Vaccine 39 (2021) B12–B26

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Adverse events associated with the use of recommended vaccines during pregnancy: An overview of systematic reviews ☆

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ARTICLE INFO

Article history:
Available online 21 September 2020

Keywords:
Pregnancy
Vaccination
Adverse effects
Epidemiological study
Meta-analysis
Systematic review

ABSTRACT

Introduction: Maternal immunization is aimed at reducing morbidity and mortality in pregnant women and their newborns. Updated evidence synthesis of maternal-fetal outcomes is constantly needed to ensure that the risk-benefit of vaccination during pregnancy remains positive.
Methods: An overview of systematic reviews (OoSRs) was performed. We searched The Cochrane Library, MEDLINE and EMBASE for SRs including recommended vaccines for maternal immunization reporting the following: abortion, stillbirth, chorioamnionitis, congenital anomalies, microcephaly, neonatal death, neonatal infection, preterm birth (PTB), low birth weight (LBW), maternal death and small for gestational age (SGA) from 2010 to April 2019. Quality and overlap of SRs was assessed.
Results: Seventeen SRs were identified, eight of them included meta-analysis; quality was high in three SRs, moderate in six SRs, low in two SRs, and critically low in six SRs. Stillbirth and PTB were the most frequently reported outcomes by 15 and 13 SRs, respectively, followed by abortion (9 SRs), congenital anomalies (9 SRs), SGA (8 SRs), neonatal death (8 SRs), LBW (4 SRs), chorioamnionitis (3 SRs), maternal death (1 SR). SRs included mainly observational evidence for influenza and Tdap vaccines (11 SRs and 4 SRs, respectively); limited evidence was found for hepatitis (1 SR), yellow fever (1 SR), and meningococcal (1 SR) vaccines. Most of the SRs found no effect. Eight SRs found benefit/protection of influenza vaccine (for stillbirth, neonatal death, preterm birth, LBW), or Tdap vaccine (for preterm birth and SGA); one found a probable risk (chorioamnionitis/Tdap). The SRs for Hepatitis B, meningococcal and yellow fever vaccines were inconclusive.
Conclusions: Definite risks were not identified for any vaccine and outcome; however better evidence is needed for all outcomes and vaccines. The available evidence in the SRs to support vaccine safety was based mainly on observational data. More RCTs with adequate reporting of maternal-fetal outcomes and larger high-quality observational studies are needed.

Contents

☆ Publication of this supplement was supported by the Pan American Health Organization (PAHO). The views expressed herein are those of the authors and do not necessarily reflect the official policy or position of PAHO.
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https://doi.org/10.1016/j.vaccine.2020.07.048
0264-410X/

1. Introduction

Maternal immunization is a promising strategy to reduce morbidity and mortality in pregnant women and their newborns [1]. However, many countries, mostly low- or middle-income countries, have not yet introduced this strategy into their national immunization programmes [2].

Vaccines have been associated with fewer concerns of pharmacovigilance than other biological medicines [3,4]. Moreover, live vaccines are not routinely given to pregnant women, and immunization with inactivated vaccines or toxoids during pregnancy is not expected to be associated with an increased risk to the fetus [5,6]. However, additional surveillance activities (including studies) are recommended to gain information on vaccine safety with regard to adverse events following immunization (AEFI) in the mother or the baby, to ensure that the risk-benefit balance remains positive in pregnant women and their newborns [1,7].

Systematic reviews and meta-analyses of Randomized Clinical Trials can also be used to confirm the safety of a drug or group of drugs when a signal arises from other methods, and their use is currently considered to be third generation pharmacovigilance, over spontaneous reports, and observational studies, which are considered first and second pharmacovigilance generation respectively [8]. The updated evidence from systematic reviews [or overviews] of reviews can provide support for designing and planning new recommendations, studies, and/or meta-analyses [9].

We conducted an overview of systematic reviews reporting data on safety after immunization with recommended vaccines during pregnancy in the Maternal and Neonatal Immunization Field Guide for Latin America and the Caribbean [6].

2. Methods

We conducted an overview of reviews according to a protocol that was registered in PROSPERO [registration number: CRD42018091216]. We adhered to the guidance provided by Cochrane [10] and reported our findings according to the PRISMA statement [11]. We included published systematic reviews that explicitly stated pre-defined eligibility criteria for studies, reported a search in at least two databases, and included controlled studies. Reviews that provided an assessment or discussion of the risk of bias in identified studies were analyzed separately from reviews not assessing the risk of bias in included primary studies.

We considered eligible those reviews assessing the safety of the following vaccines administered during pregnancy [6]: a) Hepatitis A/B; b) Influenza (including H1N1); c) Meningococcal disease; d) Poliomyelitis; e) Rabies; f) Tetanus/Diphtheria/Pertussis [including Tdap); g) Yellow fever. Our pre-defined primary outcomes included: a) Neonatal death (fetal death, newborn death); b) Neonatal infection (unrelated to the infection that prevents the vaccine given); c) Chorioamnionitis; d) Congenital anomalies; e) Microcephaly; f) Preterm birth (<37 weeks); g) Abortion (<24 weeks); h) Stillbirth ($\geq$24 weeks). As a secondary outcome, we also assessed: a) LBW (<2500 g); b) Maternal death during the follow-up period; c) SGA. We included reviews regardless of the geographic area covered. Reviews of effectiveness were included if they also reported disaggregated data for safety outcomes.

We searched the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effect through The Cochrane Library. Additionally, we searched MEDLINE and EMBASE up to April 2019. We designed search strategies (Appendix, Table S1.) adapted to the requirements of each database, which included a combination of controlled vocabulary, search terms, and filters to retrieve systematic reviews. In addition, we searched the lists of references from eligible reviews for additional ones. We included reviews published from 2010 onwards to prioritize the applicability of findings [12]. For eligible Cochrane reviews, we included the most recently updated version.

Two researchers independently screened results from search strategies, based on references, title and abstract, and confirmed the studies' eligibility by obtaining a full copy of relevant articles. We solved disagreements by discussion until consensus was reached or by involving a third researcher. For each included review, one researcher obtained data, in a pre-piloted form, on review characteristics [study design (included), and population, vaccine, and outcomes assessed], an appraisal of its quality, and its findings and effect estimate for the main outcomes. A second researcher cross-checked the data extracted for accuracy. We summarized data from this extraction process into descriptive tables. We assessed the methodological quality from the included reviews with the AMSTAR-II checklist, rating the overall quality according to the limitations identified in the different domains [13]. We quantified the overlap of primary studies included in eligible SRs by calculating the corrected covered area [CCA] from the number of SRs considered eligible and all the primary studies included in those reviews [14]. We classified the degree of overlap according to the percentage overlap, indicating slight [0–5%], moderate [6–10%], high [11–15%], and very high [>15%].

As we anticipated that the reviews would report their findings using different effect estimates on multiple outcome measures, we limited the synthesis of results to a narrative summary of findings grouped by type of vaccine and outcomes of interest. We categorized the conclusions provided by the review authors by each pre-defined outcome according to the amount and robustness of available evidence into categories: inconclusive; no effect; risk; and benefit/risk protection (Table S6). We synthetized the findings from the overview, providing narrative summaries of the results obtained from the included SRs with the highest quality according to the outcomes of interest.

3. Results

We described the complete eligibility process in a PRISMA flowchart (Appendix, Fig. S1). After removing duplicates, we screened 218 unique references. We obtained 34 full-text studies for a detailed assessment, but excluded 17 of them because they did not assess safety outcomes or used any of the outcomes of interest for this overview as an effectiveness measure (6 studies), and the remaining (11 studies) for other reasons. The complete list of excluded studies is available in the Appendix, (Table S2). We included 17 systematic reviews [15–31]. Table 1 outlines the main characteristics of the included reviews. A detailed summary of each included SR is available in the Appendix (Table S3.). Most of them included data from observational studies. Influenza vaccination, including the H1N1 vaccine, was assessed in two thirds of reviews and the most common outcomes assessed by reviews were: pre-

Table 1
Characteristics from included systematic reviews.

Review type	
Narrative SR	9
SR+ MA	8
Cochrane reviews	2
Study designs included	
Randomized clinical trials (RCT)	2
Observational	7
RCT + observational studies	8
AMSTAR scores	
High	3
Moderate	6
Low	2
Critically low	6
Type of vaccine	
Hepatitis B	1
Influenza	11
Meningococcal polysaccharide	1
Tetanus-diphtheria/pertussis-containing	
Yellow fever	4
	1
Outcomes assessed	
Primary outcomes	
Abortion/Miscarriage	9
Stillbirth	13
Chorioamnionitis	3
Congenital anomalies	9
Microcephaly	0
Neonatal Death	8
Neonatal Infection	0
Preterm Birth	15
Secondary outcomes	
Low birth weight	4
Maternal death	1
Small for gestational age	8

term birth (15/17) and stillbirth (13/17), but some pre-specified outcomes of interest (microcephaly, neonatal infection and maternal death) were rarely assessed. The reviews used different definitions for the outcomes of interest, which are compiled in the Appendix (Table S4). In addition, we did not find reviews about the safety of poliomyelitis and rabies vaccines. One review assessed hepatitis B and meningococcal polysaccharide vaccines [15]. The Appendix, Table S5, shows the assessment of the methodological quality of included reviews. The reviews varied hugely in terms of their quality. Although nine reviews have a high [24,30,31] or moderate quality [17,21,23,26,28,29], six were considered to have critically low quality, because they did not perform an assessment of the risk of bias in the included primary studies [15,16,18,22,25,27] and had incomplete searches [22,25,27]. A small proportion of reviews were conducted according to a pre-established protocol [5/17]. According to the corrected covered area for those vaccines that were assessed in more than one review, the overlap was high [influenza 33%, pertussis 42%].

Tables 2–6 summarize the main results from included reviews according to our pre-defined outcomes. We summarize the main conclusions for the primary outcomes from the nine reviews with moderate or high quality [17,21,23,24,26,28–31], which varied slightly depending on the outcome and the vaccines assessed. According to six reviews [17,21,24,29–31] the influenza vaccine does not increase the risk of abortion or stillbirth, and could even have a moderate protective effect for stillbirth [17,29]. Specifically, one review reported a 20% reduction in stillbirth after H1N1 vaccination, pooling data from 11 observational studies [29]. Two reviews reported no effects from the Tdap vaccine for the risk of stillbirth [26,28]. Two reviews did not find an increase of neonatal [24,30] or maternal [24] deaths as a result of influenza vaccination. The two reviews of Tdap vaccines reached similar conclusions [26,28].

Although two reviews found an inconclusive impact of influenza vaccines on congenital malformations and called for more rigorous studies in women vaccinated during their first trimester [28,29], three additional reviews concluded that the seasonal inactivated or monovalent H1N1 pandemic vaccines during pregnancy do not increase the risk of congenital defects [23,30,31]. The conclusions from the two reviews of the Tdap vaccine were discrepant; one found that the risk of malformations associated with the vaccine is very uncertain due to the scarce data available [26], but the other concluded that this immunization does not likely increase the risk of congenital anomalies [28].

Five reviews reached heterogeneous conclusions regarding the impact of the influenza vaccine on pre-term birth [17,24,29–31], most of them reporting an inconclusive effect, with different estimates depending on the trimester in which women were vaccinated [31]. On the other hand, two reviews on the Tdap vaccine reported an inconclusive effect for this outcome [26,28].

The risk of chorioamnionitis was only discussed in the reviews that assessed Tdap vaccines. One review concluded that this vaccination during pregnancy may increase the risk of chorioamnionitis according to the results of one observational study, which showed an absolute difference of 1% in the rate of this outcome between vaccinated (6%) and non-vaccinated women (5.5%) [26]. Another review found no effect [27] and a third review concluded that the risk for this outcome is inconclusive due to inconsistent effects estimates from available studies which used different study definitions of chorioamnionitis including clinical cases, histologically confirmed cases, or both [28]. We only included two reviews for

Table 2
Hepatitis B vaccination safety: findings from included reviews.

Outcomes	Review/ Quality	Studies included/ Sample	Vaccine/ Comparator	Findings reported in the review	Conclusions
Abortion Preterm Birth Stillbirth	Makris 2012 [15] Critically low quality	Randomized controlled trials (1) 100 (52 vaccinated, 48 controls) Observational studies (5) 281 vaccinated	HB recombinant vaccine HB vaccine derived from plasma of chronic HB virus carriers Control Recombinant HB vaccine (different doses) Placebo, no comparator	Review authors did not conduct a meta-analysis and described findings narratively. Major events after recombinant HB vaccine were rare. One trial did not report side effects. A cohort in 168 pregnant women reported a similar preterm birth rate to those in the general population. In a cohort in 16 women vaccinated after an in vitro fertilization, one miscarriage was reported. Only one cohort study in 72 women that received the HB vaccine derived from plasma of virus carriers reported a 1% stillbirth rate.	Inconclusive effect HB vaccine during pregnancy may have no effect on major safety outcomes. Event rates from included studies can be interpreted as close to those expected within general population.

HB: hepatitis B.

Table 3
Meningococcal disease vaccination safety: findings from included reviews.

Outcomes	Review/ Quality	Studies included/ Sample	Vaccine/ Comparator	Findings reported in the review	Conclusions
Preterm Birth Stillbirth Neonatal Death	Makris 2012 [15] Critically low quality	Randomized controlled trials (3) 420 (207 vaccinated, 213 controls) Observational studies (3) 128 vaccinated	Meningococcal polysaccharide vaccine (MPV) Control Pneumococcal Polysaccharide Vaccine or unclear comparator	Review authors did not conduct a meta-analysis and described findings narratively. One trial reported a single preterm delivery (1.3%) and two low birth weight deliveries (2.6%) in a group of 75 MPV vaccinated women. Two additional trials reported stillbirth (range 4–8%) and neonatal death rates (range 0–1.3%) that were within expected rates, according to researchers. Three additional cohort studies did not report major events.	Inconclusive effect Meningococcal polysaccharide vaccine during pregnancy may have no effect on major safety outcomes. Event rates from included studies can be interpreted as close to those expected within general population.

Table 4
Yellow fever vaccination safety: findings from included reviews.

Outcomes	Review/ Quality	Studies included/ Sample	Vaccine/ Comparator	Findings reported in the review	Conclusions
Abortion	Thomas 2012 [16] Critically low	Observational studies (8) Primary data studies: 1381 Secondary data studies 138	Yellow fever vaccination (17D or 17DD) Control Not defined	Review authors did not conduct a meta-analysis and described findings narratively. *Primary data studies*: One cohort reported 11 miscarriages from 304 pregnancies. *Secondary data studies*: One case-control study reported that vaccination did not increase the risk for spontaneous abortion (OR: 2.29; 95% CI: 0.65–8.03). One cohort including 58 pregnancies reported 7 events.	Inconclusive effect Yellow fever vaccination during pregnancy may have no effect on major safety outcomes. Review authors interpreted the rates from included studies as close to those expected within general population.
Congenital anomalies				*Primary data studies*: One study reported 10 events of malformation in new born exposed in utero to Yellow fever vaccination (3.3% from the total sample; 95% CI: 1.7–14.6%). In addition, one cohort reported no differences in malformations from 304 pregnancies. *Secondary data studies*. One cohort including 58 pregnancies reported around 4% major malformations.	
Neonatal death				*Primary data studies*: One cohort reported 2 early neonatal deaths from 304 pregnancies.	
Preterm birth				Primary data studies: One cohort reported 7.8% of premature delivery rate from 304 pregnancies.	

OR: Odds Ratio.

yellow fever [16], and hepatitis B and meningococcal polysaccharide vaccines [15] but they had major methodological limitations, as results were based on studies using external comparators with limited capacity to establish causality effects and thus conclusions may not be reliable. These two reviews concluded that the vaccines assessed have an inconclusive effect for abortion and stillbirth, neonatal deaths and preterm births [15,16], and reported that event rates collected from original studies can be extrapolated to those expected within general population. Congenital abnormalities were only assessed in the yellow fever review [16].

4. Discussion

In this OoSRs we found 17 systematic reviews reporting maternal-fetal and neonatal outcomes of interest after immunization during pregnancy. No major safety concerns with regard to maternal immunization have been identified. However, differences in the available evidence and its quality have been found. Consistently with the current recommendations for maternal immunization, influenza and pertussis vaccines were the most studied vaccines [6]. On the other hand, evidence from SRs was almost nonexistent for those vaccines indicated in exceptional situations (i.e.: Hepatitis B or yellow fever vaccines). We also found differences in the available evidence according to the type of maternal-fetal and neonatal outcome.

Preterm birth [PTB] is defined by WHO as all births before 37 completed weeks of gestation [32]. PTB is a frequent neonatal outcome with an estimated global prevalence ranging from 5 to 18% [33] and it was the most frequently reported outcome in the SRs. Seven SRs with the influenza vaccine found no difference in risk. Two SRs reported statistically significant protection associated with both seasonal and monovalent pandemic vaccines. On the other hand, four SRs of the Tdap vaccine reporting PTB found no differences in risk, or were inconclusive [28,26–28].

One of the causes of preterm birth is chorioamnionitis [33], an infection of the amniotic fluid, fetal membranes, placenta, and/or uterus. Chorioamnionitis can affect 1–2% of full term and 5–10% of preterm pregnancies, but is rarely reported to be associated with vaccines to passive pharmacovigilance systems [34]. In one SR, a small but statistically significant increased risk of chorioamnionitis associated with the Tdap vaccine was reported, based on data from a single study [risk ratio, 1.19, CI 95%: 1.13–1.26] [26]. However, two SRs were inconclusive or found no difference in the risk of

Table 5
Influenza vaccination safety: findings from included reviews.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Abortion	Bratton 2015 [19] Low quality	Observational studies (4) 40,746 (4336 vaccinated, 36,410 non-vaccinated)	seasonal or H1N1pdm09 influenza vaccination Control No vaccination	RR: 0.91; 95% CI: 0.68–1.22 (I^2 = 39.9%).	**No effect** The pooled effect estimate for spontaneous abortion was non significant in relation to non vaccinated women.
	Demichelli 2018 [30] High quality	Observational studies (8) HR adjusted data: 127,103 (27944 vaccinated, 99,159 non-vaccinated) Observational studies (2) OR adjusted data: 486 (243 vaccinated, 243 non-vaccinated)	2009/2010 H1N1 monovalent pandemic vaccine Control Placebo Seasonal influenza vaccine Control Placebo	OR adjusted data: 0.75; 95% CI: 0.62–0.90 (5 studies) HR adjusted data : 0.81; 95% CI: 0.63–1.04 (3 studies). OR unadjusted data: 0.60; 95% CI: 0.41–0.86 OR adjusted: 0.80; 95% CI: 0.36–1.78.	**No effect** Seasonal inactivated vaccine or monovalent H1N1 pandemic vaccines during pregnancy **do not increase** risk of abortion.
	McMillan 2015 [21] Moderate quality	Observational studies (10) 79,796 (16187 vaccinated, 63,609 controls)	Monovalent influenza A (H1N1) 2009 vaccine, or (H1N1) 2009 antigen containing trivalent vaccine Control No vaccination	Review authors did not conduct a meta-analysis and described findings narratively. Spontaneous abortion (defined as foetal death prior to 24 weeks gestation) ranged from HR: 0.45 to OR: 1.23, with 95% confidence intervals crossing or below the null value.	**Inconclusive effect** Maternal influenza vaccination **may not increase** risk of spontaneous abortion. As effect estimates showed imprecision and important heterogeneity it is not possible to exclude the risk of adverse effects. Studies on vaccination during their first trimester should be prioritized.
	Zhang 2017 [29] Moderate quality	Observational studies (3) 63,868 (8025 vaccinated, 55,843 controls)	H1N1 vaccination Control No vaccination	RR adjusted: 1.04; 95% CI: 0.72–1.52.	**No effect** H1N1 vaccination during pregnancy **does not increase** the risk of spontaneous abortion.
	Salam 2015 [7] High quality	Randomized controlled trial (1) 2116 (1062 vaccinated, 1054 controls)	Trivalent influenza vaccination Control Placebo	Miscarriage (24–28 weeks) RR: 0.60; 95% CI: 0.14–2.49.	**No effect** Immunisations during pregnancy with viral influenza vaccines **likely do not increase** risk of foetal death.
	Fell 2015 [8] Low quality	Observational studies (15) 268,777 (69592 vaccinated, 199,185 controls)	Seasonal trivalent inactivated influenza (TIV) or monovalent H1N1 influenza vaccine Control No vaccination	Review authors did not conduct a meta-analysis and described findings narratively. Early foetal death (prior to 20 weeks): Only one out of eight studies reported a reduced risk of foetal death between 9 and 12 weeks of gestation (adjusted HR: 0.74; 95% CI: 0.62–0.88).	**No effect** Influenza immunization during pregnancy **likely not increases** risk of foetal death. Available studies had serious limitations but results within studies were consistent.

Outcomes	Review/Quality	Studies included/ Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Stillbirth	Salam 2015 [7] High quality	Randomized controlled trial (1) 2116 (1062 vaccinated, 1054 controls)	Trivalent influenza vaccination Control Placebo	Stillbirth RR: 1.65; 95% CI: 0.73–3.76.	**No effect** Immunisations during pregnancy with viral influenza vaccines **likely do not increase** risk of foetal death.
	McMillan 2015 (20) Moderate quality	Observational studies (13) 544,581 (105895 vaccinated, 438,686 controls)	Monovalent influenza A (H1N1) 2009 vaccine, or (H1N1) 2009 antigen containing trivalent vaccine Control No vaccination	Review authors did not conduct a meta-analysis and described findings narratively. Effect estimates for the risk of foetal death (in the review, those that occurred after 24 weeks gestation) in women vaccinated during the first trimester ranged from OR: 0.23 to 2.95, with 95% confidence intervals crossing or below the null value.	**Inconclusive effect** Maternal influenza vaccination **may not increase** risk of foetal death. As effect estimates showed imprecision and an important heterogeneity it is not possible to exclude the risk of adverse effects.
	Fell 2015 [8] Low quality	Observational studies (15) 268,777 (69592 vaccinated, 199,185 controls)	Seasonal trivalent inactivated influenza (TIV) or monovalent H1N1 influenza vaccine Control No vaccination	Review authors did not conduct a meta-analysis and described findings narratively. Foetal death occurring at any time: two cohort studies that assessed the adjuvant monovalent H1N1 vaccine did not show an increased risk of foetal loss after vaccination (adjusted HR 0.79 (95%CI 0.53–1.16) and 0.88 (95%CI 0.66–1.17) respectively)	**No effect** Influenza immunization during pregnancy **likely not increases** risk of foetal death. Available studies had serious limitations but results within studies were consistent.

				Late foetal death (≥20 weeks): Some studies did not report adjusted effect measures. High heterogeneity in the rest (RR ranged from 0.44 to 1.44).	
	Giles 2019 [31] High quality	Observational studies (20) 152,713 women vaccinated (145,185 included in risk adjusted analyses)	Inactivated influenza vaccination Control No vaccination	OR adjusted: 0.84; 95% CI 0.65–1.08.	**No effect** Immunisation during pregnancy with inactivated influenza vaccines **likely do not increase** risk of foetal death.
	Bratton 2015 [19] Low quality	Observational studies (7) 145,960 (41301 vaccinated, 104,659 non-vaccinated)	Seasonal or H1N1pdm09 influenza vaccination Control No vaccination	RR: 0.73; 95% CI: 0.55–0.96 (I^2 = 68%).	**Moderate/Large benefit** Vaccinated women **likely reduced** their likelihood of stillbirth.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Stillbirth (continued)	Galvao 2013 [9] Moderate quality	Observational studies (1) 84,843 (8690 vaccinated, 76,153 controls)	Influenza vaccination Control No vaccination	OR unadjusted data: 0.61; 95% CI: 0.42–0.88.	**Moderate/Large benefit** Vaccinated women **likely reduced** their likelihood of stillbirth.
	Meijer 2015 [22] Critically low quality	Observational studies (28) 3876	Influenza vaccination Control Unclear	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. None of the included studies showed an increase in the stillbirth risk after influenza immunization, but larger studies reported a statistically significant reduction of the outcome.	**No effect** Influenza immunization during pregnancy **likely reduces** risk of this outcome. Despite the inconsistency of results from included studies vaccines seem to be safe.
	Zhang 2017 [29] Moderate quality	Observational studies (10) 808,551 (171,906 vaccinated, 636,645 controls)	H1N1 vaccination Control No vaccination	HR adjusted: 0.80; 95% CI: 0.69–0.92 (I^2 = 7.7%) **vaccination during pregnancy lowered the incidence of stillbirth by 20%.**	**Moderate/Large benefit** H1N1 vaccination during pregnancy **likely reduces** the incidence of stillbirth.
Neonatal death	Demichelli 2018 [30] High quality	Observational studies (3) OR adjusted data: 90,679 (8541 vaccinated, 82,138 non-vaccinated)	2009/2010 H1N1 monovalent pandemic vaccine Control Placebo	OR adjusted data: 1.09; 95% CI: 0.40–2.95 2 studies.	**No effect** Seasonal inactivated vaccine or monovalent H1N1 pandemic vaccines during pregnancy **do not increase** risk of neonatal death.
			Seasonal influenza vaccine Control Placebo	OR unadjusted data: 0.55; 95% CI: 0.35–0.88 1 study.	
	Galvao 2013 [9] Moderate quality	Observational studies (1) 84,843 (8690 vaccinated, 76,153 controls)	Influenza vaccination Control Placebo or no vaccination	OR unadjusted data: 0.55; 95% CI: 0.35–0.88.	**Small benefit** Influenza vaccination during pregnancy **may decrease** the risk of neonatal death **slightly**.
	Salam 2015 [7] High quality	Randomized controlled trial (1) 2083 (1041 vaccinated, 1042 controls)	Trivalent influenza vaccination Control Placebo	Perinatal death (stillbirth and death during first week of life) RR: 1.32; 95% CI: 0.73–2.38.	**No effect** Immunisation during pregnancy with viral influenza vaccines **likely not increases** risk of perinatal death.

Outcomes	Review/ Quality	Studies included/ Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Congenital		**anomalies**	Demichelli 2018 [30] High quality	Observational studies (6) OR adjusted data: 304,415 (35,017 vaccinated, 269,398 non-vaccinated)	2009/2010 H1N1 monovalent pandemic vaccine Control Placebo
	OR adjusted	**No effect** Seasonal inactivated			

(*continued on next page*)

	data: 1.11; 95% CI: 0.99–1.23 (6 studies). Seasonal influenza vaccine	vaccine or monovalent H1N1 pandemic vaccines during pregnancy **do not increase** risk of congenital malformation.	OR unadjusted data: 0.55; 95% CI: 0.08–3.73 (2 studies).		
	Control Placebo				
	McMillan 2015 [21] Moderate quality	Observational studies (12) 297,243 (46,137 vaccinated, 251,106 controls)	Monovalent influenza A (H1N1) 2009 vaccine, or (H1N1) 2009 antigen containing trivalent vaccine Control No vaccination	Review authors did not conduct a meta-analysis and described findings narratively. Effect estimates for the risk of congenital malformations in women vaccinated during the first trimester ranged from OR 0.67 to 2.18, with 95% confidence intervals crossing or below the null value.	**Inconclusive effect** Maternal influenza vaccination **may not increase** risk of congenital malformations. As effect estimates showed imprecision and an important heterogeneity it is not possible to exclude the risk of adverse effects. Studies in women vaccinated during their first trimester should be prioritized.
	Polyzos 2015 [23] Moderate quality	Observational studies (15) 282,931	Inactivated influenza vaccine (seasonal trivalent or monovalent H1N1, adjuvant or non-adjuvant) Control No vaccination	OR: 0.96; 95% CI: 0.86–1.07 (I^2 = 36%).	**No effect** Influenza immunization during pregnancy at any trimester **does not increase** risk for congenital defects.
	Zhang 2017 [29] Moderate quality	Observational studies (9) 385,062 (47,483 vaccinated, 337,579 controls)	H1N1 vaccination Control No vaccination	OR adjusted: 1.14; 95% CI: 1.01–1.29 Sensitivity analysis of adjusted estimates after excluding studies of non adjuvanted H1N1 vaccine: OR adjusted: 1.15; 95% CI: 1.02–1.30.	**Inconclusive effect** H1N1 vaccination during pregnancy **may not increase** the risk of congenital anomalies. Although a sensitivity analysis showed a potential increase of this outcome, studies of vaccination during early pregnancy was not associated with congenital abnormalities.
	Giles 2019 [31] High quality	Observational studies (12) 169,829 women vaccinated (157,601 included in risk adjusted analyses)	Inactivated influenza vaccination Control No vaccination	OR adjusted: 1.03; 95% CI: 0.99–1.07.	**No effect** Influenza immunization during pregnancy **does not increase** risk for congenital defects.

Outcomes	Review/ Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Preterm birth	Demichelli 2018 [30] High quality	Observational studies (11) OR adjusted data: 279,609 (69,190 vaccinated, 210,419 non-vaccinated) HR adjusted data: 16,963 (5263 vaccinated, 11,700 non-vaccinated)	2009/2010 H1N1 monovalent pandemic vaccine Control Placebo	OR adjusted data: 0.84; 95% CI: 0.76–0.93 (7 studies). HR adjusted data: 1.11; 95% CI: 0.46 to 2.68 (2 studies).	**No effect** Seasonal inactivated vaccine or monovalent H1N1 pandemic vaccines during pregnancy **do not increase** risk of prematurity.
		124,755 (59479 vaccinated, 65,276 non-vaccinated)	Seasonal influenza vaccine Control Placebo	OR adjusted data: 0.93; 95% CI: 0.82–1.06 (2 studies).	
	Fell 2015 [8] Low quality	Observational studies (19) 633,932 (278,907 vaccinated, 355,025 controls)	Seasonal trivalent inactivated (TIV) or monovalent H1N1	Review authors did not conduct a meta-analysis and described findings narratively.Most studies (18/19) did not show a harmful effect with a broad range of estimates (from 0.63 to 1.20) . Only 1 study reported an increased risk of preterm birth but with a	**No effect** Influenza immunization during pregnancy **likely not increases** risk of preterm birth. Available studies had serious limitations but results within studies were consistent.

		Control Unclear	very imprecise effect estimate.	
Galvao 2013 [9] Moderate quality	Randomized controlled trials(1) 340 (172 vaccinated, 168 controls)observational studies (4) 92,925 (7665 vaccinated, 85,260 controls)	Influenza vaccination Control Placebo, no vaccination	Review authors did not conduct a *meta*-analysis and described findings tabulated and narratively. For this outcome conflicting results were found across the studies.	**Inconclusive effect** The effect of vaccination during pregnancy in the risk of preterm labour is very uncertain due to the heterogeneity from effect estimates and their precision.
Meijer 2015 [22] Critically low quality	Observational studies (28) 3876	Influenza vaccination Control Unclear	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. None of the included studies showed an increase in the preterm birth risk after influenza immunization.	**No effect** Influenza immunization during pregnancy **likely not increases** risk of preterm birth. Despite the inconsistency of results from included studies vaccines seem to be safe.
Nunes 2016 [25] Critically low quality	Observational studies (5) 145,638 (62829 vaccinated, 62,809 controls)	Seasonal trivalent inactivated Control No vaccination	OR: 0.87; 95% CI: 0.77–0.98.	**Small benefit** Influenza vaccination during pregnancy **likely decreased** risk of preterm births **slightly**.
	Observational studies (11) 606,644 (270,418 vaccinated, 336,226 controls)	A/H1N1pdm09 monovalent Control No vaccination	OR: 0.92; 95% CI: 0.85 to 0.99.	

Outcomes	Review/ Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Preterm birth (continued)	Salam 2015 [7] High quality	Randomized controlled trial (2) 213 (130 vaccinated, 83 controls)	Haemophilus influenza type B (Hib) vaccination Control Placebo	RR: 1.28; 95% CI: 0.12–13.86.	**Inconclusive effect** The effect of Hib vaccination during pregnancy in the risk of preterm labour is very uncertain due to the limitations from the evidence and the imprecision of its estimates.
		Randomized controlled trial (1) 2118 (1062 vaccinated, 1054 controls)	Trivalent influenza vaccination Control Placebo	RR: 0.92; 95% CI: 0.53–1.59.	**No effect** Immunisation during pregnancy with viral influenza vaccines **likely not increases** risk of preterm labour.
	Zhang 2017 [29] Moderate quality	Observational studies (12) 484,291 (115,980 vaccinated, 368,311 controls)	H1N1 vaccination Control No vaccination	RR adjusted: 0.92; 95% CI: 0.84–1.01.	**No effect** H1N1 vaccination during pregnancy **does not increase** the risk of preterm delivery.
	Giles 2019 [31] High quality	Observational studies (26) 184,305 women vaccinated (173,131 included in risk adjusted analyses)	Inactivated influenza vaccination Control No vaccination	OR adjusted: 0.86; 95% CI: 0.78–0.96 Estimates differed depending on the trimester in which women were vaccinated (OR for vaccination during 1st trimester 1.08; 95% CI 0.92–1.28; OR for 2nd/3rd trimester 0.96; 95% CI 0.87–1.06).	**Inconclusive effect** Inactivated influenza vaccine during pregnancy **may not reduce** the incidence of preterm births. Considerable uncertainty due to the heterogeneity of effect estimates depending on the trimester in which women were vaccinated.
Low birth weight	Nunes 2016 [25] Critically low quality	Observational studies (2) 20,940 (3781 vaccinated, 17,159 controls)	Seasonal trivalent inactivated influenza vaccine Control No vaccination	OR: 0.74; 95% CI: 0.61–0.88; I^2 = 0%).	**Small benefit** Influenza vaccination during pregnancy **likely decreased** risk of preterm births **slightly**.
		Observational studies (7) 395,045 (215,684 vaccinated, 179,361 controls)	A/H1N1pdm09 monovalent vaccine Control No vaccination	OR = 0.88; 95% CI: 0.79–0.98 (I^2 = 61.6%).	
	Giles 2019 [31] High quality	Observational studies (12) 84,314 women vaccinated (81,609 included in risk adjusted analyses)	Inactivated influenza vaccination Control No vaccination	OR adjusted: 0.82; 95% CI: 0.76–0.89 Estimates differed depending on the trimester in which women were vaccinated (OR for vaccination during 1st trimester 1.00; 95% CI 0.80–1.24; OR for 2nd/3rd trimester 0.97; 95% CI 0.71–1.32).	**Inconclusive effect** Inactivated influenza vaccine during pregnancy **may not reduce** the incidence of low birth weight births. Considerable uncertainty due to the heterogeneity of effect estimates depending on the trimester in which women were vaccinated.
Maternal death	Salam 2015 [7] High quality	Randomized controlled trial (1) 2116 (1062 vaccinated, 1054 controls)	trivalent influenza vaccination Control Placebo	RR: 4.96; 95% CI: 0.24–103.24.	**No effect** Vaccination during pregnancy (with viral vaccines) **likely not increases** risk of maternal death.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Small for gestational age	Galvao 2013 [9] Moderate quality	Randomized controlled trials (1) 340 (172 vaccinated, 168 controls)	Influenza vaccination Control Placebo, no vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. For this outcome conflicting results were found across the studies.	**Inconclusive effect** The effect of vaccination during pregnancy in the risk of preterm labour is very uncertain due to the heterogeneity from effect estimates and their precision.
		Observational studies (2) 89,011 (9268 vaccinated, 79,743 controls)			
	Nunes 2016 [25] Critically low quality	Observational studies (3) 136,048 (61,335 vaccinated, 74,713 controls)	Seasonal trivalent inactivated influenza vaccine Control No vaccination	OR: 0.95; 95% CI: 0.86–1.06.	**No effect** Seasonal or A/H1N1pdm09 monovalent vaccines during pregnancy **may not increase** the risk of small for gestational age births.
		Observational studies (9) 292,105 (74,463 vaccinated, 217,642 controls)	A/H1N1pdm09 monovalent vaccine Control No vaccination	OR: 0.96; 95% CI: 0.90–1.03.	
	Meijer 2015 [22] Critically low quality	Observational studies (6) 1766	Influenza vaccination Control Unclear	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. None of the included studies showed an increase in the risk of a birth small for gestational age after influenza immunization.	**No effect** Influenza immunization during pregnancy **likely not increases** risk of this outcome. Despite the inconsistency of results from included studies vaccines seem to be safe.
	Zhang 2017 [29] Moderate quality	Observational studies (7) 313,458	H1N1 vaccination Control No vaccination	OR adjusted: 0.98; 95% CI: 0.91–1.06	**No effect** H1N1 vaccination during pregnancy **does not increase** the risk of small for gestational age births.
	Giles 2019 [31] High quality	Observational studies (17) 176,486 women vaccinated (164,966 included in risk adjusted analyses)	Inactivated influenza vaccination Control No vaccination	OR adjusted: 0.99; 95% CI: 0.94–1.04 (I^2 = 23.2%). Estimates differed depending on the trimester in which women were vaccinated (OR for vaccination during 1st trimester 0.90; 95% CI 0.66–1.24; OR for 2nd/3rd trimester 0.96; 95% CI 0.89–1.04).	**No effect** H1N1 vaccination during pregnancy **may not increase** the risk of small for gestational age births. Imprecision in estimates increases depending on the trimester in which women were vaccinated.

HR: Hazard Ratio; OR: Odds Ratio; RR: Risk Ratio.

Table 6
Tetanus-diphtheria and pertussis-containing vaccination safety: findings from included reviews.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Neonatal death	Furuta 2017 [26] Moderate quality	Observational study (1) 24,708 (6185 vaccinated, 18,523 controls)	Tdap vaccine Control No vaccination	Low event rate in both groups (<0.1%; RR: 1.0; 95% CI: 0.2–4.9).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of neonatal death.
	McMillan 2017 [28] Moderate quality	Observational studies (2) 32,086 (13,337 vaccinated, 18,749 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. Two retrospective cohorts did not report differences in the rate of neonatal death (rates lower to 0.1%).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of neonatal death.
Abortion	Rivero-Santana 2014 [15] Critically low quality	Observational study (1) 132	Tdap vaccine Control No comparator	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. Data obtained during 5 years from an adverse event register in 132 women (mostly vaccinated during the first trimester) reported a 16.3% spontaneous miscarriage rate.	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of abortion is very uncertain due to the scarce data available.
	Furuta 2017 [26] Moderate quality	Randomized controlled trial (1) 48 (33 vaccinated, 15 controls)	Tdap vaccine Control No vaccination	Lower rate within vaccinated women (3% vs 13%; RR: 0.2; 95% CI: 0.0–2.3) but no conclusion can be reached due to the small sample size.	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of malformations is very uncertain due to the scarce data available.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 7378 (7152 vaccinated, 226 controls)	Tdap vaccine Control No vaccination	Low rate (1%) of malformations between immunized women and their controls.	**No effect** Tdap immunization during pregnancy **likely not increases** risk of congenital malformations.
	McMillan 2017 [28] Moderate quality	Randomized controlled trials (1) 48 (33 vaccinated, 15 controls) Observational studies (4) 9926 (8456vaccinated, 1470 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. One small trial did not show differences between vaccinated and unvaccinated women (OR: 0.20; 95% CI: 0.02–2.44). Three additional retrospective cohorts showed similar results (OR estimates range from 0.80 to 0.91).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of congenital malformations.

Outcomes	Review	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Stillbirth	Furuta 2017 [26] Moderate quality	Randomized controlled trials (1) 103 (52 vaccinated, 51 controls) Observational studies (2) 25,398 (6323 vaccinated, 19,075 controls)	Tdap vaccine Control No vaccination	One trial did not report any case of intrauterine death after 24 weeks gestation. Two cohort studies did not show differences in stillbirth rates (pooled RR: 0.82; 95% CI: 0.44–1.54; I2:0%).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of stillbirth.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 24,708 (6185 vaccinated, 18,523 controls)	Tdap vaccine Control No vaccination	Low event rate (0.2%) reported without differences between vaccinated women and controls (RR 0.69; 95% CI: 0.23–1.62). These results were confirmed in other cohort studies.	**No effect** Tdap immunization during pregnancy **likely not increases** risk of stillbirth.
	McMillan 2017 [28] Moderate quality	Observational studies (3) 32,776 (13,475 vaccinated, 19,301 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively.	**No effect** Tdap immunization during pregnancy **likely not increases** risk

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				Three retrospective cohorts did not report differences in the rate of stillbirths.	of stillbirth.
Congenital anomalies	Furuta 2017 [26] Moderate quality	Randomized controlled trial (1) 48 (33 vaccinated, 15 controls9	Tdap vaccine Control No vaccination	Lower rate within vaccinated women (3% vs 13%; RR: 0.2; 95% CI: 0.0–2.3) but no conclusion can be reached due to the small sample size.	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of malformations is very uncertain due to the scarce data available.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 7378 (7152 vaccinated, 226 controls)	Tdap vaccine Control No vaccination	Low rate (1%) of malformations between immunized women and their controls.	**No effect** Tdap immunization during pregnancy **likely not increases** risk of congenital malformations.
	McMillan 2017 [28] Moderate quality	Randomized controlled trials 48 (33 vaccinated, 15 controls) Observational studies (4) 9926 (8456 vaccinated, 1470 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. One small trial did not show differences between vaccinated and unvaccinated women (OR 0.20; 95% CI: 0.02–2.44). Three additional retrospective cohorts showed similar results (OR estimates range from 0.80 to 0.91).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of congenital malformations.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions
Chorio-amnionitis	Furuta 2017 [26] Moderate quality	Observational study (1) 123,494 (26,229 vaccinated, 972,653 controls)	Tdap vaccine Control No vaccination	One observational study showed a 6% rate in vaccinated women compared to a 5.5% rate in controls (adjusted RR: 1.19; 95% CI: 1.13–1.26). Review authors highlighted that the study did not linked this highest rate with an increase in the risk of preterm birth.	**Small impact** Tdap vaccination during pregnancy **may increase** the risk of chorioamnionitis **slightly**.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 7378 (7152 vaccinated, 226 controls)	Tdap vaccine Control No vaccination	Low and comparable rate of chorioamnionitis between immunized women and their controls (6% vs 4%, p = 0.3).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of chorioamnionitis.
	McMillan 2017 [28] Moderate quality	Observational studies (3) 132,631 (34,490 vaccinated, 98,141 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. Although one observational study showed a greater rate in vaccinated women (6% in vaccinated vs 5.5% in controls; adjusted RR: 1.19; 95% CI: 1.13–1.26), two additional cohorts did not show differences (OR around 1.50 in both studies).	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of chorioamnionitis is uncertain due to the inconsistency in effect estimates.
Low birth weight	Furuta 2017 [26] Moderate quality	Observational study (1) 24,708 (6185 vaccinated, 18,523 controls)	Tdap vaccine Control No vaccination	Similar event rate between vaccinated and non-vaccinated women (2% vs 1.7%; RR: 1.2; 95% CI: 1.0 to 1.5).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of low birth weight labours.
	McMillan 2017 [28] Moderate quality	Observational studies (2) 26,467 (7294 vaccinated, 19,173 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. Two retrospective cohorts did not report differences in the rate of low birth weight (<2500 g) labours (range of rates from 2% to 9%).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of low birth weight labours.

Outcomes	Review/Quality	Studies included/Sample	Vaccine/Comparator	Findings reported in the review	Conclusions

Preterm birth	Furuta 2017 [26] Moderate quality	Randomized controlled trials (2) 151 (85 vaccinated, 66 controls) Observational studies (2) 124,133 (26,363 vaccinated, 97,770 controls)	Tdap Control No vaccination	Results differed according the study design: two trials showed a 3% rate both in vaccinated and unvaccinated women (pooled RR: 0.86; 95% CI: 0.104–5.21; I^2 = 0%), but two additional cohort studies showed a lower rate within immunized women (5.8% vs 7.8%; pooled RR: 0.75; 95% CI: 0.75–0.79; I^2 = 0%).	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of preterm birth is uncertain due to the scarce data available and the discordant results from trials and observational studies.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 7378 (7152 vaccinated, 226 controls)	Tdap vaccine Control No vaccination	Lower rate of births before 37 gestation weeks in vaccinated women (6% vs 12%, p < 0.001). These results were confirmed in other cohort studies.	**Moderate benefit** Vaccinated women **may reduce** their likelihood of preterm birth
	McMillan 2017 [28] Moderate quality	Randomized controlled trials (1) 48 (33 vaccinated, 15 controls) Observational studies (4) 133,270 (34,624 vaccinated, 98,646 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. With the exception of one retrospective cohort that showed a lower rate in vaccinated women (6% vs 12%; OR: 0.47; 95% CI: 0.31–0.71), three additional cohorts and one small trial did not show differences.	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of preterm birth is uncertain due to the discordant results from available studies.
	Rivero-Santana 2014 [15] Critically low quality	Observational study (1) 132	Tdap vaccine Control No comparator	Review authors did not conduct a meta-analysis. Data obtained during 5 years from an adverse event register in 132 women (mostly vaccinated during the first trimester) reported a 1.5% premature birth rate.	**Inconclusive effect** The effect of Tdap vaccination during pregnancy in the risk of preterm birth is very uncertain due to the scarce data available.
Small for gestational age	Furuta 2017 [26] Moderate quality	Observational study (1) 123,494 (2214 vaccinated, 8086 controls)	Tdap vaccine Control No vaccination	The study showed an 8% event rate in both groups (RR: 1.0, 95% CI: 1.0–1.1).	**No effect** Tdap immunization during pregnancy **likely not increases** risk of small for gestational age births.
	Gkentzi 2017 [27] Critically low quality	Observational study (1) 7378 (7152 vaccinated, 226 controls)	Tdap vaccine Control No vaccination	Lower rate of small for gestational age births in vaccinated women (10% vs 15%, p = 0.032). These results were confirmed in other cohort studies.	**Small benefit** Tdap vaccination during pregnancy **likely decreased** risk of small for gestational age births **slightly**.
	McMillan 2017 [28] Moderate quality	Observational studies (3) 132,631 (34,490 vaccinated, 98,141 controls)	Tdap or Tdap-IPV Control No vaccination	Review authors did not conduct a meta-analysis and described findings tabulated and narratively. Three retrospective cohorts did not report differences in the rate of small for gestational age labours.	**No effect** Tdap immunization during pregnancy **likely not increases** risk of small for gestational age labours.

Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Tdap-IPV: Tdap with inactivated poliomyelitis antigens; OR: Odds Ratio; RR: Risk Ratio.

chorioamnionitis over the background rate, respectively [27,28]. Further studies have reported inconsistent findings: in later retrospective cohort studies no risk differences were found between the group that received Tdap, and those that did not, [35,36], whereas in a larger retrospective cohort study a slightly higher risk of maternal chorioamnionitis associated with the Tdap vaccine was found [37]. Nevertheless, the excess of chorioamnionitis was not accompanied by an increase of adverse infant clinical outcomes such as preterm birth, a major sequela of chorioamnionitis [37].

The fetus is considered to be most at risk for congenital anomalies during embryogenesis and the first trimester of pregnancy [28]. However, further homogenous studies reporting congenital anomaly outcomes after first-trimester vaccination have been suggested. [28]. Current guidelines recommend pregnant women to be vaccinated against influenza at any stage of gestation, including the first trimester [6]. From the five SRs that reported the outcome with influenza vaccination, three SRs found no differences in risk and the two other SRs were inconclusive. The marginally significant increase in risk reported with the influenza vaccine in the pooled cohort studies of H1N1 vaccine was considered inconsistent [30].

One high quality SR supported that both seasonal and 2009 pandemic vaccines during pregnancy had no significant effect on abortion, based on observational data from more than 250,000 women [30]. A similar conclusion was found in five other SRs [19,20,24,29]. However, one SR was inconclusive and, although considered unlikely, the risk of abortion cannot be excluded, due to the observational nature of the evidence [21]. Much less evidence is available for the SRs of Tdap vaccines. Two SRs of Tdap vaccines found no effect [27,28], and two others were inconclusive [15,26]. More studies investigating women vaccinated during their first trimester, rather than combining all trimesters, are needed to obtain more precise estimates on the risk of spontaneous abortion [21].

Stillbirth incidence varies notably among countries, ranging from 1.2 per 1000 [1.0–1.5] in Iceland to 56.3 per 1000 [32.3–98.2] in South Sudan [38]. Stillbirth was analyzed in eight SRs of influenza and three SRs of Tetanus, Diphtheria, and Pertussis Vaccination safety. Influenza immunization was associated with a decreased risk of stillbirth in three SRs [17,19,29] in which stillbirth was reported. In one SR, the pooled estimate of seven observational studies showed a 27 to 31% decrease in stillbirths (defined as fetal loss after 20 or 22 weeks of gestational age) associated with influenza immunization and H1N1pdm09 immunization respectively, versus no vaccination. Notwithstanding, no studies of trivalent seasonal vaccines met inclusion criteria to be considered in the SR. Consistently, other SRs found that influenza immunization lowered the incidence of stillbirth by 20% [29]. Studies finding protective associations between stillbirth and vaccination have been large retrospective cohort studies including more than 50,000 women [19]. Conclusions were more conservative in other SRs due to the lack of RCTs statistically powered enough to address this outcome [22]. More RCTs reporting stillbirth are needed to draw firm conclusions. In addition, more homogeneous outcome definitions of stillbirth would also be necessary to avoid misclassification with abortion [31,39]. Further studies should also consider the evidence gaps identified to date, including the timing of vaccination, data on exposure to the trivalent seasonal influenza vaccine, and larger sample sizes [19]. On the other hand, three SRs found no effect of Tetanus, Diphtheria, and Pertussis vaccination on stillbirth. Pooled estimates from 25,398 babies (6323 from vaccinated mothers) found no differences in risk versus non-vaccinated women (28). Although the estimates for this outcome do not indicate an association with vaccine administration, it has to be noted that the available evidence in the SRs comes from only three retrospective cohort studies plus one small RCT (n = 151) which represents less than a half of the cumulative overall evidence available for stillbirth and influenza immunization. Moreover, the only SR that reported hepatitis vaccination safety regarding stillbirth was inconclusive due to the insufficient evidence provided by comparative cohorts with less than 100 patients that did not find increased risk associated with vaccination [15]. However, much more data is needed and vaccination should be limited to pregnant women who are identified as being at risk for HBV infection during pregnancy, according to current recommendations [6].

A reduction in the infant (<1 year) case fatality rate has been observed in the ecological analyses of LAC countries that introduced maternal immunization for pertussis during pregnancy [40]. However, no difference in risk was found for neonatal death and Tdap vaccination in two SRs [26,28]. Similarly, two SRs of the influenza vaccine found no risk differences in the rate of neonatal death [20,30]. A protective effect was reported for seasonal influenza vaccines in one SR [17]; however, conclusions were drawn from data of one single study. In a recently published large cohort study from administrative Canadian databases, no differences in under-5 mortality were found in vaccinated women who received pandemic H1N1 influenza vaccination during pregnancy (vs non vaccinated) [41].

Although it is estimated that 15% to 20% of all births worldwide are LBW, representing more than 20 million births a year [42], only four SRs reported this adverse outcome [25,26,28,31]. No effect was found in two SRs of the Tdap vaccination [26,28]. A beneficial effect of influenza vaccination was reported by a SR of critically low quality [25], but another SR was inconclusive [31]. Moreover, SGA babies are at higher risk of early mortality, especially in low-and middle-income countries [43]. No differences in risk were found in four SRs with influenza vaccine [25,29], whereas one SR was inconclusive [17,22]. Similarly, no effect was observed in two SRs with Tdap vaccination. Moreover, one low quality SR found a small benefit of the vaccination [26–28].

Limitations

There are some limitations in our study which must be mentioned. As in any SR publication, bias cannot be ruled out. Moreover, a considerable overlap in evidence was found in the primary studies included in the SRs of influenza and pertussis immunization. Although we searched for routine maternal-fetal and neonatal outcomes, none of the SRs examined and reported all (of the) outcomes of interest. In addition, the sample population considered in some SRs could be insufficient to address the risk for the less frequent outcomes. Furthermore, the main source of evidence in the SRs was observational studies, which are prone to bias and confounding, a limitation also recognized by the WHO [44]. Residual confounding can play a major role in the small size effects suggested by the SRs [45]. On the other hand, pregnant women can be at higher risk of infections, such as severe influenza [46], and pregnancies complicated by infection are also at higher risk of adverse pregnancy outcomes, including congenital anomalies, spontaneous abortion and stillbirth, preterm birth and LBW [47]. More evident benefits of vaccination would have been expected in low- and middle-income countries in which related morbidity and mortality is higher [48,49]. However, since most of the evidence included in the SRs comes from studies in high-income countries, generalization of the results is limited. Lastly, pooled efficacy results from clinical trials have supported the label extension of the indication of influenza vaccine to pregnant women [50,51], however the latest safety evidence from these trials has not yet been considered in (the) updated MA.

In conclusion, the PAHO/WHO recommendations for Maternal Immunization are supported by current evidence. Definite risks were not identified for any vaccine or outcome of interest. In spite of this, better evidence is needed for all outcomes and vaccines that are broadly administered. The findings from our overview suggest

that influenza vaccines do not increase the risk for the outcomes of interest. Pertussis vaccines likely do not increase the risk of adverse outcomes, but more uncertainties exist on their net effect. The available cumulative evidence in the SRs to support vaccine safety was based mostly on observational data. More RCT with adequate reporting of maternal-fetal outcomes and larger high-quality observational studies are needed, especially in low- and middle-income countries. This could be addressed improving the efficiency of randomised trials adopting innovative methodological designs (ie, adaptive design trials, basket trials, registry trials, umbrella protocols) and reducing the administrative complexity among other potential measures [52].

CRediT authorship contribution statement

Diego Macias Saint-Gerons: Conceptualization, Writing - original draft, Writing - review & editing. **Iván Solá Arnau:** Conceptualization, Methodology, Writing - review & editing. **Bremen De Mucio:** Methodology, Writing - original draft. **Ingrid Arévalo-Rodríguez:** Methodology. **Alicia Alemán:** Writing - original draft. **José Luis Castro:** Conceptualization, Supervision. **Alba María Ropero Álvarez:** Conceptualization, Writing - original draft, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the Pan American Health Organisation (PAHO), its Board of Directors, or the countries they represent.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.07.048.

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