[17]:1954–63.
33. Kim S-Y, Nguyen C, Russell LB, Tomczyk S, Abdul-Hakeem F, Schrag SJ, et al. Cost-effectiveness of a potential group B streptococcal vaccine for pregnant women in the United States. Vaccine. 2017;35[45]:6238–47.
34. Larson HJ. Maternal immunization: The new 'normal' [or it should be]. Vaccine. 2015 Nov 25;33[47]:6374–5.
35. Li X, Willem L, Antillon M, Bilcke J, Jit M, Beutels P. Health and economic burden of respiratory syncytial virus [RSV] disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries. BMC Med. 2020;18:1–16.

36. Modjarrad K, Giersing B, Kaslow DC, Smith PG, Moorthy VS. WHO consultation on respiratory syncytial virus vaccine development report from a World Health Organization meeting held on 23–24 March 2015. Vaccine. 2016;34[2]:190–7.
37. Pecenka C, Munthali S, Chunga P, Levin A, Morgan W, Lambach P, et al. Maternal influenza immunization in Malawi: Piloting a maternal influenza immunization program costing tool by examining a prospective program. Plos One. 2017;12[12]:e0190006.
38. Regan AK. The safety of maternal immunization. Hum Vaccines Immunother. 2016;12[12]:3132–6.
39. Russell LB, Pentakota R, Toscano CM, Cosgriff B, Sinha A. What Pertussis Mortality Rates Make Maternal Acellular Pertussis Immunization Cost-Effective in Low- and Middle-Income Countries? A Decision Analysis. Clin Infect Dis. 2016 Dec 1;63:S227–35.
40. Russell LB, Kim S-Y, Cosgriff B, Pentakota SR, Schrag SJ, Sobanjo-ter Meulen A, et al. Cost-effectiveness of maternal GBS immunization in low-income sub-Saharan Africa. Vaccine. 2017 Dec 14;35[49, Part B]:6905–14.
41. Rasmussen SA, Watson AK, Kennedy ED, Broder KR, Jamieson DJ. Vaccines and pregnancy: past, present, and future. In: Seminars in Fetal and Neonatal Medicine. Elsevier; 2014. p. 161–9.
42. Saso A, Kampmann B. Vaccination against respiratory syncytial virus in pregnancy: a suitable tool to combat global infant morbidity and mortality? Lancet Infect Dis. 2016;16[8]:e153–63.
43. Sato R, Takasaki Y. Psychic vs. economic barriers to vaccine take-up: evidence from a field experiment in Nigeria. World Bank Econ Rev. 2019;33[3]:622–42.
44. Swamy GK, Beigi RH. Maternal benefits of immunization during pregnancy. Vaccine. 2015 Nov;33[47]:6436–40.
45. Sobanjo-ter Meulen A, Duclos P, McIntyre P, Lewis KD, Van Damme P, O'Brien KL, et al. Assessing the evidence for maternal pertussis immunization: a report from the Bill & Melinda Gates Foundation symposium on pertussis infant disease burden in low-and lower-middle-income countries. Clin Infect Dis. 2016;63[suppl_4]:S123–33.
46. Van Bellinghen L-A, Dimitroff A, Haberl M, Li X, Manton A, Moeremans K, et al. Is adding maternal vaccination to prevent whooping cough cost-effective in Australia? Hum Vaccines Immunother. 2018;14[9]:2263–73.
47. Vizzotti C, Juarez M, Bergel E, Romanin V, Califano G, Sagradini S, et al. Impact of a maternal immunization program against pertussis in a developing country. Vaccine. 2016 Dec 7;34[50]:6223–8.
48. Saso A, Kampmann B. Maternal Immunization: Nature Meets Nurture. Front Microbiol. 2020;11.
49. Rosa W, editor. Transforming Our World: The 2030 Agenda for Sustainable Development. In: A New Era in Global Health. New York: Springer Publishing Company; 2017. Available from: http://connect.springerpub.com/lookup/doi/10.1891/9780826190123.ap02
50. Ortiz JR, Neuzil KM, Ahonkhai VI, Gellin BG, Salisbury DM, Read JS, et al. Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings. Vaccine. 2012;30[50]:7134–40.
51. Vizzotti C, Neyro S, Katz N, Juárez MV, Carrega MP, Aquino A, et al. Maternal immunization in Argentina: a storyline from the prospective of a middle income country. Vaccine. 2015;33[47]:6413–9.
52. Swamy GK, Metz TD, Edwards KM, Soper DE, Beigi RH, Campbell JD, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in pregnant women and their infants: Results from a randomized placebo-controlled phase II trial. Vaccine. 2020 Oct 14;38[44]:6930–40.
53. Dangor Z, Lala SG, Cutland CL, Koen A, Jose L, Nakwa F, et al. Burden of Invasive Group B Streptococcus Disease and Early Neurological Sequelae in South African Infants. PLoS ONE. 2015 Apr;10[4]:1–13.
54. Shi T, McAllister DA, O'Brien KL, Simoes EA, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. The Lancet. 2017;390[10098]:946–58.
55. Nyiro JU, Bukusi E, Mwaengo D, Walumbe D, Nyaguara A, Nyawanda B, et al. Implications of gestational age at antenatal care attendance on the successful implementation of a maternal respiratory syncytial virus [RSV] vaccine program in coastal Kenya. BMC Public Health. 2020;20[1]:1–11.
56. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Apr 21;0[0]:null.
57. Englund JA. Maternal immunization–Promises and concerns. Elsevier; 2015.
58. de Jongh TE, Gurol–Urganci I, Allen E, Zhu NJ, Atun R. Integration of antenatal care services with health programmes in low–and middle–income countries: systematic review. J Glob Health. 2016;6[1].

59. Valentijn PP, Schepman SM, Opheij W, Bruijnzeels MA. Understanding integrated care: a comprehensive conceptual framework based on the integrative functions of primary care. Int J Integr Care. 2013 Mar 22;13.
60. World Health Organization. WHO consultation on applying surveillance information for evidence based decisions on seasonal influenza vaccine composition and vaccination timing in the tropics and subtropics: Bangkok, Thailand, 26–28 April 2016. Geneva: World Health Organization; 2016. Available from: https://apps.who.int/iris/handle/10665/252613
61. Hardt K, Bonanni P, King S, Santos JI, El-Hodhod M, Zimet GD, et al. Vaccine strategies: Optimising outcomes. Vaccine. 2016;34[52]:6691–9.
62. Kochhar S, Edwards KM, Alvarez AMR, Moro PL, Ortiz JR. Introduction of new vaccines for immunization in pregnancy–programmatic, regulatory, safety and ethical considerations. Vaccine. 2019;37[25]:3267–77.
63. Dawa J, Chaves SS, Nguz AB, Kalani R, Anyango E, Mutie D, et al. Developing a seasonal influenza vaccine recommendation in Kenya: process and challenges faced by the National Immunization Technical Advisory Group [NITAG]. Vaccine. 2019;37[3]:464–72.
64. Fleming JA, Munthali A, Ngwira B, Kadzandira J, Jamili-Phiri M, Ortiz JR, et al. Maternal immunization in Malawi: a mixed methods study of community perceptions, programmatic considerations, and recommendations for future planning. Vaccine. 2019;37[32]:4568–75.
65. Kobayashi M, Schrag SJ, Alderson MR, Madhi SA, Baker CJ, Sobanjo-ter Meulen A, et al. WHO consultation on group B Streptococcus vaccine development: Report from a meeting held on 27-28 April 2016. VACCINE. 2019 Nov 28;37[50, SI]:7307–14.
66. Van Olmen J, Criel B, Van Damme W, Marchal B, Van Belle S, Van Dormael M, et al. Analysing health systems to make them stronger. Antwerp, Belgium: ITGPress; 2010.
67. Sobanjo-ter Meulen A, Munoz FM, Kaslow DC, Klugman KP, Omer SB, Vora P, et al. Maternal interventions vigilance harmonization in low-and middle-income countries: Stakeholder meeting report; Amsterdam, May 1–2, 2018. Vaccine. 2019;37[20]:2643–50.
68. PATH. Advancing RSV maternal immunization: a gap analysis report. Seattle: PATH; 2018;
69. Giles ML, Mason E, Muñoz FM, Moran AC, Lambach P, Merten S, et al. Antenatal care service delivery and factors affecting effective tetanus vaccine coverage in low-and middle-income countries: Results of the Maternal Immunisation and Antenatal Care Situational analysis [MIACSA] project. Vaccine. 2020;38[33]:5278–85.
70. Alvarez AMR, Vilajeliu A, Magariños M, Jauregui B, Guzmán L, Whittembury A, et al. Enablers and barriers of maternal and neonatal immunization programs in Latin America. Vaccine. 2020;
71. Larson Williams A, Mitrovich R, Mwananyanda L, Gill C. Maternal vaccine knowledge in low-and middle-income countries—and why it matters. Hum Vaccines Immunother. 2019;15[2]:283–6.
72. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015 Nov;33[47]:6420–9.
73. Otieno NA, Otiato F, Nyawanda B, Adero M, Wairimu WN, Ouma D, et al. Drivers and barriers of vaccine acceptance among pregnant women in Kenya. Hum Vaccines Immunother. 2020;16[10]:2429–37.
74. Pathirana J, Nkambule J, Black S. Determinants of maternal immunization in developing countries. Vaccine. 2015;33[26]:2971–7.
75. Gauld N, Martin S, Sinclair O, Petousis-Harris H, Dumble F, Grant CC. A qualitative study of views and experiences of women and health care professionals about free maternal vaccinations administered at community pharmacies. Vaccines. 2020;8[2]:152.
76. Allen E, Schellenberg J, Berhanu D, Cousens S, Marchant T. Associations between increased intervention coverage for mothers and newborns and the number and quality of contacts between families and health workers: An analysis of cluster level repeat cross sectional survey data in Ethiopia. PLoS ONE. 2018;13[8].
77. Fleming JA, Munthali A, Ngwira B, Kadzandira J, Jamili-Phiri M, Ortiz JR, et al. Maternal immunization in Malawi: A mixed methods study of community perceptions, programmatic considerations, and recommendations for future planning. Vaccine. 2019 Jul 26;37[32]:4568–75.
78. Gauld N, Martin S, Sinclair O, Petousis-Harris H, Dumble F, Grant CC. A qualitative study of views and experiences of women and health care professionals about free maternal vaccinations administered at community pharmacies. Vaccines. 2020;8[2]. Available from:
79. Groman D, Higgins D, Khan S, Simpson E, Pecenka C, Newhouse L, et al. Lessons learned from the Advancing Maternal Immunization collaboration: identifying evidence gaps for informed respiratory syncytial virus maternal immunization decision-making. Gates Open Res. 2019;3.

80. Mehanna A, Ali MH, Kharboush I. Knowledge and health beliefs of reproductive-age women in Alexandria about tetanus toxoid immunization. J Egypt Public Health Assoc. 2020 Aug 27;95[1]:22.
81. Shakarishvili G, Atun R, Berman P, Hsiao W, Burgess C, Lansang MA. Converging Health Systems Frameworks: Towards A Concepts-to-Actions Roadmap for Health Systems Strengthening in Low and Middle Income Countries. Global Health Gov. 2020;3:2.
82. De Savigny D, Adam T. Systems thinking for health systems strengthening. Geneva:World Health Organization; 2009.
83. Agyepong IA, Kwamie A, Frimpong E, Defor S, Ibrahim A, Aryeetey GC, et al. Spanning maternal, newborn and child health [MNCH] and health systems research boundaries: conducive and limiting health systems factors to improving MNCH outcomes in West Africa. Health Res Policy Syst. 2017 Jul 12;15[1]:54.
84. World Health Organization. Strategies toward ending preventable maternal mortality [EPMM] Geneva: World Health Organization. Available from: http://www.who.int/reproductivehealth/topics/maternal_perinatal/epmm/en/
85. Amponsah-Dacosta E, Kagina BM, Olivier J. Health systems constraints and facilitators of human papillomavirus immunization programmes in sub-Saharan Africa: a systematic review. Health Policy Plan. 2020 May 3;czaa017.
86. Ferrer HB, Trotter C, Hickman M, Audrey S. Barriers and facilitators to HPV vaccination of young women in high-income countries: a qualitative systematic review and evidence synthesis. BMC Public Health. 2014 Jul 9;14[1]:700.
87. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Methodol. 2005 Feb 1;8[1]:19–32.
88. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth. 2020 Oct;18[10]:2119–26.
89. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews [PRISMA-ScR]: checklist and explanation. Ann Intern Med. 2018;169[7]:467–73.
90. Kinney M, Walugembe D, Wanduru P, Waiswa P, George A. Maternal and perinatal death surveillance and response in low- and middle-income countries: a scoping review of implementation factors. Health Policy Plan. 2021 Mar 13;36.
91. Maitra C, Hodge A, Jimenez Soto E. A scoping review of cost benefit analysis in reproductive, maternal, newborn and child health: What we know and what are the gaps? Health Policy Plan. 2016 Dec;31[10]:1530–47.
92. Basera TJ, Schmitz K, Price J, Willcox M, Bosire EN, Ajuwon A, et al. Community surveillance and response to maternal and child deaths in low- and middle-income countries: A scoping review. PLOS ONE. 2021 Mar 16;16[3]:e0248143.
93. Peterson J, Pearce PF, Ferguson LA, Langford CA. Understanding scoping reviews: Definition, purpose, and process. J Am Assoc Nurse Pract. 2017;29[1]:12–6.
94. Brice R. CASP CHECKLISTS [Internet]. CASP - Critical Appraisal Skills Programme. [cited 2021 May 17]. Available from: https://casp-uk.net/casp-tools-checklists/
95. Nagata JM, Hernández-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. Social determinants of health and seasonal influenza vaccination in adults≥65 years: a systematic review of qualitative and quantitative data. BMC Public Health. 2013 Apr 25;13[1]:388.
96. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016 Dec;5[1]:210.
97. Pluye P, Robert E, Cargo M, Bartlett G, O'cathain A, Griffiths F, et al. Proposal: A mixed methods appraisal tool for systematic mixed studies reviews. Montr McGill Univ. 2011;2:1–8.
98. Sezgin D, O'Donovan M, Cornally N, Liew A, O'Caoimh R. Defining frailty for healthcare practice and research: A qualitative systematic review with thematic analysis. Int J Nurs Stud. 2019 Apr 1;92:16–26.
99. Perman S, Turner S, Ramsay AIG, Baim-Lance A, Utley M, Fulop NJ. School-based vaccination programmes: a systematic review of the evidence on Organization and delivery in high income countries. BMC Public Health. 2017 Mar 14;17[1]:252.
100. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8[1]:1–10.
101. Vaismoradi M, Snelgrove S. Theme in Qualitative Content Analysis and Thematic Analysis. Forum Qual Sozialforschung Forum Qual Soc Res. 2019 Sep 26;20[3].
102. Malterud K. Qualitative research: standards, challenges, and guidelines. The lancet. 2001;358[9280]:483–8.

103. Johnson JL, Adkins D, Chauvin S. A Review of the Quality Indicators of Rigor in Qualitative Research. Am J Pharm Educ. 2020 Jan;84[1].
104. Sandelowski M, Leeman J. Writing Usable Qualitative Health Research Findings. Qual Health Res. 2012 Oct 1;22[10]:1404–13.

Part B: Journal Manuscript

Health systems determinants of delivery and uptake of maternal vaccines in low and middle-income countries: A qualitative systematic review

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Abstract

Background: Maternal vaccination has been widely recognised as a key component of the comprehensive package of ANC aimed at improving maternal and child health. Low- and middle-income countries are currently falling short of maternal and neonatal mortality targets, with gaps in quality health services and a high burden of vaccine-preventable diseases. Strategies toward ending preventable maternal mortality necessitates a health systems approach to respond to maternal health. This review explored the health systems determinants of delivery and uptake of maternal vaccines in low-and middle-income countries.

Methods: A qualitative systematic review of literature published between 2009 and 2021 from low- and middle-income countries was conducted. Six electronic databases were searched and PRISMA guidelines for systematic reviews were followed for record identification. Thematic analysis was conducted to identify key themes in the literature and interpreted within a hybrid health systems and immunisation conceptual framing that explores the interacting systems determinants that influence maternal vaccination outcomes.

Results: The database search yielded 1242 records, of which 47 were included, covering 28 LMICs. Most studies were from the South America region (28/47) and included pregnant women as the primary population study group (38/47). Included literature explored mainly Influenza (25/47) and Tetanus toxoid (18/47) vaccines during pregnancy. Systems hardware including lack of clear policy guidelines, ineffective cold-chain management and limited reporting and monitoring systems are barriers to vaccine delivery. Systems software including healthcare provider recommendations, high-level of trust and higher levels of maternal education are enablers to maternal vaccine uptake.

Conclusions: This review places a health system's lens on maternal vaccination, highlighting complexities of how systems hardware and software interact to produce maternal and neonatal health outcomes. Recommendations are made for health policy-makers to address identified barriers and enablers to vaccine delivery and uptake and for future research agendas. This review study contributes to the increasing body of work in MCH that can inform future introduction of new maternal vaccines in LMICs.

Key words: Vaccine, Pregnancy, Maternal Health, Health System, Low- and Middle- Income Countries

[9] See Appendix F for journal manuscript submission guidelines.

[10] For the purpose of this thesis, the student is the first and sole author of this systematic review.

Background

Pregnant women are more susceptible to vaccine-preventable diseases (VPDs) with more severe adverse outcomes and mortality rates compared to the general population [1]. Vaccination during pregnancy ('maternal vaccination') has been widely recognised as a key component of the comprehensive package of antenatal care (ANC) aimed at improving maternal and child health (MCH). This is because maternal vaccines not only protect pregnant women against VPDs like tetanus, influenza and pertussis, but also protect neonates against infection or disease severity in their first weeks of life during the most vulnerable period [2].

Globally, maternal tetanus vaccination programmes have been considered a major public health success in reducing the burden of the disease since the initiation of the global Maternal and Neonatal Tetanus Elimination (MNTE) programme in 1989. This MNTE programme reduced neonatal tetanus by 96% in targeted countries [3] and has since emerged as a platform for introduction of new and underutilized maternal vaccines [4,5]. Seasonal maternal influenza vaccination has been recommended by the WHO since 2005 [6]. After the 2009 H1N1 pandemic, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunisation (SAGE) further recommended that pregnant women be prioritized for seasonal influenza vaccination as a high-risk group in 2012 [6,7]. Following this recommendation, wide acceptance of maternal flu vaccinations has contributed to a shift in acceptance of other maternal vaccines in many countries [7]. The diphtheria, tetanus and pertussis combination vaccine (Tdap) was first recommended for pregnant women by WHO in 2015 [8,9]. Additional vaccines recommended for administration during pregnancy in endemic countries or during outbreaks include the meningococcal A, yellow fever, cholera, Ebola, Hepatitis E, rabies and tick-borne encephalitis vaccines [2,8]. Vaccines against Group B streptococcal disease (GBS) and respiratory syncytial virus (RSV) are currently in late-stage clinical trials and have yet to be licensed for use in pregnant women [9,10]. In addition to vaccines against GBS and RSV, recent COVID-19 vaccines have also been targeted for pregnant women, with preliminary data indicating vaccine safety and efficacy in preventing disease and adverse outcomes [11]. Pregnant women are classified in the high-priority use group by WHO SAGE Roadmap for Prioritizing use of COVID-19 vaccines, and by late 2021, 176 countries had policies for COVID-19 vaccination during pregnancy [12].

It is estimated that 89% of pregnancies worldwide occur in low- and middle income countries (LMICs) [13]. Despite the success of global efforts such as MNTE, 18 LMICs have yet to eliminate neonatal tetanus [23]. Additionally, vaccine coverage continues to vary between countries, with some LMICs reporting coverage as low as 11% for influenza [14], while high-income countries (HICs) report coverage over 60% in pregnant women [15]. This is concerning considering the high burden of VPDs in LMICs, and the fact that neonatal and maternal mortality rates have declined the slowest in LMICs compared to HICs over the last decade [1,16].

Maternal vaccination efforts fall at the intersection of maternal healthcare services and routine immunisation programmes, usually embedded in broader health services. Despite the near-universal successes of national Expanded Programme on Immunisation (EPI), programmatic challenges and systems- level challenges to routine immunisation remain [17]. Current maternal vaccination programmes in LMICs are characterised by various factors that affect delivery (on the vaccine supply side) and uptake (on the vaccine demand side) [18]. Barriers to implementation of maternal health interventions have been shown to be shared across LMIC contexts and include a limited health workforce, shortage of health resources, varied willingness of pregnant women to accept vaccines, inability to collect high-quality data due to staff shortage, inadequate funding and infrastructure, and

policy implementation issues [17]. The substantial cost associated with developing new maternal vaccine delivery platforms creates an additional barrier to vaccine programme implementation in LMICs where several health programmes compete for limited budgets and health infrastructure [18]. Considering the shared health systems barriers in LMICs, understanding the complexities of maternal vaccinations in LMICs can guide the implementation of new and under-utilised vaccines towards strengthening MCH.

Current global interests aim to understand and address the barriers to effective maternal vaccination programmes in LMICs. Considering the urgency to expand the reach of new and under-utilised vaccines among pregnant women, there is a need to strengthen the evidence-base within this field. The current COVID-19 pandemic and wide-scale roll-out of COVID-19 vaccines has further highlighted the need to apply a health systems lens to delivery and uptake of maternal vaccines. It is with this in mind that a qualitative systematic review study was conducted to explore the question: *what are the health systems determinants of maternal vaccine delivery and uptake in LMICs?* Primary objectives of the review were to describe the health systems determinants of the delivery and uptake of maternal vaccines in LMICs and improve our understanding of how these determinants may serve as barriers or enablers to effective maternal vaccination programmes in LMICs. Drawing on the findings of this review, policy- and practice- relevant recommendations are proposed to support current and future maternal vaccination programmes in LMICs.

Methods

An exploratory systematic review study was conducted in two phases: a scoping review followed by a qualitative systematic review. The study was conducted in line with the PRIMSA Preferred Reporting Items for Systematic Reviews and Meta-analysis [19] (Figure 1).

Search strategy

Guided by a search strategy (Appendix A) informed by an initial broad scoping review, relevant literature sources were sought through electronic databases, namely, PubMed, Scopus (Medline and Embase), Web of Science, WHO Institutional Repository for Information Sharing, and EBSCOHost (Academic Premier, Africa Wide information, CINAHL, Health Source Nursing Academic, Medline, APA Psych, and APA PsycInfo). A supplementary search was conducted in Google Scholar to identify records that other electronic databases may have missed.

Eligibility criteria

Evidence sources were only included if they met the following criteria: involved human participants in quantitative, qualitative and mixed-methods empirical studies; primary studies conducted in LMICs; published in English; and explore maternal vaccination as a subtheme or involved pregnant women as a subset of a population involved in a vaccine-related study. Searches were restricted to literature published between 2009 until date of search (2021), an identified period in the preceding scoping review as a crucial stage in the development of research within the field of maternal vaccination in LMICs. Studies were deemed ineligible if they met the following criteria did not directly measure or explore maternal vaccination; measured only epidemiologically outcomes in relation to vaccine products; or were conducted in HICs.

Study selection

Literature from search yields were exported into Zotero (v.61) reference manager, with duplicates removed and titles, abstracts and full texts screened for inclusion using the Rayyaan systematic review

management online platform [22]. Duplicate records from search yields were detected and deleted. Titles and abstracts of records were then screened according to above criteria. Review of full-text was conducted to screen for relevance to the aims of this review and stipulated inclusion/exclusion criteria. This study is limited to peer-reviewed records.

Study appraisal

The quality of empirical quantitative, qualitative and mixed-methods studies was appraised during review of relevant full-text records, using the Joanna Briggs Institute Critical Appraisal Checklists and the Mixed Methods Appraisal Tool [23,24]. Studies considered to be 'low quality' by these checklists were not automatically excluded from the research, particularly if findings were relevant, unless the study design and/or results were considered unreliable and there was minimal congruity between research philosophy, aims and methods.

Data extraction

Data were extracted by the primary author from the included studies guided by a data extraction sheet designed for this review, informed by the scoping review (Appendix B, Appendix E). The core variables sought for extraction were identified as part of scoping review exercise and included findings on *decision-making*, *financing, implementation and delivery, health workforce and information systems* as they pertained to maternal vaccination programmes in LMICs.

Conceptual framework

Exploring health systems elements that contribute to maternal health outcomes, in the context of vaccination programmes, requires an understanding of the interaction among the delivery of maternal healthcare services, vaccination programmes and health systems. Various conceptual frameworks for health systems research exist and have evolved over time, ranging from descriptive and analytical to deterministic and predictive [25]. Shared health systems critical functions, otherwise classically known as "building blocks", include: service delivery, health workforce, health information, technologies and commodities, demand generation, financing and governance [23,24].

A framework that describes the 'health systems shelter' has been applied for exploration of MCH has also been proposed previously, and offers a useful basis for unpacking systems complexities in terms of health systems hardware, software and values [26]. While systems hardware refers to tangible systems building blocks such as resources and financing, software refers to people, processes, networks and behaviours that drive systems [28]. Complementing this framework is a previously published logic model that integrates health systems critical functions with national immunisation programme components of: (i) policy, standards, and guidelines, (ii) governance, Organization, and management, (iii) human resources for health, (iv) vaccine cold-chain and logistics, (v) service delivery, (vi) communication and community partnerships, (vii) data generation and (viii) sustainable financing [20,28]. Logical frameworks specifically addressing analysis of immunisation services in the context of health systems have been applied to LMIC contexts, [29]. Considering the burden of VPDs and maternal mortality in LMICs, the WHO's Strategies Toward Ending Preventable Maternal Mortality points to a systems approach to MCH in terms of hard- and software [27].

Drawing on these previous frameworks, a conceptual framing for this systematic review was applied to interpretation of the findings when describing, analysing and making sense of how health systems hardware, software and context interact as barriers or enablers to influence maternal vaccination

delivery and uptake. The description of health systems determinants of delivery and uptake as hard- and software allows for understanding of how and why determinants interact to produce maternal vaccination outcomes [26]. The capacity of health systems to support maternal vaccination programmes in LMICs is not comprehensively captured in the published literature, necessitating the development of a new conceptual framing to address this gap. In this framing, health systems are interpreted by the context in which they exist, indicating how service delivery of vaccines during pregnancy falls at the intersection of vaccination programmes and maternal healthcare, incorporating elements of the 'health systems shelter' framing by Agyepong et al. [27] and the logic framework for health systems analysis of national immunisation programmes [29]. For the purpose for this review, 'health systems determinants' refers to any factors relating directly to health systems, including but not limited to the system building blocks of service delivery, human resources, information systems, medical products, financing and/or leadership and governance [26].

Data synthesis

Descriptive and analytical data were extracted from studies, regardless of significance. Results from qualitative studies and data helped contextualise quantitative data through identification of concepts using thematic analysis [30]. Thematic inductive analysis was applied to elicit meaning of data extracted, as has been applied in previous reviews on vaccine uptake and delivery and to develop themes [31–33]. Themes were described through complex interpretation of the extracted data, to reveal or identify underlying complexities at the intersection of health systems and maternal vaccination programmes. Building on the descriptive themes, analytical themes allow application of the conceptual framing to inform the evidence synthesis of this review. This conceptual framing enables abovementioned descriptive themes of delivery and uptake to be interpreted and understood through the barriers and enables of systems hardware and software, within certain contexts.

Results

1,242 records were identified through the electronic database search. Once duplicates were removed and titles and abstracts were screened, 73 relevant records were identified. Upon full-text review and appraisal, 26 records were excluded and a total of 47 articles were included in the final systematic review for data extraction (Figure 1). Articles excluded after full-text review were either of low methodological quality, had misleading abstracts or did not explicitly investigate vaccines during pregnancy. All literature included were published between 2012 and 2021.

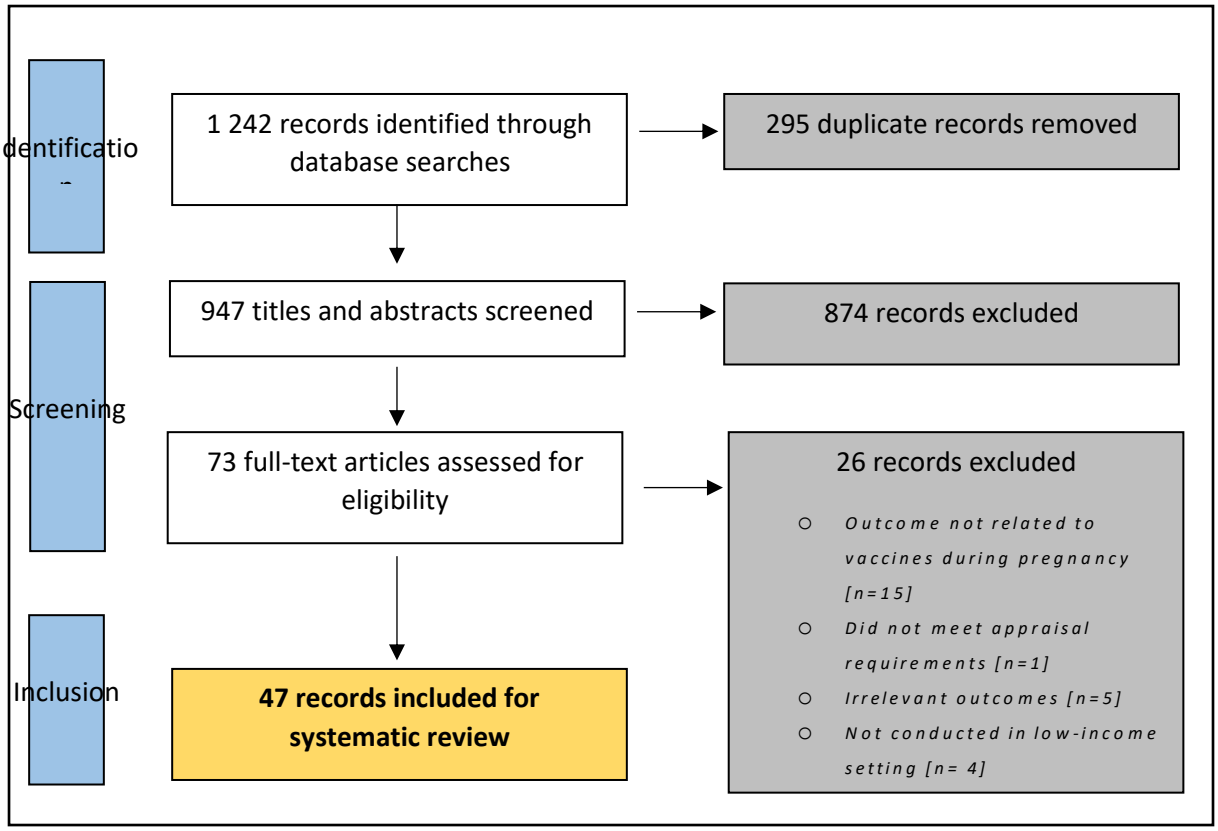

Figure 1 PRISMA flow diagram for identification, screening and inclusion of literature for qualitative systematic review. Note: supplementary searches using Google Scholar yielded no additional studies. [19] *[Source, author]*

Characteristics of included studies and study participants

All records included in this review were published, peer-reviewed articles, the majority (31/47) of which were qualitative or quantitative cross-sectional studies. Of the remaining records, six adopted a mixed-methods study design, one was a randomized control trial, and one a cohort study. Overall, the quality of included studies was acceptable, although articles which reported using qualitative designs tended to omit acknowledgement of authors' reflexivity and positionality within the study.

The distribution of literature by country and vaccine of focus is presented in Figure 2. In total, 28 LMICs were represented in the included literature, with studies from Kenya, Tanzania, South Africa, Malawi, Ivory Coast, Sierra Leone, Zambia, Senegal, The Gambia, India, Argentina, Mexico, Brazil, Peru, Honduras, Chile, Paraguay, Uruguay, El Salvador, Nicaragua, China, Thailand, Taiwan, Iran, Indonesia, Malaysia, Vietnam and Morocco. Regionally, South American countries predominated the evidence-base on maternal vaccination (25/47), with a notable gap in evidence from Central and North Africa, Eastern Europe and the Eastern Mediterranean regions.

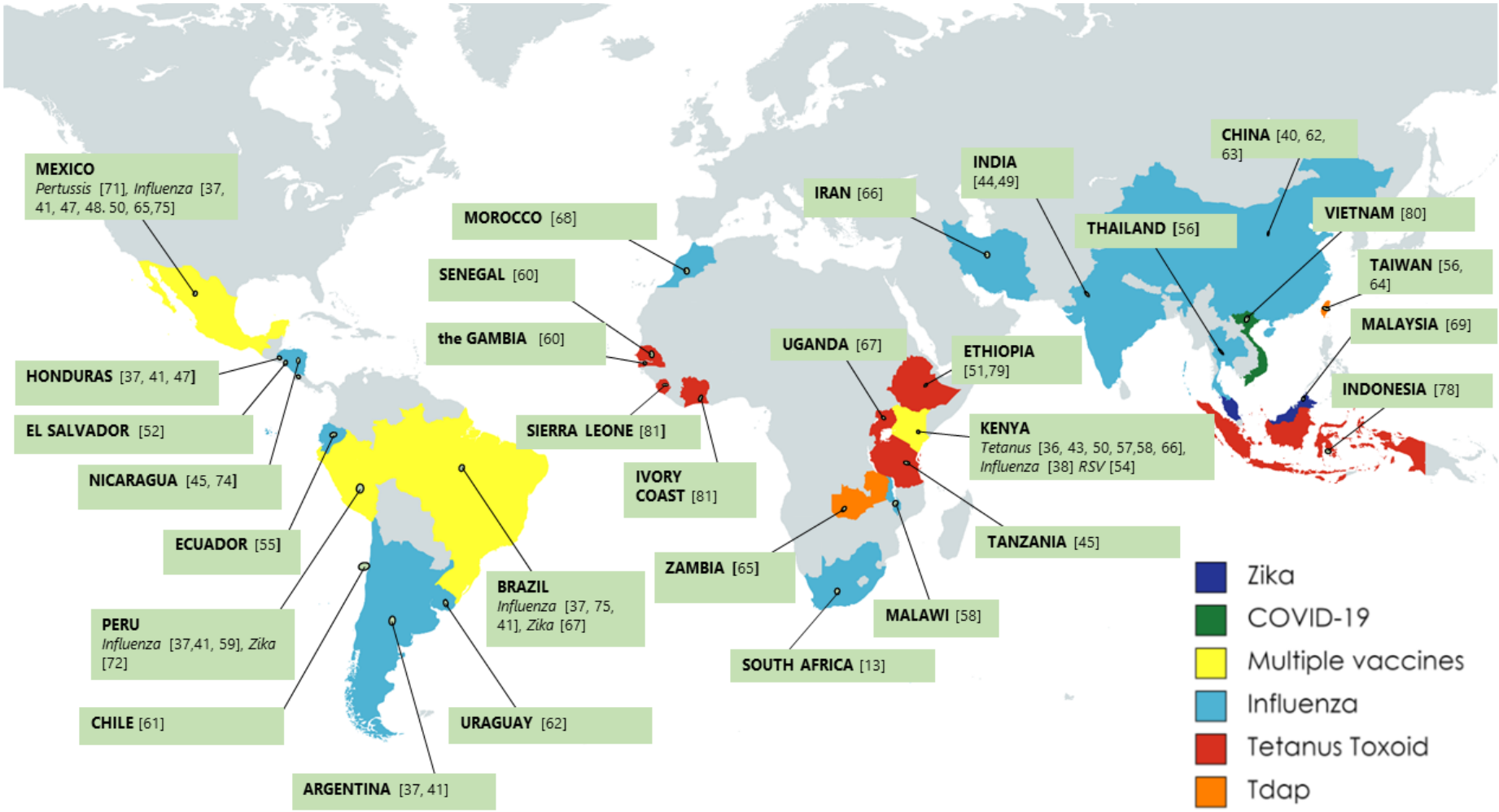

Figure 2 Geographical distribution of included studies, by vaccine type. References to relevant literature are cited in square brackets. Multiple vaccines refer to studies investigating administration of more than one maternal vaccine type. This figure refers only to the maternal vaccines reported in included studies and does not reflect the entirety of vaccines available in the countries represented here [Source; author].

With regards to the types of vaccines studies, the literature appears to be dominated by investigations focused on Tetanus Toxoid (18/47) and influenza (25/47) vaccines administered during pregnancy (Figure 3). The remainder of studies focused on the Zika virus vaccine (3/47); the Tetanus, Diphtheria and pertussis (Tdap) vaccine (2/47); the COVID-19 vaccine (1/47); the pertussis vaccine (1/47) and maternal vaccines (5/47) in general without specific focus on any one vaccine type. Several studies investigated administration of more than a single vaccine type.

The following population groups participated in the studies included in this review: pregnant women (30/47); community members (14/47); healthcare providers ranging from community health workers to obstetricians (11/47); and policy-makers (4/47) (Table 1). Special population groups such as migrants, or high-risk groups such as pregnant women or women of child-bearing age living with HIV/AIDS were not represented. Where healthcare providers are concerned, a heavy focus on public sector providers was noted, except for a small proportion of studies that explored providers' influence on maternal vaccine delivery and uptake in the private health sector (8/47). Also worth noting was the absence of studies that explored the role of other key health actors, such as community leaders, traditional healers, faith-based actors and non-profit/non-governmental providers in maternal vaccination programmes.

Table 1 Representation of participants involved in included studies on maternal vaccination in LMICs

Population group	Description	Total studies (N=47)	Total participants (n)
Pregnant women	Women pregnant at time of study	30	79 367
Community members	Women of childbearing age, Partners of pregnant women, family, broader community	14	56 210
Healthcare providers	Obstetricians, physicians, nurses, community health workers	11	1 169
Policy-makers and health leadership	Technical advisory group members, health ministry, facility managers, researchers	4	153

[Source, author].

Health systems determinants of maternal vaccine delivery[11]

Policy, leadership and governance emerged as one of the determinants of delivery of maternal vaccines in LMICs (Table 2). Of the four studies that explored experiences of policy-makers and health leadership across multiple LMICs, two found that the majority of countries studied had a maternal vaccine policy or guideline in place [34,35]. In Kenya [36], Argentina, Brazil, Honduras, Mexico and Peru [35], the formation and dissemination for such policies and guidelines were experienced as being predominantly of a top-down approach, as described by policy- and decision-makers. This approach to policy formulation and dissemination served as a barrier to effective delivery of maternal vaccines, resulting in negative effects as seen in Thailand [37] and China [34,35] where healthcare providers reported experiencing poor communication on appropriate maternal vaccine guidelines from their national governments to facility-level staff. At facility level, the lack of clearly communicated policies

[11] For the purpose of this review, 'maternal vaccine delivery' refers to supply-side factors that affect optimal provision of vaccines

and guidelines on maternal vaccination resulted in critical vaccine implementation gaps[12]. In Brazil [36] and Kenya [37], adoption of a top-down approach to policy formulation on maternal vaccination excluded consultation with relevant stakeholders such as primary care clinicians and community-based Organizations. Reliance on guidelines from the WHO and Centers for Disease Control and Prevention in place of context-specific national guidelines was reported in Taiwan, highlighting the lack of a co-ordinated, contextually-appropriate approach to vaccination policy development [39]. The experience in Argentina, Brazil, Honduras, Mexico and Peru was similar, in that the lack of co-ordination was evident in the discrepancies in vaccine delivery guidelines for healthcare providers working in the public, private and informal health sectors [40]. An in-depth study of Kenya's National Immunisation Technical Advisory Group (NITAG) revealed that their maternal vaccination policy borrowed from vaccine policies of other countries [36], which could be categorized as a systems hardware barrier to maternal vaccine delivery.

Further hardware determinants were described in terms availability of sustainable financing mechanisms to support maternal vaccination programmes. In South America [Honduras, Brazil, Mexico, Peru and Argentina], the use of pooled procurement funding mechanisms earmarked for implementation of maternal vaccines was identified as a health systems enabler of effective vaccine delivery [37]. Most countries in this region were reported to rely on domestic funding, with the exception of Honduras which receives supplementary GAVI (Vaccine Alliance) funding for procurement of maternal vaccines [36]. While Thailand reported health insurance as being a contributor to funding ANC [39], a multi-country study indicated that the majority of LMICs rely more on patient out-of-pocket payments than health insurance for ANC including maternal vaccination services (Table 2) [41]. Funding sources also play a role in vaccine decision-making and formulation of recommendation needed to guide the delivery of maternal vaccines in LMICs. In Kenya, decision-makers reported that reliance on international and donor-funding was a key enabler as the availability of funding supported the feasibility of recommendations [37]. On the other hand, lack of budgets at facility-level was identified as a barrier to providing educational resource materials on vaccination to healthcare providers and pregnant women in Kenya [40].

[12] For the purposes of this review, implementation refers to vaccine distribution, cold-chain management, coverage, utilisation and availability of platforms for delivery of maternal vaccines.

Table 2 Descriptive themes on health systems determinants of maternal vaccine delivery in LMICs

	Descriptive themes relating to maternal vaccine delivery (supply-side)	
Health systems determinant	**➔ Enablers of vaccine delivery**	**⟶ Barriers to vaccine delivery**
Policy, leadership and governance		Top-down policy formulation and implementation omits key stakeholder engagement [Brazil, Kenya, Thailand] Lack of co-ordinated national approach to vaccine policy formulation leads to reliance on international guidelines without consideration for local contexts (Taiwan, Argentina, Brazil, Honduras, Mexico, Peru) Lack of communication from leadership to facility-based healthcare providers on maternal vaccination guidelines (China, Thailand, Kenya)
Financing	Pooled procurement funding for vaccine delivery services (Brazil, Mexico, Honduras, Peru) Reliance on donor funding informs feasibility of vaccine policy recommendations at national level (Kenya)	Reliance on out-of-pocket payments negatively affects pregnant women's access to lifesaving vaccines Weak facility-level budget compromises vaccine education and awareness efforts (Kenya)
Implementation: vaccine products and service delivery	Increased ANC visits (Sierra Leone, Ethiopia, India)	Guideline discrepancies between public and private providers (Brazil, Mexico, Honduras, Peru) Vaccine stock-outs (South Africa, Kenya, Brazil) Lack of fuel, electrical power and transport lead to vaccine shortages and impact cold-chain management (Taiwan, Kenya)
Health workforce	Training of nurses supports maternal vaccine delivery (Honduras, Brazil, Peru)	Staff shortages due to strikes or high turnover (Kenya, El Salvador) Heavy staff workloads (Nicaragua, India) Lack of clinician training and professional development (Honduras, Brazil, Peru)
Information systems	Reliance on ANC booklets/vaccine cards	Lack of formal monitoring and reporting structures (Malawi, South Africa) Lack of public/private provider co-ordination (Thailand, Kenya) Lack of electronic health records
Context	Strong political will for maternal vaccines (Brazil) Lack of political interference at facility-level (Kenya)	Gangsterism and crime (El Salvador)

[Source, author].

Shortage and unavailability of maternal vaccines was another prominent theme in the evidence-base (Table 2). In most LMICs, procurement of vaccines was predominantly through the EPI, with the exception of Honduras, Brazil, Mexico and Peru where vaccines were procured through ANC or MCH services [34]. Stockouts of vaccines emerged as a systems hardware barrier to delivering vaccines to pregnant women in South Africa [14], Kenya [40] and India [41] (Table 2). Compounding this situation further were reports of the intricate cold-chain management and storage requirements which facilities in some LMICs found difficult to maintain, for various reasons. In Kenya for example, improper vaccine cold-chain resource management was quoted as being a result of their national devolution process [41], whereas in Tanzania cold-chain limitations were the direct result of power cuts affected by seasonal weather patterns and delayed procurement of fuels like gas [43]. Furthermore, in Kenya, limited availability of transport for vaccines from county depots to facilities with proper cold storage mechanisms was a barrier to effective vaccine delivery [52]. This meant that despite willingness to be vaccinated, pregnant women reported the limited availability of vaccines to be an issue, impacting on the quality of care received. The manner which certain maternal vaccination programmes were implemented also posed additional challenges as seen in the South American region where seasonal influenza campaigns are restricted to certain months of the year, limiting delivery and subsequent uptake [36,40,47,48].

Eight studies conducted in Kenya [40], India [41,46], Thailand [36], Brazil [47], Ethiopia [48], and El Salvador [49], explored maternal vaccine delivery and uptake in the private health sector. Overall, these studies underscored the existence of weak co-ordination between public and private health sectors, as well as national immunisation and ANC and/or MCH programs where maternal vaccine delivery is concerned. In both public and private health contexts, delivery of maternal vaccines varied across platforms and facilities, with maternal vaccines being delivered at primary health clinics, antenatal clinics and hospitals. Two main modes of delivery of maternal vaccines were reported in the literature, namely, the EPI and ANC. The frequency of attendance to ANC varied by country and context. A key enabler to higher vaccine coverage, in the case of tetanus and influenza vaccines, was found to be increased frequency of antenatal visits in LMICs like Sierra Leone, Ethiopia and India (Table 2) [41,46,51]. This positive association was reported across countries, regardless of vaccination timing during pregnancy, although countries such as Kenya and Ecuador reported delivery of vaccines to pregnant women for the first time during second and third trimesters [52,53].

Experiences of healthcare providers, ranging from facility nurses to hospital-based obstetricians, further highlight systems barriers to vaccine delivery during pregnancy. Staff shortages and a lack of skilled human resources for health emerged as a prominent theme in this regards, augmented by heavy workloads at facilities and in some cases, high staff turnover [49,54]. In Kenya, delivery of vaccines to pregnant women was hindered by health worker strikes [55]. Health worker shortages and workloads were found to contribute to long waiting times for pregnant women to receive vaccines, serving as barriers to vaccine delivery in India, Mexico and Brazil [38,50]. Healthcare providers in Nicaragua and India described initiatives such as vaccine administration to women in waiting lines at antenatal clinics, as an attempt to overcome such barriers and facilitate adequate coverage [47,53]. Adequate knowledge about VPDs and vaccine effectiveness demonstrated by healthcare providers was strongly associated with recommendations to pregnant women, across multiple contexts [39,49,60]. In countries where healthcare providers fuelled vaccine hesitancy or rather promoted non-pharmaceutical interventions for VPDs, knowledge on the diseases and vaccine safety was generally

reported to be low [36]. This was particularly highlighted amongst physicians, who are somewhat neglected in terms of training and capacitation around maternal vaccination as nurses are generally the focus of continuing professional education programmes [14,38,57]. Willingness of healthcare providers to recommended maternal vaccines was low in China, although increased willingness to recommend these vaccines was associated with younger age of healthcare professionals and higher professional title [57]. Skepticism around maternal vaccines and unaddressed concerns about their safety and efficacy among healthcare providers was a key theme across relevant investigations from China [57]. It has been suggested that this lack of vaccine endorsement among healthcare providers stems from a lack of local guidelines, emphasising the dynamic interaction between health systems determinants of maternal vaccine delivery (Figure 2) [35,57,58]. These gaps in communication delay delivery and compromise adequate vaccine coverage in pregnant women, due to irregular updates to national guidelines. As such, providers in Kenya and China reported relying on regular updates on maternal vaccines through national bulletins, and in some cases, peers and colleagues [59,60].

A key health systems determinant of maternal vaccination delivery in LMICs is the health information and reporting systems that countries employ. In this review, this theme was mainly explored at facility-level, with experiences of using vaccination cards and ANC booklets [52,55]. Lack of accurate reporting of vaccine coverage has been attributed to the reliance on physical vaccination cards or ANC booklets that are frequently misplaced, contributing to challenges in monitoring of subsequent vaccine doses administered [as is required for the Tdap and Tetanus vaccines] [54,65]. In the absence of any records, this also meant that healthcare providers often relied on patient recall of prior doses administered [54]. Monitoring processes and systems were explored in two studies conducted in Malawi and South America. Notably in both studies, there was a lack of formal reporting structures for Adverse Events Following Immunization (AEFI) [14,38]. In studies that explored delivery by both public and private health sectors, it was highlighted that information sharing between private and public facilities was non-existent, subsequently revealing a lack in co-ordination between sectors as a barrier to sustainable maternal vaccination efforts [36,47,49,61]. This relates specifically to a persistent lack of strong information systems to monitor vaccine rollout and coverage amongst pregnant women. Ultimately, the reliance on systems hardware such as physical ANC records and vaccination cards, in place of coordinated electronic tracking systems, serves as a barrier to effective service delivery.

Finally, it is important to address the role local contextual determinants on the delivery of vaccines to pregnant women in LMICs. Contextual influences on maternal vaccine delivery identified in the studies included in this review highlight strong political will as an enabler to maternal vaccine policy implementation. This was described as a key factor in maternal vaccine decision-making by health leadership in Brazil [34]. In Kenya, healthcare providers reported that local political landscape did not interfere with vaccine delivery at facility-level [43]. Notably, gangsterism and violent crime served as a prominent contextual barrier to procurement and delivery of maternal vaccines in El Salvador (Table 2) [49].

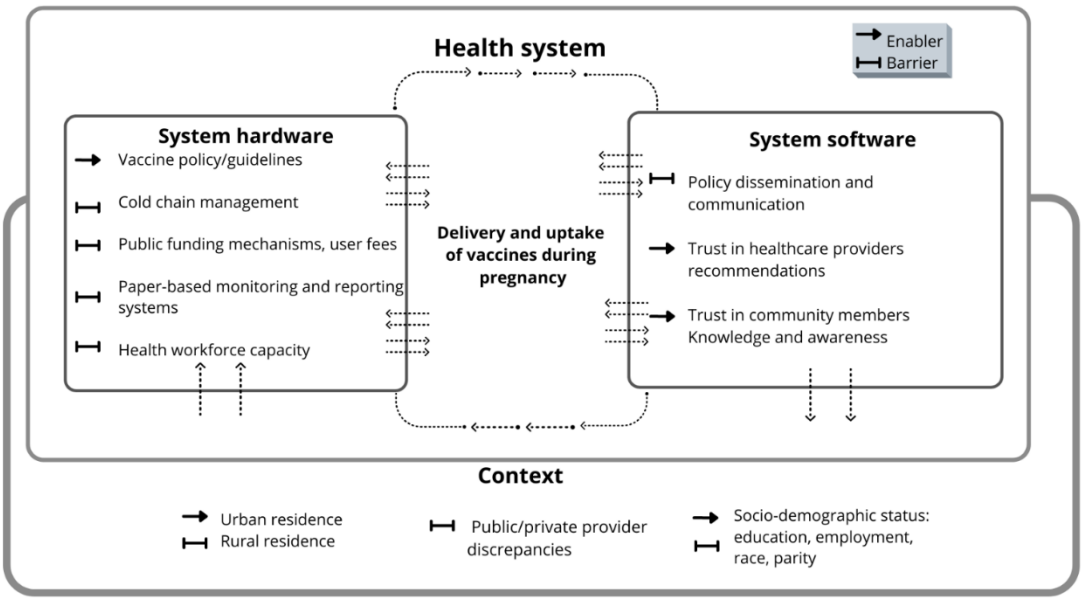

Figure 3 Conceptual framing of health systems determinants of delivery and uptake of maternal vaccines in LMICs *[Source, author].*

Health systems determinants of uptake of maternal vaccines [13]

Factors influencing individual decision-making processes are a key determinant in whether pregnant women will accept lifesaving vaccines. In all 47 studies included in this review, the role of spouses, relatives and community members as major influencers for pregnant women in terms of their willingness to accept vaccines was addressed [38,48,58,59,62–64]. The most influential factor identified was the recommendation of healthcare providers to pregnant women, which leverages the elements of trust in the health system that almost all women and community members expressed across the literature [38,61,65–67]. Healthcare provider recommendations were the driving factor for vaccine uptake during pregnancy in LMICs like Ecuador [77] and Mexico (Table 3) [78], and in Peru where maternal knowledge of vaccines during pregnancy was low and uptake was reliant on provider recommendations [69]. In Nicaragua, maternal socio-demographic factors such as age, ethnicity and employment status were reportedly not associated with vaccine uptake but rather uptake was entirely dependent on recommendations by healthcare providers [70,71]. In Kenya, recommendations came solely from ANC healthcare providers [43]. These healthcare provider recommendations thus serve as systems software enablers of maternal vaccine uptake [Figure 2]. This theme on trust as an enabler to uptake extended to national and local government for pregnant women in Kenya, where they expressed trust in government to only recommend vaccines that are safe and effective [66]. In some LMICs, the unstable political context had jeopardised this trust, and women viewed vaccine policies as control mechanisms motivated by political and/or financial gain, as was demonstrated with the maternal influenza vaccination campaign in Morocco during the H1N1 pandemic (Table 3) [65].

[13] For the purposes of this review, uptake refers to the receipt, acceptance and utilization of vaccination services by a pregnant women and women of childbearing age.

Table 3 Descriptive themes for on health systems determinants of uptake of maternal vaccines in LMICs

	Descriptive themes relating to maternal vaccine delivery (demand-side)	
Health systems determinant	➔ **Enablers of vaccine uptake**	⟞ **Barriers to vaccine uptake**
Policy, leadership and governance	High level of trust in political governance (Kenya, Ethiopia)	Low level of trust in political governance (Morocco)
Decision-making	Health care provider recommendations High level of trust in healthcare providers	Media sources fuel mistrust (Brazil)
Financing	Out-of-pocket payments associated with social standing by spouses (Malawi)	Out-of-pocket payments User fees for ANC services
Implementation: access		Punitive approach to missed ANC appointments (Malawi)
Health workforce	Education and awareness of maternal vaccines provided by healthcare providers	Low level of trust in healthcare providers due to previous negative experience (Ethiopia, Brazil)
Information systems		Reliance on maternal recall in place of patient records
Context	Higher education level of pregnant women Rural residency (Indonesia) Urban residency (Kenya)	Higher education level of pregnant women (Kenya) Rural residence Increased distance travelled to facilities Belonging to a religious group Ethiopia, Senegal) Maternal employment – employers do grant time off work to access ANC including vaccination (El Salvador)

[Source, author].

In the eight studies that explored pregnant women's access to maternal vaccination in Kenya [49,52], Brazil [44,70,71], El Salvador [72], Ethiopia [48]] and Uganda [63], it was evident that disparities in access existed between services provided by the public versus the private health sectors. The public sector was consistently reported to administer vaccines during pregnancy free-of-charge. However, not all countries offer free antenatal services, and thus services provided during an antenatal visit might require out-of-pocket payment even if the vaccine administered during that same visit was free, as was observed in Thailand [56]. Also notable were the experiences in the private healthcare sector, where pregnant women tended to access ANC through the private sector but would then be referred to a public facility just to receive their vaccines because of the free access [68]. Notably, user fees for these services were shown to be associated with a lower vaccine coverage, for Tetanus and influenza vaccines [46,60,69]. In Malawi, an authoritative and punitive approach to vaccine policy implementation where pregnant women incur penalties if ANC is missed in an effort to incentivise ANC attendance and increase vaccine coverage, rather led to unintended outcomes including low vaccine uptake among pregnant women (Table 3) [58].

While providers are a source of trusted information and education about VPDs, it was frequently reported that constraints to service delivery [such as staff shortages and high workloads] in turn affect uptake. This is because healthcare providers with high workloads tend to have limited time to spend

with each patient for education and thorough communication about maternal vaccines as reported in Kenya [61] and Thailand [56], indicating that human resource constraints serve as a hardware barrier to vaccine uptake during pregnancy and thus highlighting the interplay between health systems determinants of vaccine delivery and uptake as shown in Figure 3. Additionally, pregnant women and community members' previous negative experiences with health service delivery – although not necessarily related to vaccination – served as a software barrier to uptake of maternal vaccines in LMICs. In Ethiopia and Brazil, a commonly cited reason for this was mistreatment and disrespect from healthcare providers, deterring pregnant women from antenatal visits and subsequent vaccine uptake [47,72]. This is concerning, given the reliance on healthcare providers in individual decision-making about vaccine uptake. The theme on awareness and education identified in the literature highlights the need for credible information sharing and seeking by relevant population groups. Women in Brazil reported reliance on healthcare providers for vaccine information, but also on media sources, which have been shown to be barrier to uptake and fuel mistrust of healthcare providers' recommendations through misinformation about vaccine safety [71].

Cultural and social norms and beliefs, which varied by context, tended to influence reasons for accessing private healthcare and financing healthcare services for maternal vaccination. These contextual systems software factors are evident in beliefs held by pregnant women in Kenya who believe that paying for services incentivises healthcare providers to share sufficient information on vaccines and VPDs [55], while in Malawi paying for health services was associated with social standing as a status symbol, particularly among male spouses who deem it honourable to access paid services (Table 3) [61]. In Morocco however, women preferred accessing public services for vaccination during pregnancy for the reason that free vaccine provision was not profitable for the facility and thus incentives were altruistic and reasons for vaccination were rooted in effectiveness and not profit [65].

Sociodemographic factors like maternal education, race, socioeconomic status, and parity appeared to have a heterogenous effect on decisions to accept a vaccine during pregnancy depending on the setting studied. Reports on the effect of contextual variables such as level of maternal education, access to transport and place of residency [urban/rural] varied across the included studies. In South American countries and in Kenya for example, increased vaccine coverage was associated with urban residency, as pregnant women in rural areas reported extreme distances to ANC facilities [47,49] whereas in Indonesia [76], rural residency was associated with increased coverage and uptake. In Kenya, a higher level of education was associated with low acceptance[54]. Notably, several studies reported no significant association between vaccine coverage and acceptance with these same sociodemographic factors of residency and level of maternal education [46,60,66]. In Ethiopia, contextual factors that affected uptake included higher level of maternal education, having a TV in the house, occupational status, place of birth, and general knowledge of the tetanus vaccine [72]. In the same country, receiving more than the two/more recommended doses of tetanus vaccine during pregnancy was associated with urban residency, short travel distance to health facilities and higher level of maternal education [at least secondary school] [73]. A higher level of maternal education was also associated with increased vaccine acceptance of the COVID-19 vaccine in Vietnam [74]. Increased vaccine uptake was seen in pregnant women with higher education, younger age, rural residency and attendance of at least three ANC visits in Ivory Coast [75].

A cultural religious barrier to uptake was reported in Senegal, where a sub-population of pregnant women belonging to a specific religious group were barred by group members from accepting vaccines during pregnancy [62]. When it came to maternal occupation, it was notable that in El Salvador there was mention of the role of employers in maternal employees accessing ANC during work hours where pregnant women were not granted time off work to access clinics [61], serving as a contextual barrier to uptake of vaccines.

Discussion

This systematic review reports synthesised evidence on the health systems determinants of delivery and uptake of maternal vaccines in LMICs. The dynamic interaction between key barriers and enablers of delivery and uptake, categorized into health systems hardware and software, are also described and provide unique insights into the resultant suboptimal performance of maternal vaccination programmes observed in some LMICs. If we are to tackle the global Sustainable Development Goal to promote maternal health beyond just survival [80], then it is pertinent to implement context-specific public health interventions. Such interventions should be guided by robust evidence on the gaps in delivery and uptake of healthcare services including vaccination. Policy- and decision-makers will rely on such evidence in order to develop feasible recommendations that are immediately important for scaling-up the performance of health systems with consequent improvements in health outcomes.

Findings and recommendations for vaccine decision- and policy-makers

The identified barriers to effective delivery and uptake of maternal vaccines in LMICs which could be classified as systems hardware include the lack of coordinated, context-specific approaches to vaccine policy formulation, reliance on public funding mechanisms and out-of-pocket payments, poor cold chain systems and management processes, weak health workforce capacity including staff shortages and capabilities, and reliance on paper-based vaccine monitoring and reporting systems [37,47,53, 58]. Where clear policies and guidelines on maternal vaccination where in place, this was observed to support vaccine delivery and subsequently promote uptake among pregnant women [36,60]. It is important to address the fact that despite maternal vaccination falling at the intersection of ANC and immunisation programmes, lack of service co-ordination was identified as a prominent barrier to maternal vaccine delivery and uptake in LMICs [37,62,67,69]. This lack of co-ordination was demonstrated between public and private health sectors, and between EPI and ANC services. What this suggests is a gross underutilisation of the opportunities to leverage existing infrastructure and delivery models to improve maternal health outcomes, at least where reducing the devastating burden of VPDs is concerned. Service co-ordination remains a priority strengthening area that could reduce service delivery cost by using existing infrastructure to deliver vaccines. This would address identified barriers to vaccine uptake that included the cost of education materials and the reliance on donor funding for vaccination programmes at a local level [18,81]. Such efforts could also mitigate maternal out-of-pocket payments for accessing key healthcare services [59]. Establishing co-ordinated service delivery of currently available maternal vaccines is paramount to sustainable introduction of new and upcoming maternal vaccines like those against COVID-19, GBS and RSV [9–11]. Sustainable introduction of new maternal vaccines could in turn present unique opportunities for health systems strengthening through coordinated health service provision. This echoes findings in other LMIC settings, where the introduction of new vaccines into immunisation programmes has been shown to improve co-ordination between ministries of health and other government ministries, such as

education and social development [84]. The resource and infrastructural barriers to vaccine delivery in LMICs, demonstrated by vaccine stock-outs and ineffective cold-chain maintenance processes [14,47,56] have been reported previously [7]. Often, this is exacerbated by system shocks like the recent COVID-19 pandemic, that affects access to services in LMICs. A survey exploring the impact of COVID-19 on immunisation programmes reported that 53% of respondents in LMICs had experienced disruption to delivery of maternal vaccines; almost 10% more than those from HICs [86]. These system shocks, although on different scales, require sustainable heath system strengthening approaches. The fact that limited healthcare provider capacity was identified as a barrier to maternal vaccine delivery in LMICs [43,56] underscores the need for a health systems strengthening response which is designed to ensure that new maternal vaccine introductions are coupled with increasing the number of staff at facilities, providing regular staff training and appropriate compensation or incentives in accordance with potential short-term increases in workloads brought on by the introduction of additional or new maternal vaccines [84]. Furthermore, the issue of healthcare provider capacity should be addressed through co-ordinated delivery of vaccines between EPI and ANC, as well as co-ordination and partnerships between public and private healthcare providers [18]. Finally, weak information and reporting systems characterised by the reliance on paper-based vaccine monitoring and reporting systems, and maternal recall requires particular attention in order to support the establishment of effective and sustainable maternal vaccination programmes in LMICs [59]. The reliance on maternal recall for immunisation history is not limited to LMICs and has also been observed previously in HICs [85]. To this end, strengthening health information systems through reliable VPD surveillance and monitoring of maternal vaccine coverage would enhance policy- and decision-making, while strengthening research and patient centred care, as well as minimising the reliance on HIC data [36]. The availability of AEFI reporting systems in only two of the LMICs studied in this review points to the lack of robust monitoring systems, and over-reliance on clinical trial data and passive surveillance in these settings [90,91]. Incorporation of active surveillance and monitoring of AEFIs is urgently required and could be coupled with the introduction of new vaccines as has been done previously in HICs [87].

In terms of health system software, trust in political governance and healthcare provider recommendations on maternal vaccines emerged as a prominent theme in the evidence-base on maternal vaccine delivery and uptake. There was a particular emphasis on effective communication channels between healthcare workers and clients of the health system including pregnant women and their close contacts who play an important role in influencing their individual decisions on vaccine acceptance and uptake [68,72,76]. Having access to reliable sources of information on maternal vaccines could counter the misinformation and disinformation peddled by some media forums and religious and cultural organizations who fuel mistrust in vaccines. Evidently, there is a need to improve communication between pregnant women and healthcare providers, in order to promote vaccine uptake. This requires service delivery platforms to steer away from ‘unidirectional’ communication between healthcare providers and pregnant women, and rather encourage broader community engagement throughout the vaccination programme cascade (from the development to the implementation of vaccines). The use of tools like antenatal records and vaccination cards to enhance communication and consultation with the broader community is also worth exploring [88]. Such activities would be far-reaching in also promoting trust between healthcare providers, pregnant women and the broader community served by the health system. This is not restricted to LMICs however, as promotion of trust in healthcare providers, as well as the importance of vaccine efficacy and safety communication to pregnant women, have also been identified as enablers to uptake and

delivery in HIC settings [89]. Mistrust in vaccines and vaccine hesitancy is also not limited to LMICs but has been qualitatively recorded in HICs [84]. This calls for improved education and communication strategies that address the concerns expressed by pregnant women and improve their knowledge and awareness about maternal vaccination. Extensive knowledge of maternal vaccination appears to be associated with higher income status [86]. In this review, the influence of low level of education among women, including broader community members, was highlighted as a key sociodemographic factor and barrier to vaccine uptake [49,78,79] demonstrating that a health systems strengthening approach to vaccine programming in general requires thinking beyond just the health sector. Rather, initiatives should extend strengthening efforts to education, social and financial protection [82,83].

Another important health systems' software barrier to the delivery of maternal vaccines in LMICs is the ineffective dissemination of policies and guidelines from the national level to healthcare providers at the facility level. Globally, across both HICs and LMICs, it has been shown that healthcare provider awareness of vaccination policies enables them to recommend influenza vaccination during pregnancy, second to vaccination of the healthcare providers themselves [87]. This emphasises the need for improving communication of policy from health leadership to healthcare providers at facility level [35,57,58]. Clear dissemination process that also includes facility-level staff in policy- and decision-making processes would bridge the gap for some vaccine implementation issues and promote ownership and accountability among healthcare providers. This could further improve trust between healthcare providers and pregnant women given shared vested interest in the vaccination programme, facilitating increased uptake.

As health systems continue to adopt maternal vaccination policies for new and future vaccines like COVID-19, GBS and RSV, careful consideration of system-wide effects is paramount. The findings of this review have significant implication for establishing maternal vaccination programmes which effectively deliver existing as well as new and future vaccines. Such efforts will require a strengthened delivery response relying on the WHO's recommendation of at least eight ANC visits during pregnancy [91]. Future vaccine introduction would also benefit from effective formulation and communication of policies and guidelines which are appropriately disseminated to facility-level to sensitize healthcare providers to critical practices such the gestation administration windows. The recent introduction of new vaccines against diseases like COVID-19 is an opportunity for increasing acceptance of maternal vaccines by spouses, family and community members who were shown to influence willingness and uptake by pregnant women in multiple settings [78, 92].

Findings and recommendations for health systems and maternal vaccination research agenda

The exploratory nature of this review allowed for identification of several research gaps in the health systems and vaccination agenda for LMICs. In countries where a high level of trust in healthcare providers was reported [38,61,65–67], uptake of maternal vaccines was observed to be high. The promotion and maintenance of trust in healthcare providers could also be paramount to clinical trials of new maternal vaccines, which rely on the trust between research teams and community members [90]. In conducting research amongst pregnant women, particularly for clinical trials of future vaccines, maintaining and promoting trust among researchers, community members and healthcare providers is crucial for systems strengthening and has been shown to contribute to successful trial outcomes [91].

We identified four main areas for improvement of the research agenda relating to maternal vaccination and health systems, building on the evidence gaps identified in this review. Firstly, there is a need for further exploration of interventions for health promotion and education during pregnancy with a particular focus on preventing VPDs. This has been investigated for HICs [85], but not adequately in LMICs. Secondly, there is a need to better understand the role of policy-makers like NITAGs and how they influence maternal vaccine delivery and uptake in LMICs. Only one study conducted in Kenya explicitly reported on the involvement of NITAGs in maternal vaccination programmes [36]. Their role in maternal vaccination should be further explored, particularly with regards to evidence-based policy formation and clear messaging regarding vaccine safety and efficacy. Thirdly, there is a need to ensure that community trust and key stakeholder engagement are foundational pillars of maternal vaccination programmes and strategies in this regard should be the focus of future research in the field. Lastly, further research on vaccine implementation for pregnant women residing in LMICs within Central Africa, North Africa, Eastern Europe and Eastern Mediterranean regions is needed to build the knowledge-base and support evidence-informed interventions where needed.

Strengths and limitations of this review

Various study designs involving diverse stakeholders (pregnant women, community members, healthcare providers, policy-makers and health leadership) from across 28 LMICs were triangulated and assessed with guidance from a conceptual framing model developed in a preceding scoping review. To our knowledge, this is the first ever qualitative systematic review on the health systems determinants of maternal vaccination in LMIC. Given the influence of variabilities in context on the core outcome measures assessed in this review, it is important to caution that findings may not be generalizable to all LMICs. While a robust search strategy was used to retrieve relevant literature, it is possible that not all could be retrieved, possibly as a result of indexing within databases.

Conclusion

This qualitative systematic review contributes towards improving our narrow understanding of the health systems determinants of the performance of maternal vaccination programmes in LMICs. Considering the systems' software and hardware determinants of maternal vaccine uptake and delivery identified in this review, it is evident that formulation, dissemination and communication of context-specific policies and guidelines on maternal vaccines should be a priority focus for decision-makers in LMICs. In addition, there is a need to strengthen the role of healthcare providers as change-agents and champions of maternal vaccination. Improving knowledge and awareness of VPDs, the safety and efficacy of vaccines, among pregnant women and their close contacts who influence their individual decision-making should be prioritised. Governments in LMICs are encouraged to strengthen co-ordination between ANC, national immunization programmes, private and public health sectors, in order to increase ANC visits and vaccine uptake during pregnancy. As new and improved maternal vaccines are introduced to the market, it is recommended that health systems determinants are taken into consideration so as not to exacerbate existing barriers to maternal vaccine uptake and delivery, with the ultimate goal of establishing sustainable maternal vaccination programmes.

References

1. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. The Lancet. 2016;387[10017]:462–74.
2. Saso A, Kampmann B. Maternal Immunization: Nature Meets Nurture. Front Microbiol. 2020;11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7396522/
3. Maitra C, Hodge A, Jimenez Soto E. A scoping review of cost benefit analysis in reproductive, maternal, newborn and child health: What we know and what are the gaps? Health Policy Plan. 2016 Dec;31[10]:1530–47.
4. Regan AK. The safety of maternal immunization. Hum Vaccines Immunother. 2016;12[12]:3132–6.
5. Greenwood B. Maternal immunisation in developing countries. Vaccine. 2003;21[24]:3436–41.
6. Ortiz JR, Englund JA, Neuzil KM. Influenza vaccine for pregnant women in resource-constrained countries: a review of the evidence to inform policy decisions. Vaccine. 2011 Jun 15;29[27]:4439–52.
7. Ortiz JR, Neuzil KM, Ahonkhai VI, Gellin BG, Salisbury DM, Read JS, et al. Translating vaccine policy into action: a report from the Bill & Melinda Gates Foundation Consultation on the prevention of maternal and early infant influenza in resource-limited settings. Vaccine. 2012;30[50]:7134–40.
8. Kachikis A, Eckert LO, Englund JA. Chapter 1 - The history of maternal immunization. In: Leuridan EE, Nunes MC, Jones CE, editors. Maternal Immunization. Academic Press; 2020. p. 3–24. Available from: https://www.sciencedirect.com/science/article/pii/B9780128145821000012
9. Swamy GK, Metz TD, Edwards KM, Soper DE, Beigi RH, Campbell JD, et al. Safety and immunogenicity of an investigational maternal trivalent group B streptococcus vaccine in pregnant women and their infants: Results from a randomized placebo-controlled phase II trial. Vaccine. 2020 Oct 14;38[44]:6930–40.
10. Saso A, Kampmann B. Vaccination against respiratory syncytial virus in pregnancy: a suitable tool to combat global infant morbidity and mortality? Lancet Infect Dis. 2016;16[8]:e153–63.
11. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med. 2021 Apr 21.
12. Zavala E, Krubiner CB, Jaffe EF, Nicklin A, Gur-Arie R, Wonodi C, et al. Global disparities in public health guidance for the use of COVID-19 vaccines in pregnancy. BMJ Glob Health. 2022 Feb;7[2]:e007730.
13. Sedgh G, Singh S, Hussain R. Intended and Unintended Pregnancies Worldwide in 2012 and Recent Trends. Stud Fam Plann. 2014 Sep;45[3]:301–14.
14. Bishop K, McMorrow M, Meiring S, Walaza S, Rossi L, Mhlanga S, et al. An evaluation of an influenza vaccination campaign targeting pregnant women in 27 clinics in two provinces of South Africa, 2015–2018. BMC Health Serv Res. 2021;21[1]:1–8.
15. DiTosto JD, Weiss RE, Yee LM, Badreldin N. Association of Tdap vaccine guidelines with vaccine uptake during pregnancy. PLoS ONE. 2021 Jul 19;16[7]:e0254863.
16. Hug L, Alexander M, You D, Alkema L. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017, with scenario-based projections to 2030: a systematic analysis. Lancet Glob Health. 2019 Jun;7[6]:e710–20.
17. Shen AK, Fields R, McQuestion M. The future of routine immunization in the developing world: challenges and opportunities. Glob Health Sci Pract. 2014 Dec 1;2[4]:381–94.
18. Choudhary M, Solomon R, Awale J, Dey R. Demand-side determinants of timely vaccination of oral polio vaccine in social mobilization network areas of CORE Group polio project in Uttar Pradesh, India. BMC Infect Dis. 2018 Dec;18[1]:222.
19. Ritchie LMP, Khan S, Moore JE, Timmings C, van Lettow M, Vogel JP, et al. Low-and middle-income countries face many common barriers to implementation of maternal health evidence products. J Clin Epidemiol. 2016;76:229–37.
20. Hardt K, Bonanni P, King S, Santos JI, El-Hodhod M, Zimet GD, et al. Vaccine strategies: Optimising outcomes. Vaccine. 2016;34[52]:6691–9.
21. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;372:n71.
22. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016 Dec;5[1]:210.
23. Peters MDJ, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, et al. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth. 2020 Oct;18[10]:2119–26.

24. Pluye P, Robert E, Cargo M, Bartlett G, O'cathain A, Griffiths F, et al. Proposal: A mixed methods appraisal tool for systematic mixed studies reviews. Montr McGill Univ. 2011;2:1–8.
25. Shakarishvili G, Atun R, Berman P, Hsiao W, Burgess C, Lansang MA. Converging Health Systems Frameworks: Towards A Concepts-to-Actions Roadmap for Health Systems Strengthening in Low and Middle Income Countries. Global Health Gov. 2020;3:2.
26. De Savigny D, Adam T. Systems thinking for health systems strengthening. Geneva: World Health Organization; 2009.
27. Agyepong IA, Kwamie A, Frimpong E, Defor S, Ibrahim A, Aryeetey GC, et al. Spanning maternal, newborn and child health [MNCH] and health systems research boundaries: conducive and limiting health systems factors to improving MNCH outcomes in West Africa. Health Res Policy Syst. 2017 Jul 12;15[1]:54.
28. Van Olmen J, Criel B, Van Damme W, Marchal B, Van Belle S, Van Dormael M, et al. Analysing health systems to make them stronger. Antwerp, Belgium: ITGPress; 2010.
29. Amponsah-Dacosta E, Kagina BM, Olivier J. Health systems constraints and facilitators of human papillomavirus immunization programmes in sub-Saharan Africa: a systematic review. Health Policy Plan. 2020 May 3;czaa017.
30. Engmann C, Fleming JA, Khan S, Innis BL, Smith JM, Hombach J, et al. Closer and closer? Maternal immunization: current promise, future horizons. J Perinatol. 2020;40[6]:844–57.
31. World Health Organization. Strategies toward ending preventable maternal mortality [EPMM]. Geneva: World Health Organization; 2015. Available from: http://www.who.int/reproductivehealth/topics/maternal_perinatal/epmm/en/
32. Thomas J, Harden A. Methods for the thematic synthesis of qualitative research in systematic reviews. BMC Med Res Methodol. 2008;8[1]:1–10.
33. Vaismoradi M, Snelgrove S. Theme in Qualitative Content Analysis and Thematic Analysis. Forum Qual Sozialforschung Forum Qual Soc Res. 2019 Sep 26;20[3]. Available from: https://www.qualitative-research.net/index.php/fqs/article/view/3376
34. Nagata JM, Hernández-Ramos I, Kurup AS, Albrecht D, Vivas-Torrealba C, Franco-Paredes C. Social determinants of health and seasonal influenza vaccination in adults ≥65 years: a systematic review of qualitative and quantitative data. BMC Public Health. 2013 Apr 25;13[1]:388.
35. Ferrer HB, Trotter C, Hickman M, Audrey S. Barriers and facilitators to HPV vaccination of young women in high-income countries: a qualitative systematic review and evidence synthesis. BMC Public Health. 2014 Jul 9;14[1]:700.
36. Giles M, Mantel C, Muñoz F, Moran A, Roos N, Yusuf N, et al. Vaccine implementation factors affecting maternal tetanus immunization in low-and middle-income countries: Results of the Maternal Immunization and Antenatal Care Situational Analysis [MIACSA] project. Vaccine. 2020;38[33]:5268–77.
37. Alvarez AMR, Vilajeliu A, Magariños M, Jauregui B, Guzmán L, Whittembury A, et al. Enablers and barriers of maternal and neonatal immunization programs in Latin America. Vaccine. 2020;
38. Otieno NA, Malik FA, Nganga SW, Wairimu WN, Ouma DO, Bigogo GM, et al. Decision-making process for introduction of maternal vaccines in Kenya, 2017–2018. Implement Sci. 2021;16[1]:1–15.
39. Praphasiri P, Ditsungneon D, Greenbaum A, Dawood FS, Yoocharoen P, Stone DM, et al. Do Thai Physicians Recommend Seasonal Influenza Vaccines to Pregnant Women? A Cross-Sectional Survey of Physicians' Perspectives and Practices in Thailand. PLoS ONE. 2017;12[1]:1–12.
40. Li R, Xie R, Yang C, Rainey J, Song Y, Greene C. Identifying ways to increase seasonal influenza vaccine uptake among pregnant women in China: A qualitative investigation of pregnant women and their obstetricians. Vaccine. 2018 May 31;36[23]:3315–22.
41. Malik FA, Alonso JP, Sanclemente LN, Vilajeliu A, Gutierrez M, Gonzalez-Casanova I, et al. Health care providers perspectives about maternal immunization in Latin America. Vaccine. 2021;39:B50–4.
42. Giles ML, Mason E, Muñoz FM, Moran AC, Lambach P, Merten S, et al. Antenatal care service delivery and factors affecting effective tetanus vaccine coverage in low-and middle-income countries: Results of the Maternal Immunisation and Antenatal Care Situational analysis [MIACSA] project. Vaccine. 2020;38[33]:5278–85.
43. Bergenfeld I, Nganga SW, Andrews CA, Fenimore VL, Otieno NA, Wilson AD, et al. Provider perspectives on demand creation for maternal vaccines in Kenya. Gates Open Res. 2018;2.
44. Giduthuri JG, Purohit V, Maire N, Kudale A, Utzinger J, Schindler C, et al. Influenza vaccination of pregnant women: Engaging clinicians to reduce missed opportunities for vaccination. Vaccine. 2019;37[14]:1910–7.

45. Laizer SN, Hemed A, Cyril PM. Challenges Experienced by Healthcare Workers on Maternal Tetanus Toxoid Vaccination in Kilimanjaro Region Tanzania. Clin Immunol Res. 2021;5[2]:1–8.
46. Gonzalez-Casanova I, Chander S, Chaves SS, Otieno NA, Widdowson M-A, Verani J, et al. Antenatal care providers' attitudes and beliefs towards maternal vaccination in Kenya. Gates Open Res. 2021;4.
47. Malik AF, Belizan M, Gutierrez M, Vilajeliu A, Sanclemente LN, Casanova IG, et al. Pregnant women's perspectives about maternal immunization in Latin America. Vaccine. 2021;39:B44–9.
48. Simas C, Larson HJ, Paterson P. "Saint Google, now we have information!": a qualitative study on narratives of trust and attitudes towards maternal vaccination in Mexico City and Toluca. BMC Public Health. 2021;21[1]:1–8.
49. Giduthuri JG, Purohit V, Kudale A, Utzinger J, Schindler C, Weiss MG. Antenatal influenza vaccination in urban Pune, India: clinician and community stakeholders' awareness, priorities, and practices. Hum Vaccines Immunother. 2021;17[4]:1211–22.
50. Kfouri R de Á, Richtmann R. Influenza vaccine in pregnant women: immunization coverage and associated factors. Einstein Sao Paulo Braz. 2013 Mar;11[1]:53–7.
51. Anatea MD, Mekonnen TH, Dachew BA. Determinants and perceptions of the utilization of tetanus toxoid immunization among reproductive-age women in Dukem Town, Eastern Ethiopia: a community-based cross-sectional study. BMC Int Health Hum Rights. 2018 Jun 28;18[1]:27.
52. Fleming JA, Baltrons R, Rowley E, Quintanilla I, Crespin E, Ropero A-M, et al. Implementation of maternal influenza immunization in El Salvador: Experiences and lessons learned from a mixed-methods study. Vaccine. 2018;36[28]:4054–61.
53. Arriola CS, Suntarattiwong P, Dawood FS, Soto G, Das P, Hunt DR, et al. What do pregnant women think about influenza disease and vaccination practices in selected countries. Hum Vaccines Immunother. 2021;17[7]:2176–84.
54. Nyiro JU, Bukusi E, Mwaengo D, Walumbe D, Nyaguara A, Nyawanda B, et al. Implications of gestational age at antenatal care attendance on the successful implementation of a maternal respiratory syncytial virus [RSV] vaccine program in coastal Kenya. BMC Public Health. 2020;20[1]:1–11.
55. Erazo CE, Erazo CV, Grijalva MJ, Moncayo AL. Knowledge, attitudes and practices on influenza vaccination during pregnancy in Quito, Ecuador. BMC Public Health. 2021;21[1].
56. Kaoiean S, Kittikraisak W, Suntarattiwong P, Ditsungnoen D, Phadungkiatwatana P, Srisantiroj N, et al. Predictors for influenza vaccination among Thai pregnant woman: The role of physicians in increasing vaccine uptake. Influenza Other Respir Viruses. 2019;13[6]:582–92.
57. Otieno NA, Otiato F, Nyawanda B, Adero M, Wairimu WN, Ouma D, et al. Drivers and barriers of vaccine acceptance among pregnant women in Kenya. Hum Vaccines Immunother. 2020;16[10]:2429–37.
58. Fleming JA, Munthali A, Ngwira B, Kadzandira J, Jamili-Phiri M, Ortiz JR, et al. Maternal immunization in Malawi: a mixed methods study of community perceptions, programmatic considerations, and recommendations for future planning. Vaccine. 2019;37[32]:4568–75.
59. Garcia PJ, George PE, Romero C, Soto G, Carcamo C, Bayer AM. "The flu… is a little more complicated than a cold": Knowledge, beliefs, and practices related to influenza and influenza vaccination among at-risk populations and health professionals in Peru. Vaccine. 2020 Nov 10;38[48]:7688–95.
60. Johm P, Nkoum N, Ceesay A, Larson H, Kampmann B. Factors influencing acceptance of vaccination during pregnancy in The Gambia and Senegal. Vaccine. 2021;
61. Giles ML, Mantel C, Muñoz FM, Moran A, Roos N, Yusuf N, et al. Vaccine implementation factors affecting maternal tetanus immunization in low- and middle-income countries: Results of the Maternal Immunization and Antenatal Care Situational Analysis [MIACSA] project. Vaccine. 2020;38[33]:5268–77.
62. Wang J, Sun D, Abudusaimaiti X, Vermund SH, Li D, Hu Y. Low awareness of influenza vaccination among pregnant women and their obstetricians: a population-based survey in Beijing, China. Hum Vaccines Immunother. 2019;15[11]:2637–43.
63. Wang R, Tao L, Han N, Liu J, Yuan C, Deng L, et al. Acceptance of seasonal influenza vaccination and associated factors among pregnant women in the context of COVID-19 pandemic in China: a multi-center cross-sectional study based on health belief model. BMC Pregnancy Childbirth. 2021;21[1]:1–14.
64. Li W-F, Huang S-Y, Peng H-H, Chang Y-L, Chang S-D, Cheng P-J, et al. Factors affecting pregnant women's decisions regarding prenatal pertussis vaccination: A decision-making study in the nationwide Prenatal Pertussis Immunization Program in Taiwan. Taiwan J Obstet Gynecol. 2020;59[2]:200–6.

65. Simas C, Paterson P, Lees S, Larson HJ. “From my phone, I could rule the world”: Critical engagement with maternal vaccine information, vaccine confidence builders and post-Zika outbreak rumours in Brazil. Vaccine. 2021;39[33]:4700–4.
66. Nganga SW, Otieno NA, Adero M, Ouma D, Chaves SS, Verani JR, et al. Patient and provider perspectives on how trust influences maternal vaccine acceptance among pregnant women in Kenya. BMC Health Serv Res. 2019;19[1]:1–13.
67. Kajungu D, Muhoozi M, Stark J, Weibel D, Sturkenboom MCJM. Vaccines safety and maternal knowledge for enhanced maternal immunization acceptability in rural Uganda: A qualitative study approach. PLoS ONE. 2020;15[12]:1–17.
68. Lohiniva A-L, Barakat A, Dueger E, Restrepo S, El Aouad R. A Qualitative Study of Vaccine Acceptability and Decision Making among Pregnant Women in Morocco during the A [H1N1] pdm09 Pandemic. PLoS ONE. 2014;9[10]:1–6.
69. Wong VWY, Fong DYT, Lok KYW, Wong JYH, Sing C, Choi AY-Y, et al. Brief education to promote maternal influenza vaccine uptake: A randomized controlled trial. Vaccine. 2016;34[44]:5243–50.
70. Otieno NA, Nyawanda B, Otiato F, Adero M, Wairimu WN, Atito R, et al. Knowledge and attitudes towards influenza and influenza vaccination among pregnant women in Kenya. Vaccine. 2020;38[43]:6832–8.
71. Varan AK, Esteves-Jaramillo A, Richardson V, Esparza-Aguilar M, Cervantes-Powell P, Omer SB. Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City. Vaccine. 2014;32[7]:785–92.
72. Carcelen A, Vilajeliu A, Malik F, Gilman R, Omer S. Perceptions and attitudes towards vaccination during pregnancy in a peri urban area of Lima, Peru. VACCINE. 2021 Jul 30;39:B27–33.
73. Arriola CS, Vasconez N, Thompson M, Mirza S, Moen AC, Bresee J, et al. Factors associated with a successful expansion of influenza vaccination among pregnant women in Nicaragua. Vaccine. 2016 Feb;34[8]:1086–90.
74. Arriola CS, Vasconez N, Bresee J, Ropero AM. Knowledge, attitudes and practices about influenza vaccination among pregnant women and healthcare providers serving pregnant women in Managua, Nicaragua. Vaccine. 2018 Jun;36[25]:3686–93.
75. Mendoza-Sassi RA, Linhares AO, Schroeder FMM, Maas NM, Nomiyama S, César JA. Vaccination against influenza among pregnant women in southern Brazil and associated factors. Cienc E Saude Coletiva. 2019;24[12]:4655–64.
76. Fleming JA, Baltrons R, Rowley E, Quintanilla I, Crespin E, Ropero A-M, et al. Implementation of maternal influenza immunization in El Salvador: Experiences and lessons learned from a mixed-methods study. Vaccine. 2018;36[28]:4054–61.
77. Larson Williams A, Mitrovich R, Mwananyanda L, Gill C. Maternal vaccine knowledge in low-and middle-income countries—and why it matters. Hum Vaccines Immunother. 2019;15[2]:283–6.
78. Arifin H, Widiasih R, Pradipta RO, Kurniawati Y. Regional disparities and their contribution to the coverage of the tetanus toxoid vaccine among women aged 15-49 years in Indonesia. F1000Research. 2021;10:437.
79. Gebremedhin TS, Welay FT, Mengesha MB, Assefa NE, Werid WM. Tetanus Toxoid Vaccination Uptake and Associated Factors among Mothers Who Gave Birth in the Last 12 Months in Errer District, Somali Regional State, Eastern Ethiopia. BioMed Res Int. 2020;1–8.
80. Nguyen LH, Hoang MT, Nguyen LD, Ninh LT, Nguyen HTT, Nguyen AD, et al. Acceptance and willingness to pay for COVID-19 vaccines among pregnant women in Vietnam. Trop Med Int Health TM IH. 2021 Oct;26[10]:1303–13.
81. Yaya S, Kota K, Buh A, Bishwajit G. Antenatal visits are positively associated with uptake of tetanus toxoid and intermittent preventive treatment in pregnancy in Ivory Coast. BMC Public Health. 2019;19[1]:1467.
82. World Health Organization. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division.Geneva: World Health Organization; 2019. Available from: https://apps.who.int/iris/handle/10665/327595
83. Elmusharaf K, Byrne E, O’Donovan D. Strategies to increase demand for maternal health services in resource-limited settings: challenges to be addressed. BMC Public Health. 2015 Dec;15[1]:870.
84. Wang SA, Hyde TB, Mounier-Jack S, Brenzel L, Favin M, Gordon WS, et al. New vaccine introductions: Assessing the impact and the opportunities for immunization and health systems strengthening. Vaccine. 2013 Apr;31:B122–8.

85. Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review. Vaccine. 2018 May;36[20]:2751–9.
86. Gauld N, Martin S, Sinclair O, Petousis-Harris H, Dumble F, Grant CC. A qualitative study of views and experiences of women and health care professionals about free maternal vaccinations administered at community pharmacies. Vaccines. 2020;8[2]:152.
87. World Health Organization. Global vaccine action plan 2011-2020. Geneva: World Health Organization. Available from: https://www.who.int/publications-detail-redirect/global-vaccine-action-plan-2011-2020
88. Sheikh K, Ranson MK, Gilson L. Explorations on people centredness in health systems. Health Policy Plan. 2014 Sep 1;29[suppl_2]:ii1–5.
89. Morales KF, Menning L, Lambach P. The faces of influenza vaccine recommendation: A Literature review of the determinants and barriers to health providers' recommendation of influenza vaccine in pregnancy. Vaccine. 2020 Jun;38[31]:4805–15.
90. World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016.
91. Divala TH, Mungwira RG, Laufer MK. Moving targets: The challenges of studying infectious diseases among pregnant women in resource limited settings. Vaccine. 2015 Nov;33[47]:6401–5.
92. Godongwana M, Myburgh N, Adedini SA, Cutland C, Radebe N. Knowledge and attitudes towards maternal immunization: perspectives from pregnant and non-pregnant mothers, their partners, mothers, healthcare providers, community and leaders in a selected urban setting in South Africa. Heliyon. 2021 Jan;7[1]:e05926.

APPENDIX A.

Table 1 Literature search strategy for qualitative systematic review

Query	Key terms
1	Maternal OR antenatal OR prenatal OR pregnancy OR trimester OR “maternal health services” OR “maternal health”
2	Vaccine OR immunization OR “immunization schedule” OR “immunization programs” OR “maternal vaccine” OR “vaccine during pregnancy”
3	#1 AND #2
4	“Respiratory syncytial virus vaccine” OR “COVID 19 vaccine” OR “Cytomegalovirus vaccine” OR “Ebola virus vaccine” OR “Influenza vaccine” OR “Diptheria tetanus acellular pertussis vaccine” OR “Tetanus vaccine” OR “pneumococcal vaccine” OR “oral Poliovirus vaccine” OR “Streptococcus Agalactiae” OR “Meningococcal vaccine” OR “Herpes simplex virus vaccine” OR “Group B Streptococcus”
5	#3 AND #4
6	“mass vaccination” OR “vaccine coverage” OR “vaccine introduction” OR “immunization communication” OR “immunization performance” OR “vaccine implementation” OR “vaccine introduction” OR “vaccine uptake” OR “immunization access” OR “vaccine supply” OR “vaccine distribution” OR acceptability OR “program legislation” OR “community and partnership” OR “program finance” OR “program management” OR “immunization program organization” OR “immunization program administration”
7	"Facilities and Services Utilization” OR "Delivery of Health Care" OR "Health system" OR "global health" OR "health information systems" OR "health financing" OR governance OR "policy" OR "health workforce" OR "healthcare personnel" OR "medical technologies" OR “medical products” OR "health systems strengthening" OR "health systems performance" OR "integrated health systems” OR "primary health care" OR "primary health service" OR “health system building blocks” OR “health system function” OR “health system capacity”
8	#6 OR #7
9	#5 AND #8
10	"deprived countries" OR "developing countries" OR "less developed country" OR "low gross national" OR “low income” OR “middle income” OR LMIC OR LLMIC OR "low income countries" OR "middle income country" OR "middle income economies" OR "poor economy" OR "third world" OR "transitional country" OR "under developed economies"
11	Afghanistan OR Albania OR Algeria OR “American Samoa” OR Angola OR Armenia OR Azerbaijan OR Bangladesh OR Belarus OR Byelarus OR Belorussia OR Belize OR Benin OR Bhutan OR Bolivia OR Bosnia OR Botswana OR Brazil OR Bulgaria OR Burma OR “Burkina Faso” OR Burundi OR “Cabo Verde” OR “Cape verde” OR Cambodia OR Cameroon OR “Central African Republic” OR Chad OR China OR Colombia OR Comoros OR Comores OR Comoro OR Congo OR “Costa Rica” OR “Côte d'Ivoire” OR Cuba OR Djibouti OR Dominica OR “Dominican Republic” OR Ecuador OR Egypt OR “El Salvador” OR Eritrea OR Ethiopia OR Fiji OR Gabon OR Gambia OR Gaza OR “Georgia Republic” OR Georgian OR Ghana OR Grenada OR Grenadines OR Guatemala OR Guinea OR “Guinea Bisau” OR Guyana OR Haiti OR Herzegovina OR Hercegovina OR Honduras OR India OR Indonesia OR Iran OR Iraq OR Jamaica OR Jordan OR Kazakhstan OR Kenya OR Kiribati OR Korea OR Kosovo OR Kyrgyz OR Kirghizia OR Kirghiz OR Kirgizstan OR Kyrgyzstan OR “Lao PDR” OR Laos OR Lebanon OR Lesotho OR Liberia OR Libya OR Macedonia OR Madagascar OR Malawi OR Malay OR Malaya OR Malaysia OR Maldives OR Mali OR “Marshall Islands” OR Mauritania OR Mauritius OR Mexico OR Micronesia OR Moldova OR Mongolia OR Montenegro OR Morocco OR Mozambique OR Myanmar OR Namibia OR Nepal OR Nicaragua OR Niger OR Nigeria OR Pakistan OR Palau OR Panama OR “Papua New Guinea” OR Paraguay OR Peru OR Philippines OR Phillippines OR Philipines OR Phillipines OR Principe OR Romania OR Rwanda OR Ruanda OR Samoa OR “Sao Tome” OR Senegal OR Serbia OR “Sierra Leone” OR “Solomon Islands” OR Somalia OR “South Africa” OR “South Sudan” OR “Sri Lanka” OR “St Lucia” OR “St Vincent” OR Sudan OR Suriham OR Suriname OR Swaziland OR Syria OR “Syrian Arab Republic” OR Tajikistan OR Tadzhikistan OR Tadjikistan OR Tadzhik OR Tanzania OR Thailand OR Timor OR Togo OR Tonga OR Tunisia OR Turkey OR Turkmen OR Turkmenistan OR Tuvalu OR Uganda OR Ukraine OR Uzbek OR Uzbekistan OR Vanuatu OR Vietnam OR “West Bank” OR Yemen OR Zambia OR Zimbabwe
12	#10 OR #11
13	#9 AND #12
FILTERS	ENGLSH + FULL TEXT + HUMAN

APPENDIX B

Table 1 Data extraction table for qualitative systematic review *[Source author]*

Study characteristics								Data extraction				
Author, year published	Year of study	Title	Journal	Country[s]	Study design	Study aim	Vaccine type[s]	Context	Vaccine decision-making	Planning and implementation	Delivery and uptake	Monitoring and reporting systems

APPENDIX C.

Critical Appraisal tools for use in JBI Systematic Reviews

All systematic reviews incorporate a process of critique or appraisal of the research evidence. The purpose of this appraisal is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. All papers selected for inclusion in the systematic review [that is – those that meet the inclusion criteria described in the protocol] need to be subjected to rigorous appraisal by two critical appraisers. The results of this appraisal can then be used to inform synthesis and interpretation of the results of the study. JBI Critical appraisal tools have been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer review. Although designed for use in systematic reviews, JBI critical appraisal tools can also be used when creating Critically Appraised Topics [CAT], in journal clubs and as an educational tool.

JBI Critical Appraisal Checklist for Qualitative Research

Reviewer_ _ _ _ _____Date_____

Author_____Year_____ Record Number_____

		Yes	No	Unclear	Not applicable
1.	Is there congruity between the stated philosophical perspective and the research methodology?	□	□	□	□
2.	Is there congruity between the research methodology and the research question or objectives?	□	□	□	□
3.	Is there congruity between the research methodology and the methods used to collect data?	□	□	□	□
4.	Is there congruity between the research methodology and the representation and analysis of data?	□	□	□	□
5.	Is there congruity between the research methodology and the interpretation of results?	□	□	□	□
6.	Is there a statement locating the researcher culturally or theoretically?	□	□	□	□
7.	Is the influence of the researcher on the research, and vice-versa, addressed?	□	□	□	□
8.	Are participants, and their voices, adequately represented?	□	□	□	□
9.	Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	□	□	□	□
10.	Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments [Including reason for exclusion]: _____

JBI Critical Appraisal Checklist for analytical cross sectional studies

Reviewer_ _ _ _ _____Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments [Including reason for exclusion]

_____

_____

_____

_____

JBI Critical Appraisal Checklist for cohort studies

Reviewer_____Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	□	□	□	□
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were confounding factors identified?	□	□	□	□
5. Were strategies to deal with confounding factors stated?	□	□	□	□
6. Were the groups/participants free of the outcome at the start of the study [or at the moment of exposure]?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	□	□	□	□
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	□	□	□	□
10. Were strategies to address incomplete follow up utilized?	□	□	□	□
11. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments [Including reason for exclusion]:_____

JBI Critical Appraisal Checklist for randomized Controlled trials

Reviewer_ _ _ _ _____Date_____

Author_____Year_____ Record Number_____

		Yes	No	Unclear	NA
1.	Was true randomization used for assignment of participants to treatment groups?	□	□	□	□
2.	Was allocation to treatment groups concealed?	□	□	□	□
3.	Were treatment groups similar at the baseline?	□	□	□	□
4.	Were participants blind to treatment assignment?	□	□	□	□
5.	Were those delivering treatment blind to treatment assignment?	□	□	□	□
6.	Were outcomes assessors blind to treatment assignment?	□	□	□	□
7.	Were treatment groups treated identically other than the intervention of interest?	□	□	□	□
8.	Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	□	□	□	□
9.	Were participants analyzed in the groups to which they were randomized?	□	□	□	□
10.	Were outcomes measured in the same way for treatment groups?	□	□	□	□
11.	Were outcomes measured in a reliable way?	□	□	□	□
12.	Was appropriate statistical analysis used?	□	□	□	□
13.	Was the trial design appropriate, and any deviations from the standard RCT design [individual randomization, parallel groups] accounted for in the conduct and analysis of the trial?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments [Including reason for exclusion]

_____

_____

_____

APPENDIX D.

Table 1 MMAT Critical Appraisal Tool

Mixed-methods studies	**Methodological quality criteria**
Mixed methods [MM] research involves combining qualitative [QUAL] and quantitative [QUAN] methods. In this tool, to be considered MM, studies have to meet the following criteria [Creswell and Plano Clark, 2017]: [a] at least one QUAL method and one QUAN method are combined; [b] each method is used rigorously in accordance to the generally accepted criteria in the area [or tradition] of research invoked; and [c] the combination of the methods is carried out at the minimum through a MM design [defined *a priori*, or emerging] and the integration of the QUAL and QUAN phases, results, and data. Common designs include [this list if not exhaustive]: **Convergent design** The QUAL and QUAN components are usually [but not necessarily concomitant. The purpose is to examine the same phenomenon by interpreting QUAL and QUAN results [bringing data analysis together at the interpretation stage], or by integrating QUAL and QUAN datasets [e.g., data on	5.1. Is there an adequate rationale for using a mixed methods design to address the research question? *Explanations* The reasons for conducting a mixed methods study should be clearly explained. Several reasons can be invoked such as to enhance or build upon qualitative findings with quantitative results and vice versa; to provide a comprehensive and complete understanding of a phenomenon or to develop and test instruments [Bryman, 2006].
	5.2. Are the different components of the study effectively integrated to answer the research question? *Explanations* Integration is a core component of mixed methods research and is defined as the "explicit interrelating of the quantitative and qualitative component in a mixed methods study" [Plano Clark and Ivankova, 2015, p. 40]. Look for information on how qualitative and quantitative phases, results, and data were integrated [Pluye et al., 2018]. For instance, how data gathered by both research methods was brought together to form a complete picture [e.g., joint displays] and when integration occurred [e.g., during the data collection-analysis or/and during the interpretation of qualitative and quantitative results].

same cases], or by transforming data [e.g., quantization of qualitative data]. **Sequential explanatory design** Results of the phase 1 - QUAN component inform the phase 2 – QUAL component. The purpose is to explain QUAN results using QUAL findings. E.g., the QUAN results guide the selection of QUAL data sources and data collection, and the QUAL findings contribute to the interpretation of QUAN results. **Sequential exploratory design** Results of the phase 1 - QUAL component inform the phase 2 – QUAN component. The purpose is to explore, develop and test an instrument [or taxonomy], or a conceptual framework [or theoretical model]. E.g., the QUAL findings inform the QUAN data collection, and the QUAN results allow a statistical generalization of the QUAL findings key references: Creswell et al. [2011]; Creswell and Plano Clark, [2017]; O'Cathain [2010]	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? *Explanations* This criterion is related to meta-inference, which is defined as the overall interpretations derived from integrating qualitative and quantitative findings [Teddlie and Tashakkori, 2009]. Meta-inference occurs during the interpretation of the findings from the integration of the qualitative and quantitative components, and shows the added value of conducting a mixed methods study rather than having two separate studies.
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? *Explanations* When integrating the findings from the qualitative and quantitative components, divergences and inconsistencies [also called conflicts, contradictions, discordances, discrepancies, and dissonances] can be found. It is not sufficient to only report the divergences; they need to be explained. Different strategies to address the divergences have been suggested such as reconciliation, initiation, bracketing and exclusion [Pluye et al., 2009b]. Rate this criterion 'Yes' if there is no divergence.
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved? *Explanations* The quality of the qualitative and quantitative components should be individually appraised to ensure that no important threats to trustworthiness are present. To appraise 5.5, use criteria for the qualitative component [1.1 to 1.5], and the appropriate criteria for

	the quantitative component [2.1 to 2.5, or 3.1 to 3.5, or 4.1 to 4.5]. The quality of both components should be high for the mixed methods study to be considered of good quality. The premise is that the overall quality of a mixed methods study cannot exceed the quality of its weakest component. For example, if the quantitative component is rated high quality and the qualitative component is rated low quality, the overall rating for this criterion will be of low quality.

[Source; [24]]

APPENDIX E.

Table 1 Extraction table summary for qualitative systematic review

Article number	Author	Year published	Title	Country/ies	Vaccine	Participants	Health systems determinants of delivery	Health systems determinants of uptake
1	Otieno *et al.*	2020	Drivers and barriers of vaccine acceptance amongst pregnant women in Kenya	Kenya	Tetanus & Influenza	Pregnant women	Tetanus and influenza vaccines available and recommended	Healthcare workers main source of recommendation for vaccine
2	Otieno *et al.*	2020	Knowledge and attitudes towards influenza and influenza vaccination among pregnant women in Kenya	Kenya	Influenza	Pregnant women		Willingness to accept vaccine associated with belief that any maternal vaccines offered by public healthcare ['government'] are trustworthy and beneficial
3	Nyiro *et al.* 2020	2020	Implications of gestational age at antenatal care attendance on the successful implementation of a maternal respiratory syncytial virus [RSV] vaccine program in coastal Kenya	Kenya	Tetanus, to inform RSV	Women	Median initiation of ANC at 26 weeks Only 10% of women attended >5 ANC Issues with physical ANC booklets to track vaccine coverage	Education level significantly associated with pregnant women's access of ANC 96% of women attended ANC between 24 and 36 weeks
4	Nganga *et al.*	2019	Patient and provider perspectives on how trust influences maternal vaccine acceptance among pregnant women in Kenya	Kenya	Tetanus, general	Pregnant women; healthcare providers	Lack of vaccine education and communication by healthcare providers: workloads, time constraints	Trust in healthcare provider's authority Religious and cultural barriers to uptake Cost barrier in rural context Cost and provider attitudes affect uptake
5	Otieno *et al.*	2021	Decision-making process for introduction of maternal vaccines in Kenya, 2017–2018	Kenya	General	Policy makers	WHO recommendations and funding availablity drive decision-making for vaccines Maternal immunisation policy borrowed from existing policies for other vaccines	Factors outside of policy landscape that affect uptake: religious beliefs, anti-vaccine campaigns

							Gap in implementation; top down, lack of communication to facility-level	
6	Chander *et al.*	2020	Antenatal care providers' attitudes and beliefs towards maternal vaccination in Kenya	Kenya	Tetanus, influenza	Healthcare providers	Restricted resources: logistical and human Good availability of vaccines Public facilities had good education material and vaccine supply Healthcare providers not regularly updated on vaccination guideline changes	High levels of trust between pregnant women and providers
7	Bergenfield *et al.*	2018	Provider perspectives on demand creation for maternal vaccines in Kenya	Kenya	Tetanus	Healthcare providers	Devolution: county-based issues for supply, cold-chain and financing Limited acceptance of influenza vaccine among healthcare providers	Barrier to uptake: cost of ANC, distance to facility in rural areas Decision-making: women have limited agency, reliance on relatives
8	Giduthuri *et al.*	2019	Influenza vaccination of pregnant women: Engaging clinicians to reduce missed opportunities for vaccination	India	Influenza. Intervention: 2 strategic interactions with HCPs	Women; community members Healthcare providers	Vaccination records [logs] difficult to maintain by healthcare workers Vaccine availability differs by economic class: "slum" compared to "middle class"	
9	Giduthuri *et al.*	2021	Antenatal influenza vaccination in urban Pune, India: clinician and community stakeholders' awareness, priorities, and practices	India	Influenza	Women; community members; Healthcare providers	Lack of healthcare provider awareness for influenza vaccine recommendation Lack of clear policy in facilities	Perception that payment for services equates to vaccine information sharing and informed consent to vaccines Barrier to uptake: cost [in slum areas], knowledge of vaccine Decision-making: reliance on relatives

10	Malik *et al*.	2020	Health care providers perspectives about maternal immunization in Latin America	Argentina, Brazil, Honduras, Mexico, Peru	Tetanus and influenza	Healthcare providers	Lack of co-ordinated approach between private and public sectors: recommendation discrepancies Lack of funding for research Stockouts jeopardise trust in providers Lack of training for physicians	Accessing care is a challenge in rural/marginalised areas Many women experience long waiting times at facilities
11	Malik *et al*.	2020	Pregnant women's perspectives about maternal immunization in Latin America	Argentina, Brazil, Honduras, Mexico, Peru	Influenza	Pregnant women	Long waiting times a facilities Understaffed Vaccine shortages	Healthcare providers are trusted for vaccine recommendations Bad attitude of providers and treatment of pregnant women barrier to uptake Reliance on social media for vaccine information
12	Alvarez *et al*	2020	Enablers and barriers of maternal and neonatal immunization programs in Latin America	Latin America: Argentina, Brazil, Honduras, Mexico, Peru	General	Healthcare providers decision makers, community members, pregnant women	Considerations for vaccine policy: political will, feasibility, technicalities Top-down policy communication Domestic pooled funding Limited service provider and platform coordination	Incentive: cash offers for vaccine
13	Simas *et al*	2021	"Saint Google, now we have information!": a qualitative study on narratives of trust and attitudes towards maternal vaccination in Mexico City and Toluca	Mexico	General	Women	Experienced shortages; reliance on private care if public is saturated. Dual reliance on public and private providers	Dimensions of trust: safety, information; health system Relatives influence decision-making

14	Gonzalez-Block *et al*.	2020	Influenza vaccination hesitancy in five countries of South America. Confidence, complacency and convenience as determinants of immunization rates	South America [Brazil, Paraguay, Chile, Peru, Uruguay]	Influenza	Pregnant women		Less than half of the pregnant women had been vaccinated in the last year Confidence is the key factor among pregnant women for vaccine hesitancy across countries.
15	Praphasiri *et al*.	2017	Do Thai Physicians Recommend Seasonal Influenza Vaccines to Pregnant Women? A Cross-Sectional Survey of Physicians' Perspectives and Practices in Thailand	Thailand	Influenza	Healthcare providers	Ministry of Health Guidelines unclear Healthcare provider knowledge of guidelines, vaccine safety facilitate high vaccine coverage Storage issues reported Influenza not part of routine ANC monitoring	Vaccines provided free of charge
16	Kaoiean *et al*.	2019	Predictors for influenza vaccination among Thai pregnant woman: The role of physicians in increasing vaccine uptake	Thailand	Influenza	Pregnant women and Healthcare providers	All health care providers knew about national policy for influenza vaccine during pregnancy, but only 28% stated that they were frequent recommenders.	Awareness of National policy in vaccination seemed to be associated with likelihood of vaccinating Social demographic factors like age, income, employment status/education did NOT associate with uptake. Those who received recommendations from HCP were twice more likely to receive vaccine
17	Wang *et al*.	2019	Low awareness of influenza vaccination among pregnant women and their obstetricians: a population-based survey in Beijing, China	China	Influenza	Pregnant women; Healthcare providers	Healthcare provider willingness to recommend vaccine was very low, associated with higher professional title but younger HCP age Unwillingness was associated with safety concerns and AEFI	Positive association with vaccine uptake and history of prior vaccination; perceived benefits and knowledge of influenza; provider recommendation; media coverage

18	Wang *et al*.	2021	Acceptance of seasonal influenza vaccination and associated factors among pregnant women in the context of COVID-19 pandemic in China: a multi-center cross-sectional study based on health belief model	China	Influenza	Pregnant women		Acceptance significantly associated with provider and family-member recommendations Low acceptance levels attributed to lack of knowledge of vaccine purpose and safety
19	Richun *et al* 2018	2018	Identifying ways to increase seasonal influenza vaccine uptake among pregnant women in China: A qualitative investigation of pregnant women and their obstetricians	China	Influenza	Pregnant women, Healthcare providers	Lack of National influenza guidelines Lack of provider awareness of global CDC and WHO guidelines Provider reliance on non-pharmaceutical interventions	Lack of awareness and effectiveness of vaccine barrier to uptake Decision-making: influenced by health ministry, family members, providers
20	Kfouri & Richtmann	2013	Influenza vaccine in pregnant women: immunization coverage and associated factors	Brazil	Influenza	Women	97% of the sample had been vaccinated during pregnancy 78% informed during antenatal period	Uptake associated with awareness of vaccine benefit to neonate
21	Medonza-Sassi *et al*.	2019	Vaccination against influenza among pregnant women in southern Brazil and associated factors	Brazil	Influenza	Women	Most women vaccinated in their third trimester; majority had received it in their lifetime. Prenatal care split between public and private fairly evenly; with 80% accessing care in first trimester. Delivery in private care decreased vaccination coverage compared to public	Private sector charges for vaccine Education level does seem to be a significant factor for influenza uptake Delayed prenatal care associated with lower vaccine uptake

22	Simas *et al.*	2021	''From my phone, I could rule the world": Critical engagement with maternal vaccine information, vaccine confidence builders and post-Zika outbreak rumours in Brazil	Brazil	General; Zika	Pregnant women		Prenatal experience was at private facilities, but vaccinating would happen at public [preference] Lack of trust around Zika vaccines: government mistrust, safety concerns. The vaccination card/booklet is used for info reference and vaccine record
23	Carcelen *et al.*	2020	Perceptions and attitudes towards vaccination during pregnancy in a peri urban area of Lima, Peru	Peru	General; Zika	Pregnant women	Two thirds of women had been vaccinated during pregnancy	Most told about vaccinations during ANC; low vaccine hesitancy Lack of vaccine information is main barrier to uptake. Provider recommendation facilitates uptake
24	Garcia *et al.*	2020	''The flu... is a little more complicated than a cold": Knowledge, beliefs, and practices related to influenza and influenza vaccination among at-risk populations and health professionals in Peru	Peru	Influenza	Pregnant women	Pregnant women not perceived to be 'high risk group to decision-makers Vaccine shortage/supply issues; late arrival; long waiting times	Barrier to uptake: providers themselves, particularly doctors, are vaccine hesitant
25	Varan *et al.*	2014	Intention to accept Bordetella pertussis booster vaccine during pregnancy in Mexico City	Mexico	Tetanus, influenza, pertussis	Women		Most respondents attended ANC during third trimester. Majority received recommendation for tetanus, but was lower for influenza. Health Ministry, providers and media are sources of information
26	Honarvar *et al.*	2012	Acceptance and rejection of influenza vaccination by pregnant women in southern Iran	Iran	Influenza	Pregnant women	Only pregnant women with a history of chronic disease have been included in National Immunisation Programme	Social determinants were not NB factors that affect likelihood of vaccination Uptake VERY low of influenza [6%]: lack of knowledge and information
27	Laizer *et al.*	2021	Challenges Experienced by Healthcare Workers on Maternal Tetanus Toxoid	Tanzania	Tetanus	Healthcare providers	Unreliable Tetanus vaccine storage [interrupted power supply] leads to reliance	Follow-up doses jeopardised because of local cultural birth norms Delayed ANC Decision-making: spousal influence

			Vaccination in Kilimanjaro Region Tanzania				on other sources that take long to procure [like gas] Movement of vaccines from district to facility is a barrier; transportation issues. Division of labour between nurses and doctors: lack of coordinated team-work	
28	Johm *et al.*	2021	Factors influencing acceptance of vaccination during pregnancy in The Gambia and Senegal	Senegal, Gambia	Tetanus	Women	Vaccines not integrated in ANC [Senegal]	Some communities have sense of honour in being able to pay for services; reluctant to receive free vaccines at no cost Need for sensitisation of community for new vaccines High trust in providers
29	Giles *et al.*	2020	Vaccine implementation factors affecting maternal tetanus immunization in low- and middle-income countries: Results of the Maternal Immunization and Antenatal Care Situational Analysis [MIACSA] project	Range of LMICs	Tetanus	Policy-makers; Healthcare providers; pregnant women	Policy and targets set at national level not necessarily known at facility level EPI is the procurement platform for most countries Nurses trained frequently	
30	Anatea *et al.*	2018	Determinants and perceptions of the utilization of tetanus toxoid immunization among reproductive-age women in Dukem Town, Eastern Ethiopia: a community-based cross-sectional study	Ethiopia	Tetanus	Women	Facility waiting times and staff treatment of patients affect delivery 60% had less than 4 ANC visits	Variables that significantly affected utilisation: education level, TV in the house, occupation status, place of birth, knowledge of Tetanus vaccine
31	Gebremedhin *et al.*	2020	Tetanus Toxoid Vaccination Uptake and Associated Factors among Mothers Who Gave Birth in the Last 12	Ethiopia	Tetanus	Women		Barriers to uptake include Very long travel times to facilities and Low satisfactory knowledge of vaccine Increased uptake with urban residency, short travel distance, maternal education

			Months in Errer District, Somali Regional State, Eastern Ethiopia					
32	Arifin *et al.*	2021	Regional disparities and their contribution to the coverage of the tetanus toxoid vaccine among women aged 15–49 years in Indonesia	Indonesia	Tetanus	Pregnant women	Coverage was associated with residence [rural/urban], wealth quintiles, health insurance, education level, age, employment status.	More likely to get vaccinated in rural areas Compliance and trust in healthcare providers
33	Bishop *et al.*	2021	An evaluation of an influenza vaccination campaign targeting pregnant women in 27 clinics in two provinces of South Africa, 2015 – 2018	South Africa	Influenza	Pregnant women	Barriers to delivery: stock outs, cold chain management and waste Did not affect staff functions for ANC High coverage associated with provider training	High coverage associated with maternal education
34	Erazo *et al*	2020	Knowledge, attitudes and practices on influenza vaccination during pregnancy in Quito, Ecuador	Ecuador	Influenza	Women	High ANC attendance: 80% attended over 4 visits Increased ANC visits associated with vaccination during pregnancy Reliance on self-reporting because women lack documentation	Knowledge of vaccine and perception of safety and effectiveness significantly higher in vaccinated women Lack of healthcare provider recommendation is main barrier to uptake
35	Nguyen *et al.*	2021	Acceptance and willingness to pay for COVID-19 vaccines among pregnant women in Vietnam	Vietnam	COVID-19	Women		Education associated with vaccine acceptance: higher education more likely to vaccinate
36	Fleming *et al.*	2018	Implementation of maternal influenza immunization in El Salvador: Experiences and	El Salvador	Influenza	Community members; Healthcare providers	Primary delivery through vaccination weeks Notable increased acceptance of vaccine by	Public facilities offer vaccine free of charge; private providers often refer to them Providers trusted

			lessons learned from a mixed-methods study				HCPs over time, which improved acceptance by community	Decision-making: reliance on family and community Crime major barrier to access
37	Fleming *et al.*	2019	Maternal immunization in Malawi: A mixed methods study of community perceptions, programmatic considerations, and recommendations for future planning	Malawi	Influenza and tetanus	Healthcare providers; policy makers, community members; pregnant women.	Local laws aimed to increase health coverage, like laws requiring tetanus vaccination, incentivised Lack of resources to cope with waste Information documented at facility & community level, but not shared between sites: difficult to track vaccination and doses	Community health workers main source of info, followed by HCPs Concern that injectable contraceptive concerns overlap/confuse vaccine perceptions Purchasing of vaccines by community members deems the vaccines safe Religious affiliation and family opinions barrier to uptake
38	Kajungu *et al.*	2020	Vaccines safety and maternal knowledge for enhanced maternal immunization acceptability in rural Uganda: A qualitative study approach	Uganda	Tetanus	Women and Healthcare providers	Vaccine only offered 2 days of the week, weekdays Long waiting times Lack of sufficient healthcare providers	women who use traditional healers and do not access facilities Fear of mandatory HIV testing for ANC also wards women off. High willingness to receive vaccines if sensitised to them
39	Lohiniva *et al*	2014	A Qualitative Study of Vaccine Acceptability and Decision Making among Pregnant Women in Morocco during the A (H1N1) pdm09 Pandemic	Morocco	Influenza	Women		Distrust of vaccination intent: for-profit by manufacturers and fear of foreign interference Barrier to uptake: lack of sufficient information from provider or no recommendation at all
40	Yaya *et al*	2019	Antenatal visits are positively associated with uptake of tetanus toxoid and intermittent preventive treatment in pregnancy in Ivory Coast	Ivory Coast	Tetanus	Pregnant women	79% had adequate tetanus coverage [>2 doses]	Higher uptake was seen in group with higher education, younger in age, rural residency, at least 3 ANC visits.

41	Yaya *et al*.	2020	Prevalence and predictors of taking tetanus toxoid vaccine in pregnancy: a cross-sectional study of 8,722 women in Sierra Leone	Sierra Leone	Tetanus	Women		Higher tetanus coverage associated with increased ANC, Higher wealth quintile, rural residency.
42	Larson Williams *et al*	2018	''When you are injected, the baby is protected:" Assessing the acceptability of a maternal Tdap vaccine based on mothers' knowledge, attitudes, and beliefs of pertussis and vaccinations in Lusaka, Zambia	Zambia	Tdap	Women		Limited knowledge and misconceptions around vaccines and associated diseases community rumours fuel hesitancy Barrier to uptake: partner/spousal hesitancy
43	Giles *et al*	2020	Antenatal care service delivery and factors affecting effective tetanus vaccine coverage in low- and middle-income countries: Results of the Maternal Immunisation and Antenatal Care Situational analysis [MIACSA] project	Range of LMICs	Tetanus	Pregnant women; Healthcare providers	20% of countries indicated ANC being funded partial by out of pocket payments	Imposing user fees was significantly associated with lower tetanus vaccine coverage
44	Arriola *et al*	2018	Knowledge, attitudes and practices about influenza vaccination among pregnant women and healthcare providers serving pregnant women in Managua, Nicaragua	Nicaragua	Influenza	Pregnant women; Healthcare providers	Most countries reported that ANC was dependent on national budget, and half of the countries benefit from external donor funding Predominant reliance on passive reporting for diseases Higher ANC visit recommendation was associated with higher vaccine coverage	Major barrier to uptake was unawareness of vaccine Social demographic factors had no association with uptake Less than half received recommendations from healthcare providers
45	Arriola *et al*	2016	Factors associated with a successful expansion of	Nicaragua	Influenza	Pregnant women	Majority received influenza vaccine in the third trimester	No association of vaccine with social demographics

			influenza vaccination among pregnant women in Nicaragua				Unavailability of vaccines at some facilities was a barrier to delivery High healthcare provider belief that vaccines are effective, and most knew of the tetanus vaccine recommendation	
46	Li *et al*	2019	Factors affecting pregnant women's decisions regarding prenatal pertussis vaccination: A decision-making study in the nationwide Prenatal Pertussis Immunization Program in Taiwan	Taiwan	Tdap	Pregnant women	71% of women had received vaccine 73% attended >4 ANC visits	Social demographics NOT associated with uptake Uptake is associated with sufficient information provision around the vaccine Provider recommendations influential to uptake
47	Wong *et al.*	2017	Attitudes towards Zika screening and vaccination acceptability among pregnant women in Malaysia	Malaysia	Zika	Pregnant women		Willingness to take vaccine if recommended by healthcare provider Decision-making Friends, family and spouses cited as major influences for vaccine recommendation

[Source, author]

APPENDIX F.

BMC Public Health: Submission Guidelines

Criteria

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a complete CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered. Studies reporting descriptive results from a single institution will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience. Authors can receive free advice on how and where to share their research data, according to their specific research community, from a team of research data editors by contacting our Research Data Helpdesk.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section. Please note that your manuscript must include a 'Declarations' section including all of the subheadings [please see below for more information].

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications

- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively [before enrollment of the first participant], you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords
Three to ten keywords representing the main content of the article.

Background
The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods
The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results
This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion
This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions
This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations
If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations
All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements

- Authors' information [optional]

Please see below for details on the information to be included in these sections. If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate
Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent [even where the need for approval was waived]
- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner. If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript contains any individual person's data in any form [including any individual details, images or videos], consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication. You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage [including after publication].See our editorial policies for more information on consent for publication. If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials
All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access. Data availability statements can take one of the following forms [or a combination of more than one if required for multiple datasets]:

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].

- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].
- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here. BioMed Central also requires that authors cite any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier [such as a DOI] and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:
Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system [GIDMaPS] data sets. figshare.
2014. http://dx.doi.org/10.6084/m9.figshare.853801

With the corresponding text in the Availability of data and materials statement: The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number] If you wish to co-submit a data note describing your data to be published in *BMC Research Notes*, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support [example].

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If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

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Authors' contributions
The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies. Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

Acknowledgements

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If you do not have anyone to acknowledge, please write "Not applicable" in this section. Group authorship [for manuscripts involving a collaboration group]: if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the "Acknowledgements" section. Please add authors in the format First Name, Middle initial[s] [optional], Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors.Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

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Smith JJ. The world of science. Am J Sci. 1999;36:234-5.

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Article within a journal by DOI

Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. Dig J Mol Med. 2000; doi:10.1007/s801090000086.

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Wyllie AH, Kerr JFR, Currie AR. Cell death: the significance of apoptosis. In: Bourne GH, Danielli JF, Jeon KW, editors. International review of cytology. London: Academic; 1980. p. 251-306.

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Online document

Doe J. Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. 1999. http://www.rsc.org/dose/title of subordinate document. Accessed 15 Jan 1999.

Online database

Healthwise Knowledgebase. US Pharmacopeia, Rockville. 1998. http://www.healthwise.org. Accessed 21 Sept 1998.

Supplementary material/private homepage

Doe J. Title of supplementary material. 2000. http://www.privatehomepage.com. Accessed 22 Feb 2000.

University site

Doe, J: Title of preprint. http://www.uni-heidelberg.de/mydata.html [1999]. Accessed 25 Dec 1999.

FTP site

Doe, J: Trivial HTTP, RFC2169. ftp://ftp.isi.edu/in-notes/rfc2169.txt [1999]. Accessed 12 Nov 1999.

Organization site

ISSN International Centre: The ISSN register. http://www.issn.org [2006]. Accessed 20 Feb 2007.

Dataset with persistent identifier

Zheng L-Y, Guo X-S, He B, Sun L-J, Peng Y, Dong S-S, *et al.*. Genome data from sweet and grain sorghum [Sorghum bicolor]. GigaScience Database. 2011. http://dx.doi.org/10.5524/100012.