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Review

The effectiveness of influenza vaccination in pregnancy in relation to child health outcomes: Systematic review and meta-analysis

J.R. Jarvis [a,b,*], R.B. Dorey [a,e], F.D.M. Warricker [c], N.A. Alwan [b,d,1], C.E. Jones [a,e,1]

[a] University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, United Kingdom
[b] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, C Level West Wing, Mailpoint 218, Southampton General Hospital, Southampton SO16 6YD, United Kingdom
[c] Salisbury NHS Foundation Trust, Department of Gastroenterology, Salisbury District Hospital, Salisbury, Wiltshire SP2 8BJ, United Kingdom
[d] School of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, AC18, Level C, South Academic Block, University Hospital of Southampton, Southampton SO16 6YD, United Kingdom
[e] University of Southampton, Faculty of Medicine Health and Life Sciences, Tremona Road, Southampton SO16 6YD, United Kingdom

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ABSTRACT

Objectives: To determine the effectiveness of influenza vaccination during pregnancy on child health outcomes.
Design: Systematic review/meta-analysis.
Data sources: Clinical Trials.gov, Cochrane Library, EMBASE, Medline, Medline in process, PubMed and Web of Science, from 1st January 1996 to 29th June 2018. An updated Medline search was performed 30th June 2018 to 31st October 2019.
Methods: Randomised controlled trials (RCTs) and observational studies reporting health outcomes of infants and children born to women who received inactivated influenza vaccine during pregnancy. The primary outcome was infant laboratory confirmed influenza (LCI). Secondary outcomes included influenza-like illness (ILI), other respiratory illnesses, primary care, clinic visit or hospitalisations due to influenza illness and long-term respiratory childhood outcomes.
Results: 19 studies were included; 15 observational studies and 4 primary RCTs with an additional 3 papers reporting secondary outcomes of these RCTs. In a random effects meta-analysis of 2 RCTs including 5742 participants, maternal influenza vaccination was associated with an overall reduction of LCI in infants of 34% (95% confidence interval 15–50%). However, there was no effect of maternal influenza vaccination on ILI in infants ≤6 months old. Two RCTs were excluded from the meta-analysis for the outcome of LCI in infants (different controls used). Both of these studies showed a protective effect for infants from LCI, with a vaccine efficacy of up to a 70%.

Overall observational studies showed an inverse (protective) association between maternal influenza vaccination and infant LCI, hospitalisation and clinic visits due to LCI or ILI in infants and other respiratory illness in infants ≤6 months old.
Conclusions: This systematic review supports maternal influenza vaccination as a strategy to reduce LCI and influenza-related hospitalisations in young infants. Communicating these benefits to pregnant women may support their decision to accept influenza vaccination in pregnancy and increase vaccine coverage in pregnant women.
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* Corresponding author at: University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, United Kingdom.
E-mail addresses: J.Jarvis@soton.ac.uk (J.R. Jarvis), r.dorey@soton.ac.uk (R.B. Dorey), frazer.warricker@nhs.net (F.D.M. Warricker), N.A.Alwan@soton.ac.uk (N.A. Alwan), C.E.Jones@soton.ac.uk (C.E. Jones).
[1] Authors made an equal contribution.

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Contents

1. Introduction

Pregnant women and their infants are at an increased risk of severe illness from seasonal and pandemic influenza viruses [1–4]. Increased vulnerability of pregnant women to severe influenza is likely due to physiological changes and changes in cell-mediated maternal immunity during pregnancy [5,6]. The World Health Organisation (WHO) classifies pregnant women as high risk for influenza infection, recommending all pregnant women to be vaccinated, primarily for their protection, with inactivated influenza vaccine [7]. Despite this, not all countries implement maternal influenza vaccination programmes, and even where they do, vaccination uptake often remains low. For instance, in the United Kingdom (UK), just under half of pregnant women were vaccinated during the 2017/2018 influenza season [8].

Infants are highly susceptible to influenza illness, partly due to the anatomical and physical features of infancy, and due to absence of prior exposure to the virus and development of immunity. Unfortunately, no influenza vaccines are licensed for infants aged ≤6 months old [9,10]. For the infant, influenza infection is associated with increased rates of hospitalisation and higher death rates [1,11,12]. As such, protection of young infants against influenza illness remains an important public health priority [13]. One way of conferring protection to the infant is through maternal influenza vaccination [1,14]. This may provide passive protection against influenza illness, through *trans*-placental antibody transfer from the mother to the foetus [1,15]. Infants born to immune mothers may exhibit delay in onset of symptoms and shorter duration of illness [14].

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A previous systematic review and meta-analysis has shown the potential of maternal influenza vaccination as a strategy for protection of infants against laboratory confirmed influenza (LCI) and influenza associated hospitalisations [16]. Our review aims to update and expand on this through searching of additional databases and the inclusion of additional outcomes. Four key Randomised Control Trials (RCTs), all in low and middle-income settings, showed varying reductions in seasonal LCI in infants [13,15,17,18]. We aim to systematically review the existing evidence of the effect of maternal antenatal pandemic and seasonal influenza vaccination on infant health outcomes with the primary outcome being LCI in the infant. Secondary outcomes included infant ILI, other infant respiratory illness, infant primary care, clinic visit or hospitalisations due to influenza illness and long term respiratory childhood conditions.

2. Methods

This systematic review was conducted and reported in accordance with PRISMA guidelines. The completed PRISMA checklist is available in supplementary item 1. The study protocol was registered on PROSPERO, which can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018102776 [19].

2.1. Search strategy

The search included six electronic databases with articles published from 1st January 1996 to 29th June 2018: ClinicalTrials.gov, Cochrane Library, EMBASE, Medline, Medline in process, PubMed and Web of Science. An updated search, from 30th June 2018 to 31st October 2019, using the original search strategy, was performed on 31st October 2019 in Medline database. Full search strategies for all six searches are located in supplementary item 2. In addition, manual searching of reference lists of selected articles was undertaken.

2.2. Study selection and data extraction

We included all English language full text articles describing RCTs and observational studies. We included studies meeting the following criteria: published peer reviewed studies including RCTs, cohort, case-control and cross-sectional studies; included pregnant women, exposed to trivalent inactivated influenza vaccination, quadrivalent inactivated influenza vaccination and inactivated monovalent influenza vaccinations; assessed outcome measures of either incidence of LCI in child, incidence of ILI and other respiratory illnesses in child or primary care, clinic visits or hospital admissions due to LCI or ILI in child. We excluded articles not in peer-reviewed journals, case series, case reports, clinical practice guidelines, commentaries, conference abstracts, editorials, grey literature, meta-analyses, narrative reviews, studies reporting estimated influenza rates based on ecological approaches, statistical modelling or systematic reviews.

Following de-duplication in Endnote reference management software (version X8.0.2 June 2017), records were imported into Rayyan QCRI (https://rayyan.qcri.org). Records identified from the searches were exported into Endnote reference management software, where de-duplication was performed. All records were imported into Rayyan QCRI. The first author (JRJ) performed title screening using pre-specified inclusion and exclusion criteria. Abstract and full text screening was performed by two blinded authors (JRJ and FDMW, and JRJ and RBD respectively). Any disagreements were resolved through arbitration from the other authors (CEJ, NAA). In addition, manual searching of full texts' reference list was undertaken.

Data extraction was undertaken by two authors (JRJ and RBD) using an adapted and piloted Cochrane data extraction form for both the RCTs and observational studies. If reviewers did not agree, another author arbitrated. Key summary statistics included odds ratio, relative risk, rate ratios and risk ratios.

2.3. Outcome measures

The primary outcome measure was effectiveness of antenatal influenza vaccination on infant LCI. LCI was defined as a positive result on any influenza diagnostic test. Secondary outcome measures included the effectiveness of antenatal influenza vaccination on infant ILI, infant respiratory illnesses, primary care, clinic visits or hospital admissions due to LCI or ILI and any long term respiratory childhood outcomes (e.g. recurrent wheeze or asthma). The secondary outcome of ILI included studies that reported ILI, influenza (without laboratory confirmation by diagnostic test) or followed the WHO definition of ILI [20]. For some studies where the WHO definition for ILI was used, they included a reported temperature (as opposed to a recorded temperature). These studies were still included in the review given the challenges with obtaining recorded temperature in observational studies.

Outcome definitions often had heterogeneity between studies. All definitions for outcomes by study are shown in supplementary item 3.

2.4. Risk of bias assessment

For RCTs the Cochrane risk-of-bias tool was used [21]. Overall quality rating of low, uncertain or high quality was decided. For observational studies the National Heart, Lung and Blood Institute (NHLBI) Study Quality Assessment Tool was used [22]. This used a quality rating of poor, fair or good quality. The NHLBI quality assessment tool is based on quality assessment methods from the Cochrane collaboration allowing some continuity between the tools. Quality assessment for both RCTs and observational studies was performed by two blinded independent reviewers. On unblinding, a decision was made upon each quality assessment and overall ranking given. If no agreement was made a third author arbitrated.

2.5. Data synthesis

Individual study characteristics were summarised in descriptive tables. For each outcome, information on all measures provided in the paper was extracted. For observational studies the adjusted effect estimates were reported (unless stated otherwise). For RCTs vaccine unadjusted estimates were reported.

Meta-analysis of RCTs was performed when studies were deemed to have used comparable populations, interventions, and controls and reported on similar outcomes. Meta-analysis was performed in RevMan software (version 5.3 2004) [23] requiring a minimum of two studies with heterogeneity of $I^2 < 75\%$ [24]. Forest plots and I^2 statistic were used to assess heterogeneity between the studies. Funnel plots were not performed due to lack of power, as only a low number of studies were included in the meta-analysis [25]. Random effects meta-analysis was used. Reporting of this systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analyses recommendations 2009 checklist criteria [26].

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3. Results

3.1. Search results

The main search identified 7220 records. The updated search identified an additional 219 records. In total there were 7439. After de-duplication a total of 3871 titles were screened and 52 studies underwent full text review. In total, 22 papers comprising 19 studies were identified for inclusion in the systematic review (Fig. 1 showing PRISMA flow diagram [27]). Of these, four were primary RCTs, three papers which reported secondary analyses of the primary RCTs and 15 were observational studies. Two RCTs were included in the meta-analysis.

3.2. Study characteristics

The key study characteristics are shown in Table 1.

3.2.1. Study characteristics – Randomised control trials

There were four primary RCTs [13,15,17,18] reported in 7 papers, of which there were 3 papers reporting secondary analyses [28–30] from two of the primary RCTs [13,15]. The four RCTs

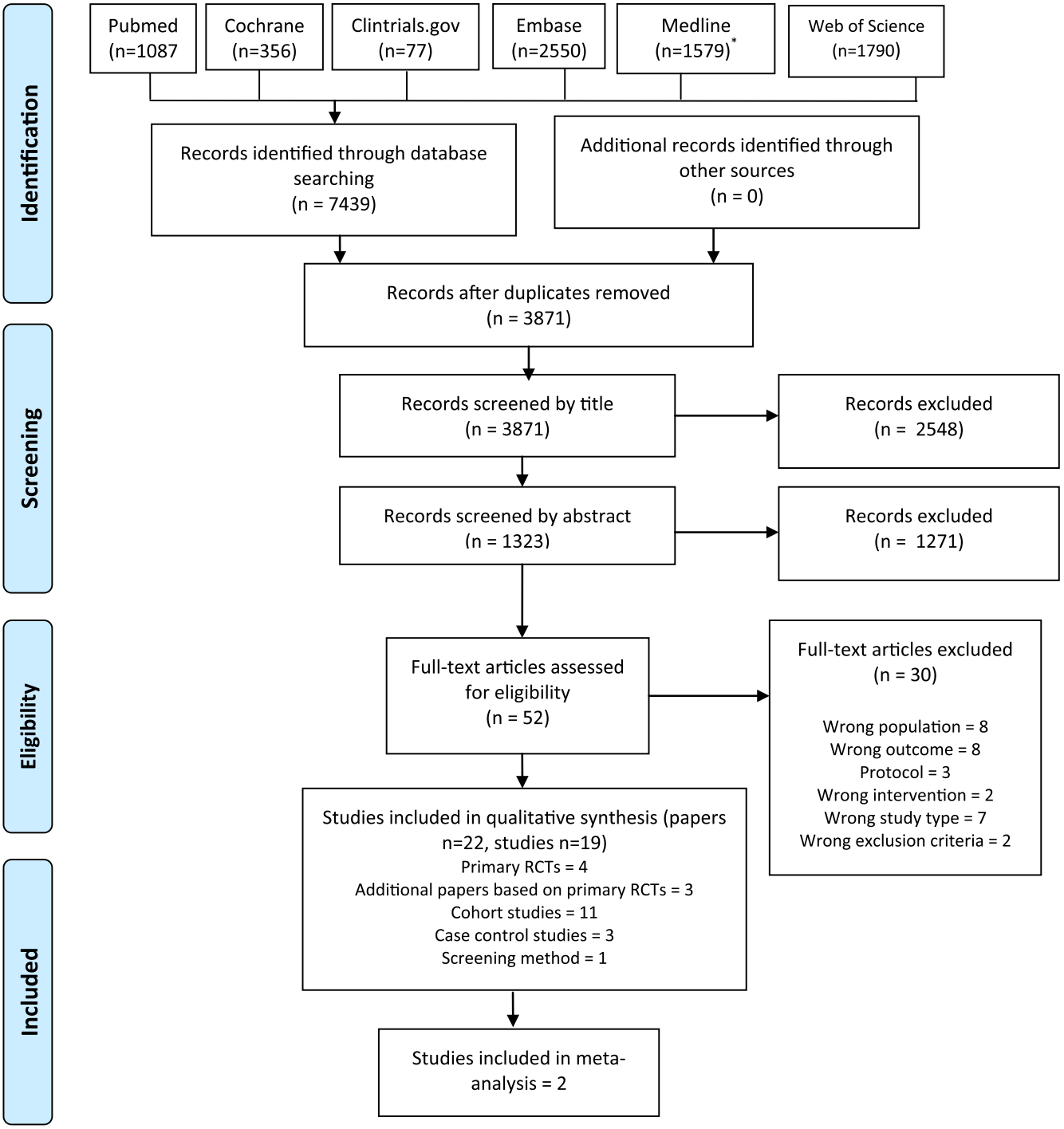

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram [27].

Table 1
Study characteristics.

Author (country, year of publication)	Country income[1]	Study setting	Time period	No of participants (intervention: controls)*	Seasonal influenza vaccine	Pandemic influenza vaccine (H1N1/09)	Assessment of vaccination	Outcomes					Quality assessment
								Infant LCI	Infant ILI	Healthcare utlisation[2]	Other[3]	Long-term[4]	
Case control													
Benowitz (US, 2010) [31]	High	Yale New Haven Children's Hospital	October 2000 to April 2009	205 (113 cases: 192 controls)	x		Subjective: Medical records and maternal report			x			Fair†
Molgaard-Nielsen (Denmark, 2019) [33]	High	Nested case control study from nationwide Danish Birth Cohort	October 2010 to December 2016	920 (460 cases: 460 controls)	X[5]		Objective: National Health Service Registry,	X					Good†
Sukumaran (US, 2018) [32]	High	5 vaccine safety datalink sites (covering regions of California, Colorado, Orlando and Wisconsin)	January 2004 to June 2014	9288 (4644 cases: 4644 controls)	x		Objective: Vaccine safety datalink			x			Fair†
Screening method													
Dabrera (UK, 2014) [45]	High	Multicentre records	September 2013 to January 2014	43	x		Objective: National electronic reporting system	x		x			Poor†
Retrospective cohort studies													
Black (US, 2004) [35]	High	Kaiser Permanente Northern California Healthcare	November 1997 to February 2002	49,585	x		Objective: Immunisation tracking system			x			Fair†
Fell (Canada, 2016) [36]	High	Multicentre records from Ontario region	November 2009 to October 2010	117,335		x	Objective: Population-based birth registry		x				Fair†
France (US, 2006) [37]	High	4 managed care organisations (Colorado, California, Oregon and Washington)	October 1995 to September 2001	41,129	x		Objective: Vaccine safety datalink			x			Fair†
Hviid (Denmark, 2017) [38]	High	Multicentre records	November 2009 to December 2014	61,359		x	Objective: National vaccination database				x	x	Good†
Regan (Australia, 2016) [39]	High	Multicentre records	April 2012 to October 2013	31,028	x		Objective: Antenatal influenza vaccination database			x			Fair†
Shakib (US, 2016) [40]	High	Intermountain facilities in 4 geographic regions of Utah and Idaho	December 2005 to March 2014	249,387	x		Subjective: Maternal reported	x	x	x			Fair†
Walsh (Canada, 2019) [44]	High	Better Outcomes Registry & Network (BORN) Ontario birth registry	November 2009 to October 2010	104,249 (children in study population)		x	Objective: Birth registry				x	x	Fair†
Prospective cohort studies													
Eick (US, 2011) [41]	High	6 Navajo hospitals and 1 on the White Mountain Apache Indian reservations	November 2002 to September 2005	1169	x		Objective and Subjective: Medical records and maternal reported	x	x				Fair†

(*continued on next page*)

Table 1 (*continued*)

Author (country, year of publication)	Country income[1]	Study setting	Time period	No of participants (intervention: controls)*	Seasonal influenza vaccine	Pandemic influenza vaccine (H1N1/09)	Assessment of vaccination	Outcomes					Quality assessment
								Infant LCI	Infant ILI	Healthcare utlisation[2]	Other[3]	Long-term[4]	
Ohfuji (Japan, 2018) [42]	High	117 maternity hospitals	September 2013 to May 2014	3841	x		Subjective: Maternal report with confirmation from paediatricians		x				Fair†
Poehling (US, 2011) [34]	High	Multicentre records from 3 counties in Tennessee, Ohio and New York	2002–2009	1510	x		Not stated	x					Poor†
Sugimura (Japan, 2016) [43]	High	Kobayashi ladies clinic, Japan	November 2010 to April 2011	200	X[5]		Subjective: Maternal report	x					Poor†
Randomised control trials													
Katz (Nepal, 2018) [28]	Low	Sarlahi district – 9 village development committees	April 2011 to September 2013	3693 (1847:1846)	X[5]		Objective: Study staff documented	x					High*
Madhi (S. Africa, 2014) [13]	Upper middle	4 antenatal clinics in Soweto	March 2011 to July 2012	2310 (1162:1148)	X[5]		Objective: Study staff documented	x	x		x		High*
Nunes (South Africa, 2017) [29]	Upper middle	4 antenatal clinics in Soweto	March 2011 to July 2012	2049 (1026:1023)	X[5]		Objective: Study staff documented				x		High*
Nunes (S. Africa, 2016) [30]	Upper middle	4 antenatal clinics in Soweto	March 2011 to July 2012	2049 (1026:1023)	X[5]		Objective: Study staff documented	x					High*
Steinhoff (Nepal, 2017) [15]	Low	Sarlahi district – 9 village development committees	April 2011 to September 2013	3693 (1847:1846)	X[5]		Objective: Study staff documented	x	x				High*
Tapia (Mali, 2016) [18]	Low	6 referral and community centres in Bamako	September 2011 to January 2014	4193 (2108:2085)	X[5]		Objective: Study staff documented	x	x				High*
Zaman (Bangladesh, 2008) [17]	Low	No further information	August 2004 to December 2005	340 (172:168)	X[6]		Objective: Study staff documented	x	x	x			High*

† Observational studies used the National Heart, Lung and Blood Institute quality assessment tool.
* RCTs used the Cochrane Risk of Bias tool.
[1] World Bank country income level.
[2] Infant primary care, clinic visits or hospital admissions due to LCI or ILI.
[3] Other infant respiratory infection.
[4] Long-term respiratory childhood outcomes.
[5] Seasonal vaccine contained Pandemic H1N1/09.
[6] Seasonal vaccine contained pandemic H1N1/09.

included 10,536 participants overall. Of the four RCTs; one was from an upper middle-income country (South Africa) [13] and three from lower middle-income countries (Bangladesh [17], Mali [18] and Nepal [15]). All RCTs were performed in countries where influenza virus circulation occurred throughout the year, apart from one study in South Africa [13]. Therefore, caution is required when extrapolating the results of this review to different settings, which may exhibit different influenza virus circulation patterns and attack rates [16].

Of the additional three papers, two [29,30] were linked to the primary paper by Madhi et al. (2014) [13] and one [28] to Steinhoff et al. 2017 [15]. Three of the RCTs included seasonal influenza vaccination which contained pandemic H1N1/09 influenza strain [13,15,18]. The remaining RCT by Zaman et al. (2008) contained pandemic H1N1/99 influenza strain [17]. None of the studies covered the pandemic H1N1 2009–2010 period, with the majority of studies, covering the time-period post the 2009 H1N1 pandemic between 2011 and 2014 [13,15,18,28–30].

Vaccine receipt was objectively reported for all RCTs, reducing the likelihood of information bias. All RCTs documented information on vaccine composition which is important to determine matching of vaccine to circulating strain of influenza.

For outcome assessment of the 4 RCTs, 3 used polymerase chain reaction (PCR) [13,15,18] and 1 rapid influenza diagnostic tests [17] to determine influenza infection. Influenza-like illness diagnosis varied between studies (supplementary item 3).

3.2.2. Study characteristics - observational studies

All 15 observational studies took place between 1995 and 2014. Overall 662,307 participants were included. Of the 15 observational studies; 3 were case control studies [31–33] of which one was a nested case control study [33], 11 cohort studies [34–44] and one used the screening method [45]. The retrospective screening method design was deemed eligible for inclusion after discussion with four of the authors. The screening method can be used to determine vaccine effectiveness in routine monitoring if the denominator data are unavailable for individuals [46]. Just under half (47%), of studies originated from the United States of America (US) [31,32,34,35,37,40,41] with the remainder from high-income non-US countries (53%) [36,38,39,42,43,45], two of which were from Japan [42,43]. All studies included pregnant women only.

Twelve of the studies covered seasonal influenza vaccine, of which only two included the pandemic influenza A (H1N1/09) strain [33,43]. Three studies looked solely at the H1N1 monovalent vaccine, which included the pandemic 2009/10 H1N1 period [36,38,44].

Vaccine receipt was objectively reported for the majority of observational studies, reducing the likelihood of information bias. Observational studies often omitted information on vaccine composition.

Within the observational studies, a combination of less sensitive and specific tests were used to determine LCI status resulting in under-estimation or over-estimation of LCI respectively. Definitions for LCI and influenza-like illness varied between studies (refer to supplementary item 3). Diagnostic tests used for LCI included PCR [33,45], Culture/PCR/direct fluorescent antibody (DFA) [40], Culture/PCR [34], serological testing [41] or rapid diagnostic testing [43]. For ILI, all studies used medical coding either using ICD 9 criteria or documentation of a medical visit or ILI diagnosis [36,40–42]. Definitions for primary care, clinic visits or hospital admissions due to laboratory confirmed influenza and/or influenza-like illness in infants included: ICD 9 coding [32,35,37], DFA [31], coding of diagnosis [38] or admission [39] or a mixture of culture/PCR/DFA or ICD 9 coding [40]. Definitions for other respiratory infections were based ICD 10 coding [38,44]. Long term respiratory child-hood conditions were based on primary or secondary diagnoses codes [38] or a dataset which used a validated algorithm to identify cases from a healthcare database [44].

3.3. Quality assessment of studies

All four primary RCTs were considered high quality with a low risk of bias. Among the 15 observational studies, 80% were of fair or good quality. A summary of quality assessment for all studies is shown in supplementary item 4.

3.4. Maternal influenza vaccination and infant laboratory confirmed influenza

3.4.1. Randomised control trials

All four primary RCTs which considered the effect of influenza vaccination during pregnancy on infant LCI up to 6 months of age [13,15,17,18] showed a protective effect; with risk ratios (RR) of 0.70 (95% Confidence Interval: 0.52–0.95) [15] to 0.37 (0.15–0.95) [17]. Secondary analysis of data from the Nepalese RCT, considered the effect of gestational timing of maternal influenza vaccination on infant LCI and found that vaccine efficacy did not vary when vaccination was given in the second compared to the third trimester of pregnancy [28]. Two studies showed that vaccine efficacy of maternal influenza vaccination on infant LCI waned over the first 6 months of life [18,30]. A Secondary analysis by Nunes et al. (2016) [30] of a subset of infants from the South African RCT [13], showed vaccine efficacy was highest at 86% (38–98%) for infants under 8 weeks of age, diminishing with increasing age. There was no protective effect of the vaccine on infant LCI when the analysis was restricted solely to infants aged between 8 and 16 weeks of age [30]. Tapia et al. (2016) [18] showed that maternal influenza vaccine efficacy decreased after 4 months of follow-up from birth in the infant, from 68% (35–85%) during the first 4 months, to 33% (4–54%) during the sixth month of follow-up. A meta-analysis of these 2 studies was not performed due to use of different controls: sterile saline placebo [30] and quadrivalent meningococcal vaccine [18].

Two of the four primary RCTs were included in a pooled meta-analysis of studies [13,15]. Two studies were excluded as effects could not be directly compared. Zaman et al. (2008) [17] was excluded due to the use of positive rapid testing as a diagnostic test and pneumococcal vaccine as the control vaccine. Tapia et al. (2016) [18] was excluded due to use of meningococcal vaccine as the control vaccine. Of the two included studies [13,15], both were comparable for pooled analysis, using PCR to diagnose LCI and the control of sterile saline placebo. The pooled estimate from the meta-analysis showed maternal influenza vaccination was associated with an overall reduction of LCI in infants of 34% (15–50%) (Fig. 2).

3.4.2. Observational studies

Five of six observational studies showed a protective relationship between influenza vaccination during pregnancy on LCI in infants less than 6 months of age [33,34,40,41,45]. Only two studies solely used PCR to diagnose influenza infection [33,45], with the others using a variety of diagnostic methods, with variable sensitivity and specificity [34,40,41,43]. Infants <6 months of age were at reduced risk from LCI with percentage risk reduction ranging between 41% (7–63%) [40] and 67% (48–79%) [41]. The prospective cohort study by Sugimura et al. (2016) [43], showed no protective effect of maternal influenza vaccination on infant LCI, however this study was of poor quality with high risk of bias.

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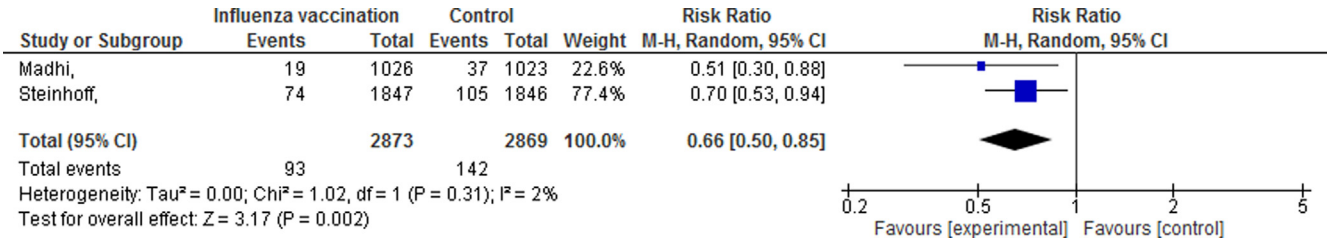

Fig. 2. Forest plot of pooled results for maternal influenza vaccination and LCI in infants.

3.5. Maternal influenza vaccination and infant influenza-like illness

3.5.1. Randomised control trials

Three out of four RCTs showed no effect of influenza vaccination during pregnancy and influenza-like illness in infants <6 months of age [13,15,18]. For these studies, all included some subjective reporting of temperature, despite a recorded temperature being a key component of ILI definition [20]. One study by Zaman et al. (2008) [17] showed a protective effect with a clinical effectiveness of 29% (7–46%) when the definition for influenza-like illness included self-reported fever, however, when the definition included recorded temperature of >38 °C, there was a non-significant finding of clinical effectiveness of 28% (−5% to 51%).

3.5.2. Observational studies

Two [40,42] out of four [36,40–42] studies showed a risk reduction of infant ILI in those whose mothers were vaccinated during pregnancy. In the study by Ohfuji et al (2018) [42] maternal influenza vaccination decreased the odds of influenza in infants (multivariate analysis with an odds ratio 0.39 (0.19–0.84). Shakib et al. (2016) [40] showed a 66% risk reduction in ILI in infants (51–76%).

3.6. Primary care, clinic visits or hospital admissions due to laboratory confirmed influenza and/or influenza-like illness in infants

3.6.1. Randomised control trials

One RCTs reported on the effect of influenza vaccination during pregnancy on clinic visits or hospital admission for ILI in infants <6 months of age [17]. Zaman et al. (2018) [17] reported a 42% (18–59%), reduction in clinic visits for respiratory illness with fever in infants <6 months of age.

3.6.2. Observational studies

Of four observational studies, three showed a reduction of clinic visits or hospital admission for LCI in infants <6 months of age born to mothers vaccinated in pregnancy [31,40,45], and one for respiratory illnesses in infants <6 months of age [39]. An additional three studies reported no effect [32,35,37]. Benowitz et al. (2010) [31] found a vaccine effectiveness of 92% (62–98%) in preventing LCI hospitalisations in infants <6 months old, however no effect on LCI hospitalisations was seen in infants ≥6 months and <12 months of age (p = 0.81). The authors covered 9 influenza seasons from 2000 to 2009. No information was provided on type of influenza vaccination. Dabrera et al. (2014) [45] showed a vaccine effectiveness of 64% (6–86%) for preventing LCI hospitalisations in infants <6 months during the 2013/14 influenza season in the UK. No information on type of vaccine was stated. Shakib et al. (2016) [40] showed a risk reduction of 84% (57–94%) for ILI hospitalisations and 83% (45–95%) for LCI hospitalisations in infants <6 months. The authors covered 9 influenza seasons from 2005 to 2014. No information was provided on type of influenza vaccination. One study reported risk reductions in hospitalisation due to respiratory illnesses [39]. The authors Regan et al. (2016) [39] showed a protective effect for hospitalisation with respiratory illness during a period of known seasonal influenza activity in infants <6 months of age (adjusted hazard ratio: 0.75 (0.56–0.99), with the magnitude of effect increasing with vaccination in the third trimester of pregnancy (adjusted hazards ratio 0.67 (0.47–0.95)).

3.7. Maternal influenza vaccination and other respiratory infections in infants

3.7.1. Randomised control trials

An RCT by Madhi et al. (2014) [13] reported on any respiratory infection in infants <6 months of age. The vaccine showed no effect in reducing any respiratory tract infections in infants with a vaccine efficacy of −1.0 (−7.1 to 4.8). In a secondary analysis of this primary RCT [13], Nunes et al. (2017) [29] found a risk reduction of 44% (1–68%) for hospitalisation of infants <6 months of age with all cause acute lower respiratory illness.

3.7.2. Observational studies

An observational study by Hviid et al. (2017) [38] showed an 8% (1–15%) rate reduction of upper respiratory tract infections in infants in a one year birth cohort with 5 years of follow-up. This was only shown when maternal vaccination occurred in the second or third trimester. However, when Bonferroni corrected for multiple testing, there was no reduced risk for URTI. No effect was shown for lower respiratory tract infections. This study looked solely at the monovalent pandemic H1N1 vaccine over one influenza season (2009–2010).

A retrospective cohort study by Walsh et al. (2019) [44] showed maternal influenza vaccination to have no effect on upper respiratory tract infections (URTI) or lower respiratory tract infections (LRTI).

3.8. Long term respiratory childhood outcomes

Two retrospective cohort studies included development of asthma in childhood as an outcome. One study was undertaken in Denmark [38], the other in Canada [44]. Both studies looked at maternal influenza vaccination (monovalent pandemic H1N1 vaccine), in pregnancy by trimester and asthma outcomes at 5 years post vaccination. The study by Hviid et al. (2017) [38] showed no evidence of a significant association between maternal vaccination during any trimester and offspring asthma (vaccination in first trimester rate ratio 1.50 (0.99–2.29) and vaccination in second or third trimester rate ratio 1.02 (0.89–1.16)). Walsh et al. (2019) [44] showed a small association between receiving the H1N1/09 monovalent influenza vaccination in pregnancy and asthma in children up to the age of 5 years (adjusted hazard ratio 1.05 (1.02–1.09)). However, when accounting for multiple statistical testing using a Bonferroni correction, this relationship was attenuated (adjusted hazard ratio 1.05 (1.00–1.11)).

3.9. Overview of results for all included studies

A summary of the results from all observational and RCT studies is shown as a forest plot, subdivided by primary or secondary outcomes (Fig. 3).

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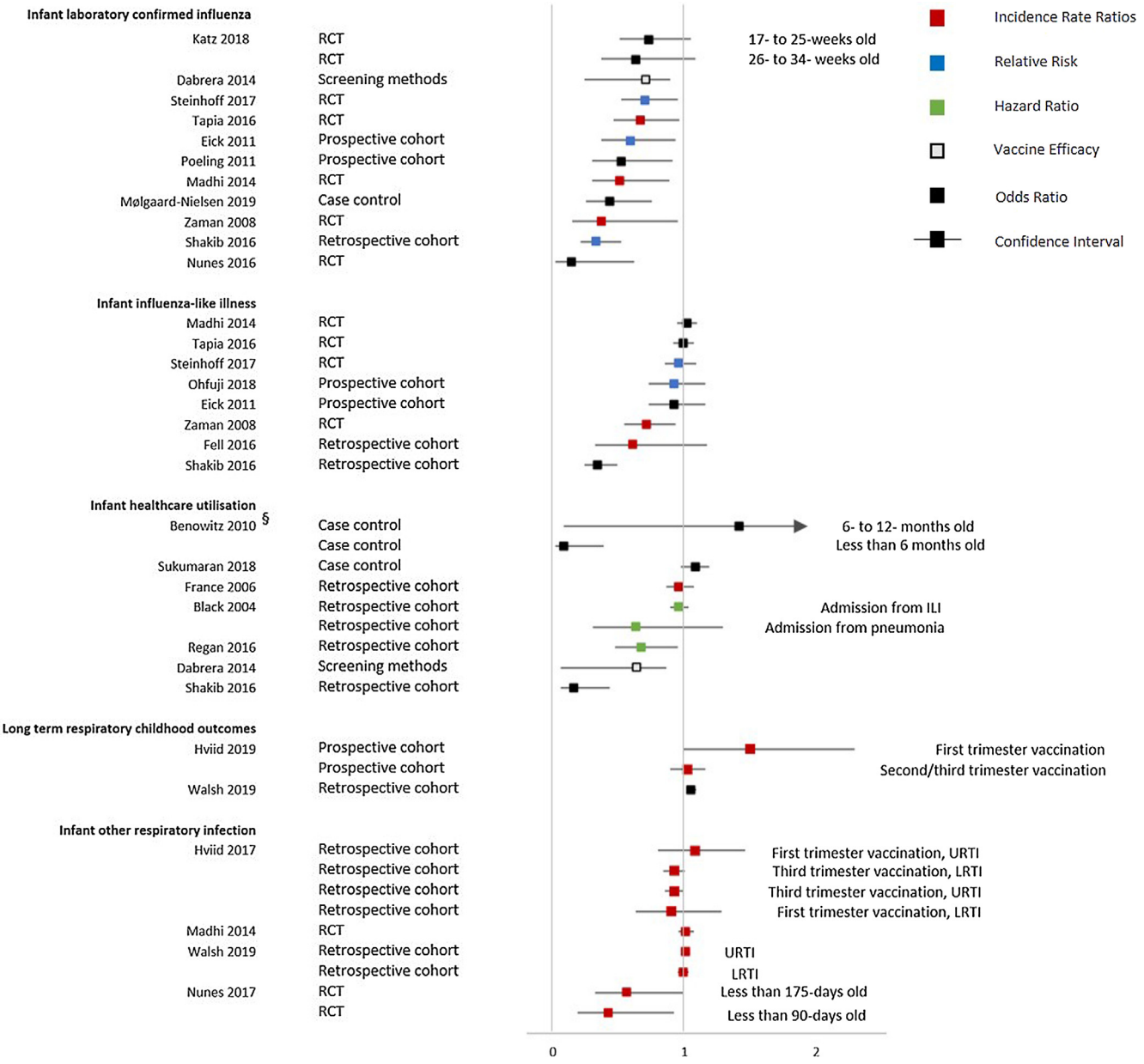

Fig. 3. Forest Plot to show summary of observational studies and RCTs results by primary and secondary outcomes. Forest plot demonstrating the effects of maternal influenza vaccination on infant outcomes (See Supplementary Table 3). (§) Benowitz 2010 – OR 1.41 (95% CI 0.085–23.57).

4. Discussion

4.1. Summary of findings

Although results ranged considerably between studies, our review shows that maternal influenza vaccination is protective against laboratory confirmed influenza in infants <6 months of age. It supports the use of maternal influenza vaccination to prevent against severe influenza illness (as determined by reduction in hospitalisations), in infants <6 months of age. In addition, maternal influenza vaccination in pregnancy appears to protect the youngest infants most effectively, with some evidence of a waning effect over time. Given that influenza vaccines are only licensed for infants 6 months of age and over, maternal influenza vaccination in pregnancy may be an important method of protecting these young infants who are at highest risk from the complications of influenza infection.

4.2. Strengths and limitations of the systematic review

4.2.1. Strengths and limitations of review process

Key strengths of this review include a comprehensive search strategy including several study designs, clear inclusion and exclusion criteria, designed in conjunction with a medical librarian. The search strategy covered a range of health databases. A high number of studies were retrieved from the search, which suggests that the search was broad enough to include all relevant articles. The majority of clinical outcomes from the individual studies were objectively measured which reduces any chance of reporting bias from the reviewers. However, limitations include limiting of the search to

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the English language. This may have excluded wider literature in other languages. This is particularly relevant given the global nature of influenza infection. The decision to exclude grey literature, although rationalised due to the control of peer-reviewing, may have meant key studies were missed which could result in publication bias.

4.2.2. Strengths and limitations of the included studies

Strengths of this review included a concise overview of the subject area collecting data on multiple outcomes including LCI and ILI. It is important to measure the burden of ILI, as ILI acts as a proxy for LCI, as not all influenza cases will present to a clinician or if they do, have further diagnostic testing. Consequently, the true burden of influenza illness will be under-estimated using LCI alone.

All RCTs included in the review were considered high quality. RCTs were only pooled in a meta-analysis when deemed of low heterogeneity between studies, adding to the rigour of our study. Two studies were excluded due to use of different comparators which may have biased the findings. No pooled meta-analysis of observational studies was performed due to the differences in study quality, in addition to the high level of heterogeneity that existed between the observational studies in terms of population studies, variations in vaccine type and different definitions of outcomes.

There were however limitations with the included studies. Heterogeneity in study outcomes existed between studies both observational and RCTs, making it difficult to compare between studies (supplementary item 3). In the observational studies a variety of diagnostic tests were used to define LCI, despite PCR considered the gold-standard diagnostic test. Sensitivity and specificity of different diagnostic tests vary, therefore detection bias may occur. In the RCTs, all but one study, used PCR to diagnose LCI.

Definitions for ILI outcome varied between studies. Although all studies, apart from one, used definitions of ILI, which incorporated maternal reported temperature they often did not include a recorded temperature of $\geq$38 °C. This is in discordance with the WHO guidelines [20]. Omitting recorded temperature from the ILI definition may over-estimate influenza illness burden through inclusion of non-specific infections. Zaman et al. (2008) [17] highlighted this where a protective effect against ILI was reported for mothers and infants <6 months old, however no effect was observed when ILI was defined as self-reported temperature, using recorded measurements. As such, caution is required when interpreting our review's findings for the effectiveness of maternal influenza vaccination for ILI in mothers and infants <6 months old.

The observational studies ranged in level of quality and were at varying levels of risk of bias. The majority of observational studies omitted many key confounders such as post-partum maternal vaccination, breast-feeding and previous seasonal influenza vaccination. Post-partum maternal vaccination may reduce the direct spread of influenza infection from the mother to the infant, preventing infant influenza illness [42]. Breast milk has been considered to provide higher protection to the infant from influenza virus infection [47]. Previous seasonal influenza vaccination in the mother may affect the future immune response either reducing or augmenting the antibody response [48]. This prevented sufficient controlling of bias in the majority of the observational studies included in this review. The 2 studies that reported on maternal influenza vaccination and the outcome of asthma in children in $\leq$5 years of age were deemed fair [44] and good quality [38]. In the study by Walsh et al. (2019) [44], there was weak evidence to suggest maternal influenza vaccination may increase risk of asthma in childhood. Asthma is a multifactorial condition and as such there will be many confounding factors which may have not been appropriately accounted for. It may have been more appropriate to have considered the outcome of pre-school wheeze as asthma can only be objectively diagnosed from 5 years onwards and often this depends on the child's ability to perform respiratory function tests. In addition setting the cut-off point at 5 years means later diagnosed asthma in the child was not investigated.

The majority of observational studies did not consider vaccine composition. Even where vaccine composition was noted, few studies matched influenza vaccine to the circulating strain for that year. This is an important consideration when determining vaccine effectiveness, as mismatching of influenza vaccine to circulating strains is likely to underestimate any true effect or even incorrectly conclude no effect exists. In addition, many studies occurred over multiple influenza seasons potentially resulting in intra-study differences in vaccine effectiveness, as matching of vaccine to circulating strains may have varied in effectiveness between years. No studies explored this issue, potentially resulting in lower estimates of effectiveness of influenza vaccination. Other components of influenza vaccines such as thimerosal preservatives and adjuvants were often omitted in observational studies. Although now considered safe by the WHO Global Advisory Committee on Vaccine Safety, this is still an important consideration when determining vaccine effectiveness [49,50].

4.3. Comparison with other studies

Our review adds to the existing body of evidence, including a recent systematic review by Nunes and Madhi (2018) [16], which shows the protective effect of maternal vaccination for infant LCI. Nunes and Madhi (2018) [16] showed a pooled risk reduction for RCTs and observational studies of 48% (33–59%). However, observational studies appeared to over-estimate the effect as when analysed using RCTs only, risk reduction was lower at 36% (22–48%) [16]. This is compatible with our findings from a pooled meta-analysis of 34% risk reduction (15–50%). Our review expands on this work through using a wide search strategy, identification of a large number of papers and consideration of multiple outcomes.

Our findings from the review of both RCTs and observational studies showed a reduced number of clinic visits and hospitalisations for ILI, LCI and respiratory illness in infants <6 months of age, from mothers who received maternal influenza vaccination during pregnancy. This highlights the potential to use maternal influenza vaccination to prevent severe influenza disease (as defined by hospitalisation) in this infant group. A reduction of 42–44% [17,30] in influenza-like illness for clinic visits and hospitalisations, although appearing modest, could have significant implications on influenza burden in both general practice and hospital settings. This finding is in contrast with a Cochrane review by Salam et al. (2015) [25], who concluded there was no effect for maternal influenza vaccination and influenza related hospitalisations in infants. However, this was based on the findings of one RCT [13]. We update with new findings published since this time.

Our review showed maternal influenza vaccination did not have an effect on influenza-like illness in infants (RR 0.99 (0.93–1.04)). This finding differs from a previous review, albeit limited by low quality of included studies [49]. This lack of effect for ILI in some studies may be explained by inter-study variations in ILI definitions. However, it may suggest that other viruses play a more important role in overall burden of ILI than influenza.

There was mixed evidence for the effectiveness of maternal influenza vaccination on other definitions of respiratory tract illnesses in infants <6 months old. One observational study reported a reduction in upper respiratory tract infections [38]. Although this was deemed significant, the higher confidence interval was close to 1 i.e. no effect (RR 0.85–0.99) [38]. In addition, when Bonferroni corrected (due to multiple comparisons), this result was not significant. An RCT showed a reduction in hospitalisations in infants for

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acute lower respiratory infections [29]. The authors suggested this finding may be caused by the influenza infection increasing the susceptibility of an infant to another bacterial infection. This may then result in influenza virus not being detectable by time at hospitalisation. Another RCT showed no effect [13]. The study which showed no effect could be explained by the higher burden of other viruses e.g. Respiratory Syncytial Virus, contributing to all respiratory infections. As such, reducing influenza burden to total respiratory infections is unlikely to be significant.

Despite the recommendation that maternal influenza vaccination can be given in any trimester of pregnancy, only one secondary paper [28] of a primary RCT [15] specifically considered gestational timing of maternal vaccination for infant outcomes. However, no first trimester vaccination was included in this study. Therefore, timing of vaccination may have been too narrow to detect any difference. It was not possible to determine whether gestational timing of influenza vaccination has an effect on maternal and infant influenza related outcomes. However, given that antibody transfer occurs during the second trimester, increasing throughout pregnancy, it is possible that greater immunity is conferred to the infant if maternal vaccination is given during later trimesters. This is supported by Katz et al. (2018) [28] who found higher antibody levels in cord blood in women vaccinated later in pregnancy, although this finding lacked adequate power. However, there is a growing body of evidence for maternal pertussis vaccination, which suggests second trimester vaccination may be more effective than third trimester vaccination, in providing increased antibodies and better immunity to the new-born infant [51,52]. This could potentially be explained by longer transfer times, allowing antibodies to accumulate in the foetus [52]. Although during the third trimester there is a peak vaccine transfer efficacy, this may be limited by a reduced exposure period [51].

Despite these findings there is some suggestion that earlier vaccination may provide a more mature antibody response. Earlier vaccination in pregnancy would also provide protection for the mother throughout gestation and ensure adequate protection during the third trimester of pregnancy when the severity of infection is greatest. The OpTIMUM study being carried out in the UK is currently looking into this effect in pertussis vaccination in pregnancy (NCT03908164) [53].

Although gestational timing of vaccination may be important in protecting the infant from influenza, there are also other important considerations including local influenza seasonality and the changing timing of peak influenza activity within this. A review by Myers et al. (2011) [54] showed greater benefits for infants from maternal influenza vaccination during pregnancy when given earlier in the influenza season. This was undertaken in the United States, where a temperate climate results in a limited influenza season. Therefore infants born just prior or early on in the influenza season were likely to benefit the most from a reduction in burden of influenza disease. In addition, an important consideration for future policy planning is the availability of influenza vaccination and any potential delays or shortages in vaccine production.

4.4. Clinical and policy implications

Given the limited immunity of infants <6 months old to influenza disease, the lack of vaccine in this age group and consequent high morbidity and mortality, protection of young infants against influenza infection remain a priority for public health. This review supports the targeting of maternal influenza vaccination to partially reduce influenza illness burden and influenza related hospitalisations in infants <6 months old. The findings from this review may incentivise mothers to become vaccinated against influenza during pregnancy if they perceive additional benefits for their unborn child [55,56]. In addition reducing influenza illness burden will significantly reduce associated healthcare costs, an important consideration for policy makers.

4.5. Unanswered questions and future research

The question of gestational timing of maternal influenza vaccination remains unanswered. This is important for planning future vaccination campaigns to protect both mother and infant through targeting vaccination to specific trimesters of pregnancy. This may prove challenging with a potential conflict between optimal gestational timing of maternal influenza vaccination and effectiveness for mother and infant outcomes. Further research on effect on long term child and maternal outcome is also needed.

Further work is required to improve transferability of results, including observational studies which consider matching of vaccine strains to circulating influenza virus and better documentation of vaccine composition. There should be agreed standardised reporting of studies on vaccine effectiveness to allow for future comparison between studies.

5. Conclusion

Our systematic review shows maternal influenza vaccination is protective against laboratory confirmed influenza in infants <6 months of age, with approximately a reduction of a third of LCI in infants. It also shows a reduction in primary care, clinic and hospitalisations for influenza illness. This supports the secondary use of maternal influenza vaccination for preventing influenza illness in infants <6 months old until infant vaccination is possible. Further research is required to expand the evidence-base for the long-term effectiveness of maternal influenza vaccination on child outcomes.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: NAA, RBD, CEJ declare no support from any organisation for the submitted work; whilst undertaking this work JRJ was funded by the University of Southampton National Institute of Health Research (NIHR) and Health Education England; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

As this is a systematic review this is not applicable. Data used for the review and meta-analysis is available in the published papers included, in their respective journals.

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Contributorship statement

NAA, JRJ and CEJ conceived and designed the study. JRJ searched all databases. JRJ screened all titles of records for inclusion. JRJ and FDMW screened all abstracts to identify all full texts for inclusion. JRJ and RBD performed full text screening and risk of bias assessment of included manuscripts. JRJ and RBD extracted data. JRJ performed analysis of data. NAA, JRJ and CEJ drafted the manuscript. All authors (NAA, RBD, JRJ, CEJ, FDMW) reviewed the final manuscript and agreed to be accountable for all aspects of the work and approved the final manuscript for submission. NAA and CEJ supervised the research. NAA and CEJ are guarantors.

All authors attest they meet the ICMJE criteria for authorship.

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Ethics approval

Not applicable.

Disclaimers

The views expressed in the submitted article are that of the authors and not an official position of the institution or funder.

Sponsorship

Not applicable.

Transparency declaration

The authors CEJ and NAA (manuscripts guarantor) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination declaration

This is a systematic review, therefore all included data is available in the respective papers accessed via the journal of publication. Dissemination to study participants or patient organisations is therefore not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.12.056.

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