BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016526
Article Type:	Research
Date Submitted by the Author:	22-Feb-2017
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Immunology (including allergy), Global health, Infectious diseases, Paediatrics
Keywords:	Influenza, Hospitalization, Infant, Systematic review

Incidence of laboratory-confirmed influenza disease among infants under six months of age: A systematic review

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Article Type: Research Article

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ABSTRACT (285 words)

Objectives: The aim of this systematic review was to assess incidence rates of laboratory-confirmed influenza (LCI) outcomes among infants under six months of age.

Design: Systematic literature search and review of indexed studies in PubMed, Embase, the Cochrane Library, and CINAHL Plus.

Setting: Population-based estimates from community or hospital settings.

Participants: Infants under six months of age.

Primary and secondary outcome measures: LCI illness in ambulatory care settings, LCI hospitalization, LCI intensive care unit admission and LCI death. Only studies with population-based incidence data were included.

Results: We identified 22 primary studies, eleven of which were from the United States (US), three were from other non-US high-income settings, and the remainder were from lower-middle- or upper-middle-income countries. Most studies (n=20) assessed incidence of LCI hospitalization, but meta-analysis to pool study-specific rates was not possible due to high statistical and methodological heterogeneity. Among US studies, the reported incidence of LCI hospitalization ranged from 9.3 to 91.2 per 10,000 infants under six months for seasonal influenza, while the only US-based estimate for pandemic H1N1 influenza was 20.2 per 10,000 infants. Reported rates for LCI hospitalization for seasonal influenza from other countries ranged from 6.3 to 73.0 per 10,000 infants under six months, with the exception of one study with an estimated rate of 250 per 10,000 infants. No events were reported in five of the eight studies that evaluated LCI death among infants under six months.

Conclusion: Our review of published studies found limited data on LCI outcomes for infants under six months, particularly from non-US settings. Globally representative and reliable

incidence data are necessary to fully evaluate influenza disease burden and the anticipated impact of maternal influenza immunization programs on morbidity and mortality in young infants.

Strengths and limitations of this study

- This review of laboratory-confirmed, population-based estimates of influenza incidence highlights the relative lack of studies that specifically report influenza outcomes among infants under the age of six months.
- The majority of data identified in this review originate from the United States, deriving primarily from just two influenza surveillance systems, posing challenges for estimating the impact of maternal influenza immunization programs on infant influenza outcomes, particularly for low- and middle-income countries.
- We were unable to perform any meta-analyses due to high methodological and statistical heterogeneity.

Keywords: Influenza, Hospitalization, Infant, Systematic review

INTRODUCTION

Influenza is a common pathogen identified in young children with acute lower respiratory infections, such as pneumonia and bronchiolitis,[1] globally accounting for approximately 10% of all respiratory hospitalizations in children under 18 years[2] and approximately 3% of post-neonatal deaths.[3] Influenza virus infection can also manifest in various other conditions including seizures, wheezing, croup, otitis media, and occasionally encephalitis and encephalopathy,[4–7] and it can progress to secondary bacterial pneumonias or exacerbate underlying chronic medical conditions.

Infants under six months of age are considered to be at high-risk for severe influenza and associated complications due to documented high rates of influenza-associated hospitalization[8–12] and mortality.[7] However, since influenza vaccines are not licensed for use in this age group due to poor immunogenic responses to the vaccine,[13] protection of newborns and young infants from influenza virus infection and related complications requires alternate strategies.[14] One such strategy is immunization of pregnant women with influenza vaccine, which has been shown to reduce influenza virus infection among young infants through transplacental transfer of maternal anti-influenza antibodies.[15–17]

A 2011 systematic review and meta-analysis by Nair et al.[1] estimated the global incidence of influenza outcomes among children under the age of five years and concluded that influenza in young children results in significant utilization of health services, particularly among infants younger than one year. However, age-specific estimates for infants under six months were not reported.[1] There is a paucity of published data on incidence of influenza outcomes among

children in this younger age group,[14] yet these data are necessary for informing evidence-based decision-making regarding vaccination programs, provision of appropriate health services, and prioritizing future research. In 2014, the World Health Organization (WHO) formed a working group, as part of a larger influenza taskforce,[18] to systematically review the evidence and estimate incidence rates of laboratory-confirmed influenza outcomes among infants less than six months of age.

METHODS

Search strategy and study selection

Our search strategy was developed by an experienced medical information specialist (BS) based on the review protocol (available from author on request) and informed by the approach used by Nair et al. in their systematic review of the global influenza burden among young children.[1] We searched PubMed, Embase, the Cochrane Library, and CINAHL Plus with Full Text on September 25, 2015. Our strategies utilized a combination of controlled vocabulary (e.g., "Influenza, Human", "Infant Mortality", "Incidence") and keywords (e.g., influenza, neonate, rate). No language or date restrictions were applied but animal-only and opinion pieces (e.g., comments, editorials, interviews) were removed from the initial search results where possible. No unpublished data were pursued or included. Specific details regarding the search strategies appear in Supplementary Appendix 1.

We used Reference Manager Version 12 to download our search results and remove duplicates. Abstracts were then exported to Abstrackr (http://abstrackr.cebm.brown.edu/) for screening and data abstraction. Two teams of two reviewers independently screened all titles and abstracts to

identify potentially relevant articles for full-text review. Disagreements between reviewers were resolved through discussion and consensus. The same two teams of reviewers carried out full-text screening to identify studies that met all the inclusion and exclusion criteria for data extraction and quality assessment. While extracting data, the reviewers also examined the reference lists to identify potentially relevant articles that may have been missed during screening.

We included studies that reported original data on population-based incidence rates for the following laboratory-confirmed influenza (LCI) outcomes among infants under six months of age: LCI illness in ambulatory care settings, LCI hospitalization, LCI intensive care unit (ICU) admission, and LCI death. We excluded studies that had less than one year of data, examined influenza as a co-infection rather than as a primary outcome, used a case definition that was not clearly defined or consistently applied, and those that were not population based or had a population denominator of fewer than 500 infants under six months of age. We included data from the comparator group of any randomized controlled trials (RCT) on influenza immunization during pregnancy if the study otherwise met our inclusion criteria.

Data extraction and quality assessment

Data from each included study were abstracted by one of two reviewers using a standardized data extraction form which was first pilot-tested to ensure a high level of agreement between reviewers. We extracted the following, where available, from each study: author; publication year; study design; study country; study population and size; age ranges studied; subject selection criteria; length of surveillance period and influenza season (particularly specifying the

2009–2010 pandemic versus other seasons); circulating influenza virus strains; definition and type of outcomes included in study; methods for ascertaining cases (e.g., active versus passive surveillance); criteria used for influenza testing; and laboratory assay used to confirm influenza diagnosis. We also extracted information, where available, on the numerator and denominator for each incidence rate; any statistical analyses performed, including variables used to compute adjusted rates; crude and adjusted incidence rates for each outcome with 95% confidence intervals (CI) or other measures of variance; and any sensitivity analyses presented in the paper. Study authors were contacted as needed to clarify data or methods. Two independent reviewers evaluated the quality of each study. Since all included studies were case series or surveillance studies that did not include comparative analyses, we used a modification of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive/Case Series to assess study quality.[19] This checklist assesses four items: clearly defined case inclusion criteria, objective assessments of exposure and outcome, and sufficient follow-up time for outcome ascertainment.

Data synthesis and analysis

We qualitatively summarized individual study characteristics in descriptive tables. For each outcome, we used the incidence rates and 95% CIs reported in the primary study when they were provided, and otherwise computed them using raw study data. We estimated the numerator or denominator values when an incidence rate was reported along with only one of the other two data points. We used Stata SE software version 12 (Stata-Corp LP, College Station, TX, USA) to generate pooled incidence estimates via random effects meta-analyses[20] and the I^2 statistic to quantitatively assess statistical heterogeneity.[21] Pooled incidence estimates were not reported when statistical heterogeneity was high (i.e., I^2 >75%); however, we explored sources of

heterogeneity through sub-group analyses, where possible, to augment our interpretation. *A priori*, we hypothesized that heterogeneity would likely arise due to differences in pandemic versus seasonal influenza, study population, case ascertainment methods, and study quality. We generated forest plots using the R package "ggplot2" (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection

We identified 8,235 records through our initial electronic literature searches; following de-duplication, 5,390 went through initial title and abstract screening. We identified 130 potentially relevant articles and excluded 110 after full-text review, leaving 20. Most manuscripts were excluded because they lacked age-specific data on infants under six months. During full-text screening, we added two articles that had been excluded by our systematic query but identified through a hand search of reference lists.[16,22] This brought the total number of primary studies included in our review to 22 (Figure 1).

Study characteristics

Half (11/22) of the studies originated from the United States[7–9,22–29] and the remainder were from lower-middle-income (n=2),[30,31] upper-middle-income (n=6),[11,16,32–35] and other non-US high-income settings (n=3)[36–38] (Table 1). There were no studies from low-income countries. Twenty studies assessed LCI hospitalization,[8,9,11,16,22–31,33–38] four studies assessed LCI illness in ambulatory care settings,[9,16,31,32] seven studies reported LCI ICU admission,[9,22,28,33,34,37,38] and eight studies reported data on LCI deaths[7,11,16,22,24,30,34,36] (Table 1). All studies were published in

2004 or later and reported data from influenza seasons between 2000 and 2012. Two studies exclusively reported influenza outcomes from the 2009 H1N1 pandemic time period,[34,38] five reported data from the 2009 pandemic time period along with other influenza seasons,[23,30–32,36] and the remainder reported LCI outcomes from seasonal influenza epidemics.[7–9,11,16,22,24–29,33,35,37] Only two studies received a score lower than 4/4 on the modified JBI Critical Appraisal Checklist — one such study did not assess all influenza outcomes using objective criteria[36] and the other did not clearly document the case definition.[38] Most studies used reverse transcription-polymerase chain reaction (RT-PCR) laboratory testing methods, either alone or in combination with other methods, to confirm influenza from patient samples (see online supplementary table S1). We were able to obtain additional clarifying data from three[16,23,34] of five studies by contacting study authors.

Laboratory-confirmed influenza illness in ambulatory care settings

Four studies, three of which were from lower-middle or upper-middle-income countries assessed LCI illness in ambulatory care settings[9,16,31,32] (Table 2). All four studies used RT-PCR to confirm influenza virus infection. In a community-based prospective cohort study conducted between 2009 and 2011 in the Cajamarca region of Peru, researchers conducted active household surveillance to identify infants with symptoms of acute respiratory illness for confirmatory influenza laboratory testing. In this study, the adjusted incidence of LCI illness among infants less than six months of age was 35 per 100 person-years of follow-up (95% CI: 26–48).[32] Using similar active surveillance methods, the RCT from South Africa reported an incidence of LCI illness among infants born to non-HIV infected women in the placebo group of 3.6 per 100 infants per season (95% CI: 2.6–5.0).[16] A population-based active surveillance study conducted

in 67 rural villages in Bangladesh (Matlab district) during the 2010 influenza season did not identify any cases of LCI severe acute respiratory infection among infants under six months.[31] Finally, data from the New Vaccine Surveillance Network (NVSN), a population-based active sentinel surveillance program operating in three regions of the United States (Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York), estimated a rate of LCI illness based on outpatient clinic visits among infants under six months of 28 per 1,000 infants (95% CI: 7–111) in 2002–2003 and 59 per 1,000 infants (95% CI: 28–128) 2003–2004.[9] We did not consider statistical meta-analysis of this outcome due to the variable geographic settings and methodologies employed by the studies. For instance, the latter NVSN study estimated incidence rates from population-based surveillance of hospitalizations and outpatient clinic visits,[9] while the study from Peru utilized community-based surveillance including a household component.[32]

Laboratory-confirmed influenza hospitalization

Graphical and tabular summaries of individual estimates originating from the 20 studies that reported incidence rates of LCI hospitalization can be found in Figure 2 and Supplementary Table S2. Ten of the 20 studies originated from the United States; six of those reported data from one of two population-based active surveillance programs: the Emerging Infections Program (EIP)[23,24] or the NVSN.[8,9,25,28] Two additional US studies led by Grijalva et al. reported estimates using methods based on data from both the EIP and NVSN systems,[26,27] and the remaining two US studies reported data from separate systems.[22,29] In the United States, estimated rates of LCI hospitalization of infants less than six months of age during seasonal epidemics varied from a low of 9.3 per 10,000 infants (95% CI: 7.9–10.9) in 2006–2007[24] to a high of 91.2 per 10,000

infants (95% CI: 67–145)[26] in 2003–2004 (Figure 2B). The only US-based estimate for the 2009 pandemic H1N1 time period was 20.2 per 10,000 infants (95% CI: 18.1–22.5).[23]

The 10 non-US studies (three from high-income countries, five from upper-middle-income countries and two from lower-middle-income countries) reported similar LCI hospitalization rates for seasonal influenza. Most incidence rates for seasonal influenza ranged from 6.2 per 10,000 infants (95% CI: 3.1–9.3) in China in 2007[33] to 73.0 per 10,000 infants (95% CI: 40.6–121.7) in Spain in 2003–2004.[11] However, a higher estimated rate was reported from one post-pandemic study of seasonal influenza from China (250 per 10,000 infants under six months in 2010–2011, 95% CI: 213–292[35]). The highest estimate from non-US based studies from the 2009 pandemic H1N1 influenza time period was 32.0 per 10,000 infants under six months (95% CI: 22.0–45.1) in Israel.[38]

Although 10 studies from the United States presented incidence rates of LCI hospitalization of infants under six months, there was overlap in a number of seasons among the eight studies utilizing data from the EIP and NVSN surveillance programs (Table 3). For instance, two studies reported the same rate from the NVSN system for the 2000–2001 season (24.0 per 10,000 infants),[9,28] and similar combined season rates for 2000–2004 from the NVSN system (reported as 43.0 per 10,000 infants[25] and 45.0 per 10,000 infants[9]). In addition, estimates are available from both the EIP and the NVSN for several years. In such instances, incidence rates from the NVSN system are consistently higher in magnitude than the EIP estimates. Moreover, Grijalva et al. combined data from the EIP and NVSN surveillance systems (using a capture-recapture methodology) and computed a higher combined incidence rate of LCI hospitalization than was provided by either system alone.[26,27] For instance, in 2003–2004, which was a more severe

influenza season, the EIP and NVSN estimates were 29.6 per 10,000 infants (95% CI: 26.7–32.8)[24] and 72.0 per 10,000 infants (95% CI: 53.0–92.0),[9] respectively. Using the combined data from both systems, the revised estimate was 91.2 per 10,000 infants (95% CI: 67.0–145.0).[26]

Laboratory-confirmed influenza ICU admission

LCI ICU admission rates for infants under six months are available from seven studies[9,22,28,33,34,37,38] (Table 4). However, all rates shown in Table 4 were computed by review authors, either due to non-reporting in the original study[9,22,28,33,34,37] or due to graphical presentation of rates in a figure only.[38] Estimated rates of LCI ICU admission for seasonal influenza ranged from a low of 0.5 per 10,000 infants (95% CI: 0.8–16.5) between 2000–2001 and 2003–2004 in the Salt Lake City area of the United States[9] to a high of 3.5 per 10,000 between 2001 and 2004 in the surveillance counties covered by the NVSN (95% CI: 1.7–6.4).[22] The absolute number of LCI ICU admissions of infants under six months was very low in all study populations (from a low of 0[28] to a high of 12 admissions[34]). Two studies were conducted during the 2009 H1N1 pandemic time period — in Argentina, Libster et al. reported a rate of LCI ICU admission of 2.9 per 10,000 infants (95% CI: 1.6–5.0)[34] and in Israel, Stein et al. reported a similar rate of 2.5 per 10,000 infants (95% CI: 0.79–6.0).[38]

Laboratory-confirmed influenza death

Eight studies included LCI death among infants under six months of age as an outcome.[7,11,16,22,24,30,34,36] In five of the eight study populations, surveillance for LCI deaths was conducted, but none were identified[11,16,22,30,36] (Table 5). Bhat et al. reported data from enhanced national-level surveillance of pediatric LCI deaths in the United States during the 2003–2004

season.[7] In this study, there were 18 deaths of infants under six months of age, corresponding to a rate of 0.88 per 100,000 infants (95% CI: 0.52–1.39), which was the highest among all pediatric age groups up to 18 years. In a smaller US surveillance study using data from the EIP system operating in 10 states, three influenza deaths of infants under six months were recorded during 2003–2004 to 2007–2008 combined, with a corresponding rate of 0.41 per 100,000 person-years (95% CI: 0.11–1.12).[24] Among all eight studies, the highest rate of LCI deaths in infants was reported in Buenos Aires, Argentina, for the 2009 pandemic H1N1 time period; two deaths were recorded, and the LCI mortality rate was 5 per 100,000 infants (95% CI: 0.82–16.1).[34]

DISCUSSION

In this systematic review, we provide a summary of published data up to September 2015 regarding the incidence of laboratory-confirmed influenza outcomes among infants under six months of age. Our review of 22 studies covering 12 influenza seasons demonstrates a relatively wide range of estimates in incidence rates for several LCI outcomes in this age group. This broad distribution is likely associated with biological variability of influenza clinical disease and epidemiology and host immunity, as well as methodological factors of the studies themselves, including differences in care provider practices for influenza testing and hospital admission. In particular, estimates of rates for LCI hospitalizations, the most frequently reported and best described outcome among these studies, ranged 10-fold, from 9.3 to 91.2 per 10,000 infants, within the United States alone, and varied even more widely in other settings. The incidence of LCI hospitalizations was generally higher during the 2009 pandemic H1N1 time period (32 to 270 per 10,000 infants) than during seasonal influenza years (6.2 to 73 LCI hospitalizations per

10,000 infants). Our work also highlights the relative lack of studies that specifically report influenza outcomes in this vulnerable age group and the limited information included in studies that do include such findings. LCI outcomes other than hospitalization, such as intensive care unit admission and death, were even less commonly assessed and varied markedly in the level of detail described. Moreover, the majority of data identified in this review come from the United States, deriving primarily from just two influenza surveillance systems, indicating the constrained geographic coverage of the collected datasets. These limitations pose challenges for estimating the impact of maternal influenza immunization programs on infant influenza outcomes, particularly for low- and middle-income countries.

Our review methodology utilized a comprehensive search strategy that emphasized high sensitivity to capture a broad set of articles for screening. We subsequently restricted our review to laboratory-confirmed, population-based estimates of influenza incidence, ensuring greater consistency and stability of rates across studies. Our review also benefits from a number of strengths regarding the original studies identified through our search. First, the majority of the data come from well-established surveillance systems that cover several seasons and include additional evaluations (e.g., capture-recapture[26,27]) to confirm the validity of their findings. This consistency adds to the stability of the range of estimates reported here and provides a better understanding of the effects of seasonal variation on annual burden estimates. Second, the included studies generally obtained high scores in the quality assessment tool providing some assurance that they met at least minimum quality criteria.

Nevertheless, there are several important limitations. Among the primary studies, the different surveillance methodologies (e.g., passive versus active surveillance; different sensitivity of diagnostic tests; recruitment only in a subset of days per week; different denominators or methods to calculate incidence rates; surveillance only during part of the year; rate adjustment for various factors) contributed to the heterogeneity of the results. We were unable to include several studies that aggregated data from infants under six months within larger age strata, thus not reporting data specific to this important age group. Future surveillance studies should report data for infants under six months, even if only as supplementary data, to facilitate future pooling and meta-analyses. The reports themselves were incomplete at times, lacking numerator data, denominator data or precision estimates, precluding the ability to perform meta-analysis. Even with full reporting of the data, key factors may have influenced the accuracy of specific surveillance approaches. Importantly, Grijalva et al.[26,27] demonstrated that the two US surveillance systems likely underestimate the incidence of LCI hospitalizations. In both 2003–2004 and 2004–2005, the incidence of LCI hospitalization was higher using the combined capture-recapture methodology than when estimated using either NVSN or EIP data alone. Finally, some studies reported only a small number of seasons or a limited geographic area which may not provide a fully representative assessment of typical influenza incidence. Finally, several of the US-based studies described overlapping seasons across multiple reports, thus contributing to a risk of duplicate counting.

Although we evaluated studies that included a narrower age range compared to the review by Nair et al.,[1] our results are generally consistent with the findings presented in that review, which reported rates of severe acute lower respiratory infection (corresponding to influenza

hospitalization) ranging from 10 to 170 per 10,000 child-years among children under one year of age. These consistent findings support the overall interpretation that influenza has a significant role in early infant respiratory morbidity. Of note, the incidence rate reported for influenza hospitalization in the placebo arm of the only randomized clinical trial included in this review[16] was at the lower end of the range of estimates (one LCI hospitalization corresponding to a rate of 9.8 per 10,000 infants; personal communication: M Nunes, 7 Dec 2016). This low rate compared with other estimates could be due to the epidemiologic characteristics of that particular influenza season or due to the close observation of subjects and opportunity for treatment and follow-up afforded by the active surveillance in the trial. Similarly, a more recent trial of maternal influenza immunization[17] published subsequent to our literature search also reported one hospitalization for laboratory-confirmed influenza in the active control arm (personal communication: M Tapia, 15 Dec 2016). Using prospective active surveillance methods, these two trials likely provide the best estimates of the incidence of LCI illness in an ambulatory setting: 3.6 per 100 infants under six months[16] and 0.17 per 1,000 infant-days of follow up.[17]

In conclusion, our systematic review demonstrates that existing data on laboratory-confirmed influenza outcomes among infants under six months of age are sparse, of varying quality, and heavily weighted toward high-income populations. More research is needed in key regions, particularly the low- and low-middle-income countries of Asia and Africa where the majority of cases occur, to obtain a more globally representative picture of the incidence of influenza outcomes among young infants. Higher quality data will be essential in order to allow global and country-level policy-makers to make evidence-based decisions that appropriately prioritize

interventions such as maternal influenza immunization for reducing influenza disease in young infants who are, themselves, not eligible for influenza vaccination.

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Contributors: NB, KMN and JRO designed the study protocol. BS designed and ran the systematic search strategy. JJ, ZM and MAK screened the articles, extracted the data and assessed the quality of individual studies. DBF, ZM, MAK and JRO contacted study authors for additional information. DBF interpreted the data and wrote the first draft of the manuscript. All

authors critically revised the manuscript for intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: This work was supported by the Bill & Melinda Gates Foundation through the World Health Organization. The research was coordinated by PATH. Drs. Fell and Katz received financial support from the World Health Organization's Initiative for Vaccine Research. The authors also acknowledge the Centers for Disease Control and Prevention (CDC), which provides financial support to the World Health Organization Initiative for Vaccine Research (U50 CK000431).

Disclaimer: Justin R. Ortiz is an employee of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

Competing interests: The authors have no conflicts to declare.

Data sharing statement: The data set is available on request from the corresponding author.

Acknowledgments: We acknowledge members of the WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling, a working group of the WHO Initiative for Vaccine Research, for their contributions through early discussions about this study. We are grateful to Glen Zinck (PATH) for his help with project organization and to Dr. Corinne Riddell (McGill University) for her assistance with producing Forest plots. We additionally

thank Dr. Kevin Pottie (University of Ottawa), Dr. Michael Gravett (University of Washington) and Dr. Dayre McNally (University of Ottawa) for their thoughtful reviews of an earlier version of this manuscript.

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Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram showing selection of studies

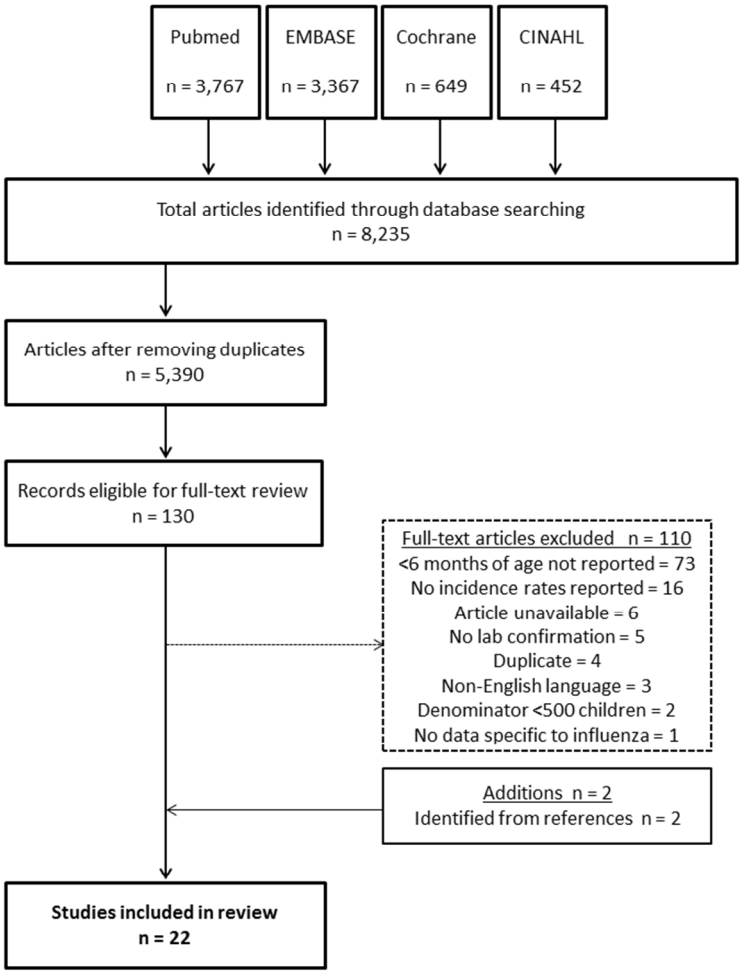


Table 1. Characteristics of the primary studies and laboratory-confirmed influenza (LCI) outcomes assessed

First author (Year)	Location	World Bank country income group [d]	World Health Organization Region [e]	Study design	Time period	Pandemic or seasonal influenza	Reported LCI outcomes			
							LCI illness in ambulatory care settings	LCI hospitalization	LCI ICU admission	LCI death
Ampofo (2006) [22]	Salt Lake City, Utah, United States	High income	Region of the Americas	Retrospective cohort	July 2001 to June 2004	Seasonal		✔	✔	✔
Bhat (2005) [7]	United States	High income	Region of the Americas	Surveillance	September 2003 to May 2004	Seasonal				✔
Broor (2014) [30]	Haryana State, India	Lower middle income	South-East Asia Region	Surveillance	August 2009 to July 2011	Pandemic H1N1 and seasonal		✔		✔
Budge (2014) [32]	Department of Cajamarca, Peru	Upper middle income	Region of the Americas	Prospective cohort	May 2009 to September 2011	Pandemic H1N1 and seasonal	✔			
Cox (2012) [23] [a,b]	United States	High income	Region of the Americas	Surveillance (EIP)	April 2008 to April 2010	Pandemic H1N1 and seasonal		✔		
Dawood (2010) [24] [b]	United States	High income	Region of the Americas	Surveillance (EIP)	2003–2004 to 2007–2008	Seasonal		✔		✔
Griffin (2004) [25] [c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001 to 2003–2004	Seasonal		✔		
Grijalva (2006) [26] [b,c]	Davidson County, Tennessee, United States	High income	Region of the Americas	Surveillance (NVSN and EIP capture-recapture study)	2003–2004	Seasonal		✔		
Grijalva (2007) [27] [b,c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN and EIP capture-recapture study)	2004–2005	Seasonal		✔		
Iwane (2004) [28] [c]	Davidson County, Tennessee; Monroe County, New York; United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001	Seasonal		✔	✔	

Ji (2010) [33]	Jiangsu province, China	Upper middle income	Western Pacific Region	Surveillance	Jan 2007 to December 2008	Seasonal		✔	✔	
Libster (2010) [34]	Buenos Aires, Argentina	Upper middle income	Region of the Americas	Case series	May 2009 to July 2009	Pandemic H1N1		✔	✔	✔
Madhi (2014) [16]	Soweto, South Africa	Upper middle income	African Region	Randomized controlled trial (RCT)	2011 to 2012	Seasonal	✔	✔		✔
Montes (2005) [11]	Regions of Basque Country, Spain	Upper middle income	European Region	Retrospective cohort	July 2001 to June 2004	Seasonal		✔		✔
Nasreen (2014) [31]	Matlab, Bangladesh	Lower middle income	South-East Asia Region	Surveillance	June 2010 to October 2010	Pandemic H1N1 and seasonal	✔	✔		
Nelson (2014) [36]	Hong Kong (China)	High income	Western Pacific Region	Retrospective cohort	April 2005 to March 2011	Pandemic H1N1 and seasonal		✔		✔
Poehling (2006) [9 c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001 to 2003–2004	Seasonal	✔	✔	✔	
Poehling (2013) [8 c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2004–2005 to 2008–2009	Seasonal		✔		
Proff (2009) [29]	Colorado, United States	High income	Region of the Americas	Surveillance	2004 to 2008 (October 1 to May 31 annually)	Seasonal		✔		
Silvennoinen (2011) [37]	Finland	High income	European Region	Retrospective cohort	July 1988 to June 2004	Seasonal		✔	✔	
Stein (2010) [38]	Israel	High income	European Region	Prospective cohort	July 12, 2009 to December 24, 2009	Pandemic H1N1		✔	✔	
Yu (2013) [35]	Jingzhou City, Hubei Province, China	Upper middle income	Western Pacific Region	Surveillance	April 2010 to April 2012	Seasonal		✔		
Total = 22 studies							**4**	**20**	**7**	**8**

[a] Although the study objective was to report data from the 2009 H1N1 influenza pandemic, the reported incidence rates from other years for comparison. As the incidence rates from 2008–2009 have not been reported elsewhere, they have been included.
[b] Emerging Infections Program (EIP).

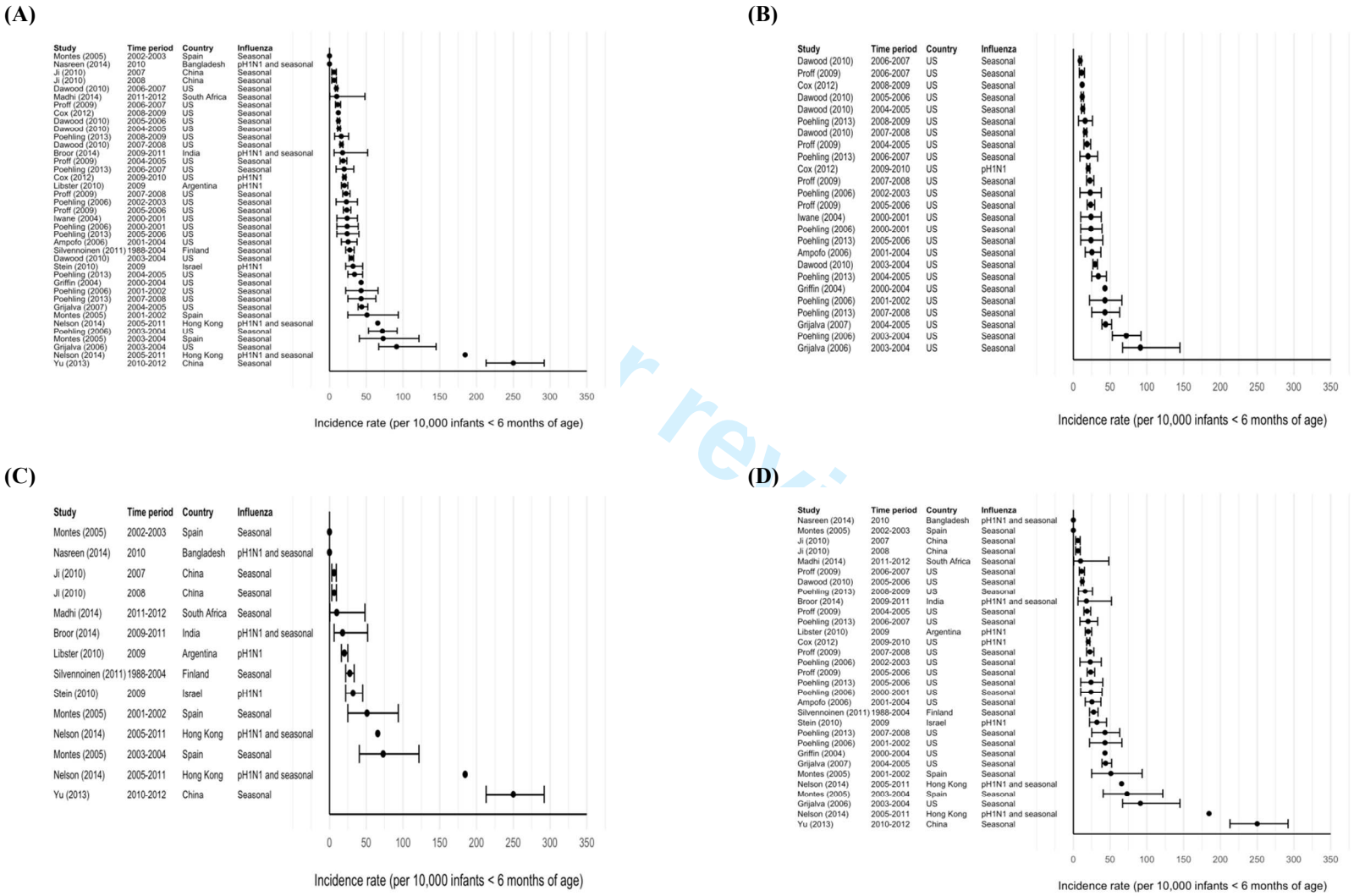
[c] New Vaccine Surveillance Network (NVSN). Surveillance was conducted from November 1 through April 30 each year, but the time period was extended if influenza was detected earlier or ended later.
[d] World Bank. World Development Indicators. Accessed: 10 Jan 2017. Available at: http://data.worldbank.org/data-catalog/world-development-indicators
[e] World Health Organization. WHO regional offices. Accessed: 10 Jan 2017. Available at: http://www.who.int/about/regions/en/

Table 2. Incidence estimates of laboratory-confirmed influenza illness in ambulatory care settings among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate (95% CI)	Adjustment
Budge (2014) [32]	May 2009 to September 2011	-- [a]	-- [a]	35 per 100 person-years (26-48)	Rate adjusted for clustering at the individual child level due to multiple episodes.
Madhi (2014) [16]	2011 to 2012	37	1,023	3.6 per 100 population (2.6-5.0)	None
Nasreen (2014) [31]	June 2010 to October 2010	0	1,264 [b]	0	None
Poehling (2006) [9]	2002–2003 to 2003–2004 [c]	20	-- [a]	2002–2003: 28 per 1,000 population (7-111) 2003–2004: 59 per 1,000 population (28-128)	Rate adjusted by multiplying the influenza burden for each age group and study year by age-specific rate of acute respiratory tract infection or fever estimated from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS).

[a] Not reported in original study and insufficient information to compute.
[b] Estimated by dividing the total number of children under 1 year in half.
[c] Rates based on number of outpatient clinic visits attributable to influenza in 2002–2003 to 2003–2004 only.

Figure 2. Incidence estimates of laboratory-confirmed influenza (LCI) hospitalization among infants under six months of age [a]



[a] Heterogeneity I^2: 100% in all sub-groups
[b] For US-based studies, only one estimate per season is reported. All estimates can be found in Supplementary Table S2.

Table 3. Incidence estimates of laboratory-confirmed influenza hospitalization among infants under six months of age from US-based influenza surveillance systems

Influenza season reported	Surveillance system		
	EIP Rate per 10,000 children (95% CI)	NVSN Rate per 10,000 children (95% CI)	EIP and NVSN combined Rate per 10,000 children (95% CI)
Individual seasons			
2000–2001		24.0 (10.0–38.0) [28]	
		24.0 (10.0–39.0) [9]	
2001–2002		43.0 (22.0–66.0) [9]	
2002–2003		23.0 (9.0–38.0) [9]	
2003–2004	29.6 (26.7–32.8) [24]	72.0 (53.0–92.0) [9]	91.2 (67.0–145.0) [a 26]
2004–2005	12.8 (11.0–14.9) [24]	34.0 (25.0–45.0) [8]	43.8 (38.9–52.1) [b 27]
2005–2006	12.1 (10.5–13.8) [24]	24.0 (10.0–40.0) [8]	
2006–2007	9.3 (7.9–10.9) [24]	20.0 (9.0–33.0) [8]	
2007–2008	16.2 (14.3–18.3) [24]	43.0 (25.0–63.0) [8]	
2008–2009	12.0 [23]	16.0 (7.0–26.0) [8]	
2009–2010 (H1N1 pandemic)	20.2 (18.1–22.5) [23]		
Combined seasons			
2000–2004		43.0 [25]	
		45.0 (34.0–55.0) [9]	
2004–2009		27.0 (21.0–33.0) [9]	

EIP: Emerging Infections Program; NVSN: New Vaccine Surveillance Network

[a] Individual estimates: EIP=34.5 per 10,000; NVSN=66.6 per 10,000.

[b] Individual estimates: EIP=17.4 per 10,000; NVSN=29.9 per 10,000.

Table 4. Incidence estimates of laboratory-confirmed influenza ICU admission among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate (95% CI)	Adjustment
Ampofo (2006) [22]	July 2001 to June 2004	9	25,710	3.5 per 10,000 population (1.7–6.4) [a]	None
Iwane (2004) [28]	2000–2001	0	8,591	0	None
Ji (2010) [33]	Jan 2007 to December 2008	3	48,147 [a]	0.62 per 10,000 person-years (1.6–17.0) [a]	None
Libster (2010) [34]	May 2009 to July 2009	12	41,000	2.9 per 10,000 population (1.6–5.0) [a]	None
Poehling (2006) [9]	2000–2001 to 2003–2004	2	40,000	0.5 per 10,000 population (0.8–16.5) [a]	None
Silvennoinen (2011) [37]	July 1988 to June 2004	5	31,884	1.6 per 10,000 population 0.6–3.5) [a]	None
Stein (2010) [38]	July 12, 2009 to December 24, 2009	4	16,000 [a]	2.5 per 10,000 population [b]	None

[a] Not reported in original study and insufficient information to compute.
[b] Estimated from Figure 2 in original study.[38]

Table 5. Incidence estimates of laboratory-confirmed influenza death among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate (95% CI)	Adjustment
Ampofo (2006) [22]	July 2001 to June 2004	0	25,710	0	None
Bhat (2005) [7]	September 2003 to May 2004	18	-- [a]	0.88 per 100,000 population (0.52–1.39)	None
Broor (2014) [30]	August 2009 to July 2011	0	-- [a]	0	None
Dawood (2010) [24]	2003–2004 to 2007–2008	3	726,886 [b]	0.41 per 100,000 person-years (0.11–1.12) [b]	None
Libster (2010) [34]	May 2009 to July 2009	2	41,000	5 per 100,000 population (0.82–16.1) [b]	None
Madhi (2014) [16]	2011 to 2012	0	1,023	0	None
Montes (2005) [11]	July 2001 to June 2004	0	5,366	0	None
Nelson (2014) [36]	April 2005 to March 2011	0	-- [a]	0	None

[a] Not reported in original study and insufficient information to compute.
[b] Computed by review authors.

Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing selection of studies

Figure 2. Incidence estimates of laboratory-confirmed influenza (LCI) hospitalization among infants under six months of age

(A) Individual season estimates from all 20 studies reporting LCI hospitalization rates of infants under six months

(B) Individual season estimates from US-based studies

(C) Individual season estimates from non-US-based studies

(D) Individual season estimates excluding overlapping years from US studies

Supplementary Appendix 1

Incidence of influenza disease among infants under six months of age: A systematic review
Final Strategies
2015 Sep 25

PubMed
Search Name: Paediatric Influenza - Incidence

Search	Query	Items found
#72	Search #69 NOT (#70 OR #71)	3767
#71	Search letter [pt] NOT (randomized controlled trial [tiab] AND letter [pt])	889583
#70	Search comment [pt] OR editorial [pt] OR interview [pt]	924773
#69	Search #67 NOT #68	3789
#68	Search Animals [mesh] NOT (Animals [mesh] AND Humans [mesh])	4044914
#67	Search #37 OR #44 OR #56 OR #66	3805
#66	Search #29 AND #65	2846
#65	Search #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	2081824
#64	Search ecological study [tw] OR ecological studies [tw]	3166
#63	Search case-control [tw] OR case-base [tw] OR case-based [tw] OR case-comparison [tw] OR case-compeer [tw] OR case-referent [tw] OR case-referrent [tw]	233343
#62	Search Case-Control Studies [mesh]	727356
#61	Search population study [tw] OR population studies [tw] OR population-based study [tw] OR population-based studies [tw] OR population analys* [tw] OR population-based analys* [tw]	36835
#60	Search followup study [tw] OR followup studies [tw] OR follow up study [tw] OR follow up studies [tw]	539346
#59	Search longitudinal [tw] OR prospective [tw] OR retrospective [tw]	1337855
#58	Search cohort [tw] OR cohorts [tw]	402430
#57	Search Cohort Studies [mesh]	1447931
#56	Search #29 AND #55	250
#55	Search #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54	402882
#54	Search control group [tw] OR control groups [tw]	323436
#53	Search Control Groups [mesh]	1452
#52	Search interrupted time series [tw]	1332
#51	Search Interrupted Time Series Analysis [mesh]	77
#50	Search controlled study [tw] OR controlled studies [tw]	50430
#49	Search Historically Controlled Study [mesh]	27
#48	Search "controlled before and after" [tw] OR "controlled before after" [tw]	659
#47	Search Controlled Before-After Studies [mesh]	54

	Search Query	Items found
#46	Search nRCT [tw] OR nRCTs [tw] OR non-RCT [tw] OR non-RCTs [tw]	382
#45	Search nonrandom* [tw] OR non-random* [tw] OR quasi-random* [tw] OR quasi-experiment* [tw]	38100
#44	Search #29 AND #43	1072
#43	Search #38 OR #39 OR #40 OR #41 OR #42	1089159
#42	Search trial [ti]	142809
#41	Search single blind* [tw] OR double blind* [tw] OR triple blind* [tw] OR single mask* [tw] OR double mask* [tw] OR triple mask* [tw] OR single dumm* [tw] OR double dumm* [tw] OR triple dumm* [tw]	189591
#40	Search randomised [tw] OR randomized [tw] OR randomly [tw] OR RCT [tw] OR RCTs [tw] OR placebo* [tw]	841995
#39	Search "clinical trials as topic" [mesh]	289409
#38	Search controlled clinical trial [pt] OR randomized controlled trial [pt]	480668
#37	Search #29 AND #36	236
#36	Search #30 OR #31 OR #32 OR #33 OR #34 OR #35	286635
#35	Search "The Cochrane database of systematic reviews"[Journal] OR "evidence report/technology assessment summary"[Journal] OR "evidence report/technology assessment"[Journal]	11600
#34	Search meta-review* [tw] OR meta-overview* [tw] OR meta-synthes* [tw] OR "review of reviews" [tw]	566
#33	Search meta-analy* [tw] OR metanaly* [tw] OR metaanaly* [tw] OR met analy* [tw] OR integrative research [tw] OR integrative review* [tw] OR integrative overview* [tw] OR research integration [tw] OR research overview* [tw] OR collaborative review* [tw]	107088
#32	Search "meta-analysis as topic" [mesh]	14167
#31	Search meta analysis [pt]	57196
#30	Search systematic [sb]	261834
#29	Search #14 AND #28	10001
#28	Search #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	5398968
#27	Search Influenza, Human/ep [mesh]	15598
#26	Search DALY [tw] OR DALYs [tw]	1575
#25	Search "disability-adjusted" [tw] AND (year [tw] or years [tw])	1705
#24	Search burden [tw] OR burdens [tw] OR death [tw] OR deaths [tw] OR epidemiolog* [tw] OR incidence [tw] OR frequenc* [tw] OR morbidit* [tw] OR mortalit* [tw] OR occurrence* [tw] OR occurence* [tw] OR outbreak* [tw] OR prevalen* [tw] OR rate [tw] OR rates [tw] OR surveillance* [tw]	5398606
#23	Search Survival Rate [mesh]	132546
#22	Search Perinatal Mortality [mesh]	982
#21	Search Infant Mortality [mesh]	25188

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#19	Search Cause of Death [mesh]	37174
#18	Search Mortality [mesh:noexp]	35224
#17	Search Morbidity [mesh]	396299
#16	Search Prevalence [mesh]	205729
#15	Search Incidence [mesh]	187146
#14	Search #6 AND #13	16201
#13	Search #7 OR #8 OR #9 OR #10 OR #11 OR #12	1653415
#12	Search ("1 month" [tw] OR "2 month" [tw] OR "2 months" [tw] OR "3 month" [tw] OR "3 months" [tw] OR "4 month" [tw] OR "4 months" [tw] OR "5 month" [tw] OR "5 months" [tw] OR "6 month" [tw] OR "6 months" [tw]) AND (age [tw] or aged [tw] OR ages [tw] OR old [tw])	386006
#11	Search ("one month" [tw] OR "two month" [tw] OR "two months" [tw] OR "three month" [tw] OR "three months" [tw] OR "four month" [tw] OR "four months" [tw] OR "five month" [tw] OR "five months" [tw] OR "six month" [tw] OR "six months" [tw]) AND (age [tw] or aged [tw] OR ages [tw] OR old [tw])	100127
#10	Search SGA [tw] OR LBW [tw] OR VLBW [tw]	10273
#9	Search neonat* [tw] OR newborn* [tw]	711217
#8	Search infant [tw] OR infants [tw] OR infancy [tw] OR baby [tw] OR babies [tw]	1081815
#7	Search Infant [mesh]	961979
#6	Search #1 OR #2 OR #3 OR #4 OR #5	108939
#5	Search H1N1 [tw] OR PH1N1 [tw] OR H3N2 [tw] OR AH1N1 [tw] OR AH3N2 [tw]	18776
#4	Search Influenza B Virus [mesh]	3184
#3	Search Influenza A Virus [mesh]	34136
#2	Search (influenza* [tw] OR flu [tw] OR grippe [tw])	108774
#1	Search Influenza, Human [mesh]	37849

Embase

Search Name: Paediatric Influenza - Incidence
Database: Embase Classic+Embase <1947 to 2015 September 24>
Search Strategy:
---

1 influenza/ (56566)
2 exp Influenza virus A/ (36192)
3 exp Influenza virus B/ (5289)
4 pandemic influenza/ (3749)
5 seasonal influenza/ (3413)
6 (influenza* or flu or grippe).ti,ab,kw. (126039)
7 (H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2).ti,ab,kw. (20337)
8 or/1-7 (143389)
9 infant/ (584948)
10 (infant or infants or infancy or baby or babies).ti,ab,kw. (497405)
11 newborn/ (525200)
12 (neonat* or newborn*).ti,ab,kw. (415750)
13 (SGA or LBW or VLBW).ti,ab,kw. (14351)
14 ((one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old)).ti,ab,kw. (14881)
15 (("1 month" or "2 month" or "2 months" or "3 month" or "3 months" or "4 month" or "4 months" or "5 month" or "5 months" or "6 month" or "6 months") adj3 (age or aged or ages or old)).ti,ab,kw. (74046)
16 or/9-15 (1314942)
17 8 and 16 (13606)
18 incidence/ (237278)
19 prevalence/ (450891)
20 exp disease surveillance/ (15135)
21 Infection rate/ (19900)
22 morbidity/ (256072)
23 newborn morbidity/ (6013)
24 mortality/ (625197)
25 infant mortality/ (22660)
26 newborn mortality/ (10384)
27 "cause of death"/ (84993)
28 survival rate/ (176633)
29 (burden or burdens or death or deaths or epidemiolog* or incidence or frequenc* or morbidit* or mortalit* or occurrence* or occurence* or outbreak* or prevalen* or rate or rates or surveillance*).ti,ab,kw. (6043641)
30 influenza/ep (10380)
31 exp Influenza virus A/ep (201)
32 exp Influenza virus B/ep (18)
33 pandemic influenza/ep (612)
34 seasonal influenza/ep (343)
35 ("disability-adjusted" adj2 (year or years)).ti,ab,kw. (1990)
36 (DALY or DALYs).ti,ab,kw. (2091)
37 or/18-36 (6386442)

38 17 and 37 (7967)
39 meta-analysis/ (99125)
40 "systematic review"/ (95683)
41 "meta analysis (topic)"/ (22361)
42 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab,kw. (111122)
43 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews").ti,ab,kw. (122272)
44 (cochrane or health technology assessment or evidence report).jw. (13908)
45 or/39-44 (263998)
46 38 and 45 (113)
47 randomized controlled trial/ or controlled clinical trial/ (524987)
48 exp "clinical trial (topic)"/ (164463)
49 (randomi#ed or randomly or RCT$1 or placebo*).ti,ab,kw. (928458)
50 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).ti,ab,kw. (184212)
51 trial.ti. (194717)
52 or/47-51 (1319714)
53 38 and 52 (744)
54 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).ti,ab,kw. (45795)
55 (nRCT or nRCTs or non-RCT$1).ti,ab,kw. (525)
56 (control* adj3 ("before and after" or "before after")).ti,ab,kw. (3869)
57 time series analysis/ (16042)
58 (time series adj3 interrupt*).ti,ab,kw. (1544)
59 controlled study/ (4737075)
60 (control* adj2 stud$3).ti,ab,kw. (221552)
61 control group/ (93065)
62 (control$ adj2 group$1).ti,ab,kw. (501642)
63 or/54-62 (5098022)
64 38 and 63 (1961)
65 cohort analysis/ (216857)
66 cohort.ti,ab,kw. (463216)
67 retrospective study/ (427824)
68 longitudinal study/ (82291)
69 prospective study/ (308661)
70 (longitudinal or prospective or retrospective).ti,ab,kw. (1180818)
71 follow up/ (983556)
72 ((followup or follow-up) adj (study or studies)).ti,ab,kw. (57996)
73 population research/ (74829)
74 ((population or population-based) adj (study or studies or analys#s)).ti,ab,kw. (17929)
75 exp case control study/ (106570)
76 (case-control* or case-base or case-based or case-comparison or case-compeer or case-referent or case-referrent).ti,ab,kw. (118283)
77 (ecological adj (study or studies)).ti,ab,kw. (3591)
78 or/65-77 (2608918)
79 38 and 78 (2060)
80 46 or 53 or 64 or 79 (3472)

81 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (22291007)
82 exp humans/ or exp human experimentation/ or exp human experiment/ (16544866)
83 81 not 82 (5747166)
84 80 not 83 (3382)
85 editorial.pt. (491119)
86 letter.pt. not (letter.pt. and randomized controlled trial/) (904244)
87 84 not (85 or 86) (3367)

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Cochrane Library

Search Name: Paediatric Influenza - Incidence
Date Run: 25/09/15 12:51:27.541
Description: WHO - 2015 Sep 25 - Final

ID	Search	Hits
#1	[mh "Influenza Human"]	1393
#2	(influenza* or flu or grippe):ti,ab,kw	6146
#3	[mh "Influenza A Virus"]	740
#4	[mh "Influenza B Virus"]	229
#5	(H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2):ti,ab,kw	855
#6	{or #1-#5}	6149
#7	[mh Infant]	13442
#8	(infant or infants or infancy or baby or babies):ti,ab,kw	40394
#9	(neonat* or newborn*):ti,ab,kw	22224
#10	(SGA or LBW or VLBW):ti,ab,kw	1208
#11	(((one or two or three or four or five or six) next (month or months)) near/3 (age or aged or ages or old)):ti,ab,kw	508
#12	(((1 or 2 or 3 or 4 or 5 or 6) next (month or months)) near/3 (age or aged or ages or old)):ti,ab,kw	3138
#13	{or #7-#12}	46302
#14	#6 and #13	1231
#15	[mh Incidence]	8037
#16	[mh Prevalence]	4006
#17	[mh Morbidity]	12265
#18	[mh ^Mortality]	505
#19	[mh "Cause of Death"]	1200
#20	[mh "Hospital Mortality "]	1103
#21	[mh "Infant Mortality"]	505
#22	[mh "Perinatal Mortality"]	65
#23	[mh "Survival Rate"]	8500
#24	(burden or burdens or death or deaths or epidemiolog* or frequenc* or incidence or morbidit* or mortalit* or occurrence* or occurence* or outbreak* or prevalen* or rate or rates or surveillance*):ti,ab,kw	292711
#25	[mh "Influenza, Human"/ep]	247
#26	("disability-adjusted" near/2 (year or years)):ti,ab,kw	40
#27	(DALY or DALYs):ti,ab,kw	42
#28	{or #15-#27}	292792
#29	#14 and #28	649

DSR - 12
DARE - 3
CENTRAL – 608
HTA – 5
NHS EED – 21

CINAHL Plus with Full Text

Search Name: Paediatric Influenza - Incidence

#	Query	Limiters/Expanders	Results
S70	S67 NOT (S68 OR S69)	Search modes - Boolean/Phrase	452
S69	PT Letter NOT (PT Letter AND PT randomized controlled trial)	Search modes - Boolean/Phrase	209,408
S68	PT comment OR PT editorial OR PT interview	Search modes - Boolean/Phrase	221,414
S67	S65 NOT S66	Search modes - Boolean/Phrase	454
S66	(MH "Animals+") NOT ((MH "Animals+") AND (MH "Human"))	Search modes - Boolean/Phrase	58,476
S65	S33 OR S40 OR S52 OR S64	Search modes - Boolean/Phrase	454
S64	S27 AND S63	Search modes - Boolean/Phrase	376
S63	S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62	Search modes - Boolean/Phrase	495,947
S62	TI (ecological W1 (study or studies)) OR AB (ecological W1 (study or studies))	Search modes - Boolean/Phrase	484
S61	(MH "Ecological Research")	Search modes - Boolean/Phrase	617
S60	TI ((case W1 control*) or "case-base" or "case-based" or "case-comparison" or "case-compeer" or "case-referent" or "case-referrent") OR AB ((case W1 control*) or "case-base" or "case-based" or "case-comparison" or "case-compeer" or "case-referent" or "case-referrent")	Search modes - Boolean/Phrase	16,368
S59	(MH "Case Control Studies+")	Search modes - Boolean/Phrase	53,567
S58	TI ((population or "population-based") W1 (study or studies or analys*)) OR AB ((population or "population-based") W1 (study or studies or analys*))	Search modes - Boolean/Phrase	13,246
S57	TI ((followup or "follow-up") W1 (study or studies)) OR AB ((followup or "follow-up") W1 (study or studies))	Search modes - Boolean/Phrase	6,843
S56	TI (longitudinal or prospective or retrospective) OR AB (longitudinal or prospective or retrospective)	Search modes - Boolean/Phrase	153,687
S55	(MH "Retrospective Design")	Search modes - Boolean/Phrase	143,341
S54	TI (cohort or cohorts) OR AB (cohort or cohorts)	Search modes -	72,938

		Boolean/Phrase	
S53	(MH "Prospective Studies+")	Search modes - Boolean/Phrase	274,540
S52	S27 AND S51	Search modes - Boolean/Phrase	52
S51	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	Search modes - Boolean/Phrase	92,060
S50	(MH "Pretest-Posttest Control Group Design")	Search modes - Boolean/Phrase	458
S49	TI (control* N2 (group or groups)) OR AB (control* N2 (group or groups))	Search modes - Boolean/Phrase	45,568
S48	(MH "Control Group")	Search modes - Boolean/Phrase	6,585
S47	TI (control* N2 (study or studies)) OR AB (control* N2 (study or studies))	Search modes - Boolean/Phrase	33,851
S46	TI time series N3 interrupt* OR AB time series N3 interrupt*	Search modes - Boolean/Phrase	594
S45	(MH "Quasi-Experimental Studies+")	Search modes - Boolean/Phrase	9,154
S44	TI (control* N3 ("before and after" or "before after")) OR AB (control* N3 ("before and after" or "before after"))	Search modes - Boolean/Phrase	851
S43	TI (nRCT or nRCTs or (non W1 RCT) or (non W1 RCTs)) OR AB (nRCT or nRCTs or (non W1 RCT) or (non W1 RCTs))	Search modes - Boolean/Phrase	127
S42	TI (nonrandom* or (non W1 random*) or (quasi W1 random*) or (quasi W1 experiment*)) OR AB (nonrandom* or (non W1 random*) or (quasi W1 random*) or (quasi W1 experiment*))	Search modes - Boolean/Phrase	9,890
S41	(MH "Nonrandomized Trials")	Search modes - Boolean/Phrase	190
S40	S27 AND S39	Search modes - Boolean/Phrase	90
S39	S34 OR S35 OR S36 OR S37 OR S38	Search modes - Boolean/Phrase	269,666
S38	TI trial	Search modes - Boolean/Phrase	54,873
S37	TI ((singl* or doubl* or trebl* or tripl*) W1 (mask* or blind* or dumm*)) OR AB ((singl* or doubl* or trebl* or tripl*) W1 (mask* or blind* or dumm*))	Search modes - Boolean/Phrase	22,455
S36	TI (randomized or randomised or randomly or RCT or RCTs or placebo*) OR AB (randomized or randomised or randomly or RCT	Search modes - Boolean/Phrase	145,346

	or RCTs or placebo*)		
S35	(MH "Clinical Trials+")	Search modes - Boolean/Phrase	192,364
S34	PT randomized controlled trial	Search modes - Boolean/Phrase	53,623
S33	S27 AND S32	Search modes - Boolean/Phrase	22
S32	S28 OR S29 OR S30 OR S31	Search modes - Boolean/Phrase	80,899
S31	TI ((systematic W1 review*) or (systematic W1 overview*) or ("evidence-based" W1 review*) or ("evidence-based" W1 overview*) or (evidence N3 (review* or overview*)) or (meta W1 review*) or (meta W1 overview*) or (meta W1 synthes*) or "review of reviews") OR AB ((systematic W1 review*) or (systematic W1 overview*) or ("evidence-based" W1 review*) or ("evidence-based" W1 overview*) or (evidence N3 (review* or overview*)) or (meta W1 review*) or (meta W1 overview*) or (meta W1 synthes*) or "review of reviews")	Search modes - Boolean/Phrase	48,222
S30	TI ((meta W1 analy*) or metanaly* or metaanaly* or (met W1 analy*) or (integrative W1 research) or (integrative W1 review*) or (integrative W1 overview*) or (research W1 integration) or (research W1 overview*) or (collaborative W1 review*)) OR AB ((meta W1 analy*) or metanaly* or metaanaly* or (met W1 analy*) or (integrative W1 research) or (integrative W1 review*) or (integrative W1 overview*) or (research W1 integration) or (research W1 overview*) or (collaborative W1 review*))	Search modes - Boolean/Phrase	27,188
S29	(MH "Meta Analysis") OR (MH "Meta Synthesis")	Search modes - Boolean/Phrase	23,728
S28	(MH "Systematic Review")	Search modes - Boolean/Phrase	34,365
S27	S14 AND S26	Search modes - Boolean/Phrase	1,303
S26	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	Search modes - Boolean/Phrase	575,777
S25	(MH "Influenza, Human+/EP")	Search modes - Boolean/Phrase	2,173
S24	TI (DALY OR DALYs) OR AB (DALY OR DALYs)	Search modes - Boolean/Phrase	338
S23	TI ("disability-adjusted" W2 (year or years)) OR AB ("disability-adjusted" W2 (year or years))	Search modes - Boolean/Phrase	314
S22	TI (burden OR burdens OR death OR deaths OR epidemiolog* OR	Search modes -	518,824

	incidence OR frequenc* OR morbidit* OR mortalit* OR occurrence* OR occurence* OR outbreak* OR prevalen* OR rate OR rates OR surveillance*) OR AB (burden OR burdens OR death OR deaths OR epidemiolog* OR incidence OR frequenc* OR morbidit* OR mortalit* OR occurrence* OR occurence* OR outbreak* OR prevalen* OR rate OR rates OR surveillance*)	Boolean/Phrase	
S21	(MH "Infant Mortality")	Search modes - Boolean/Phrase	5,927
S20	(MH "Hospital Mortality")	Search modes - Boolean/Phrase	9,665
S19	(MH "Cause of Death")	Search modes - Boolean/Phrase	8,401
S18	(MH "Mortality")	Search modes - Boolean/Phrase	17,533
S17	(MH "Morbidity+")	Search modes - Boolean/Phrase	96,224
S16	(MH "Prevalence")	Search modes - Boolean/Phrase	54,979
S15	(MH "Incidence")	Search modes - Boolean/Phrase	40,248
S14	S6 AND S13	Search modes - Boolean/Phrase	2,251
S13	S7 OR S8 OR S9 OR S10 OR S11 OR S12	Search modes - Boolean/Phrase	210,074
S12	TI (((1 or 2 or 3 or 4 or 5 or 6) W1 (month or months)) N3 (age or aged or ages or old)) OR AB (((1 or 2 or 3 or 4 or 5 or 6) W1 (month or months)) N3 (age or aged or ages or old))	Search modes - Boolean/Phrase	5,423
S11	TI (((one or two or three or four or five or six) W1 (month or months)) N3 (age or aged or ages or old)) OR AB (((one or two or three or four or five or six) W1 (month or months)) N3 (age or aged or ages or old))	Search modes - Boolean/Phrase	961
S10	TI (SGA OR LBW OR VLBW) OR AB (SGA OR LBW OR VLBW)	Search modes - Boolean/Phrase	2,175
S9	TI (neonat* OR newborn*) OR AB (neonat* OR newborn*)	Search modes - Boolean/Phrase	42,737
S8	TI (infant OR infants OR infancy OR baby OR babies) OR AB (infant OR infants OR infancy OR baby OR babies)	Search modes - Boolean/Phrase	70,500
S7	(MH "Infant+")	Search modes - Boolean/Phrase	175,001
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes -	18,305

		Boolean/Phrase	
S5	TI ((H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2) OR AB ((H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2)	Search modes - Boolean/Phrase	3,569
S4	MH "Influenza B Virus"	Search modes - Boolean/Phrase	202
S3	MH "Influenza A Virus+"	Search modes - Boolean/Phrase	4,040
S2	TI (influenza* or flu or grippe) OR AB (influenza* or flu or grippe)	Search modes - Boolean/Phrase	16,391
S1	MH "Influenza, Human+"	Search modes - Boolean/Phrase	5,660

Table S1. Methods of laboratory testing

First author (Year)	Method of laboratory testing
Ampofo (2006) [1]	7-valent direct fluorescent antibody (DFA) staining (Simufluor respiratory screen).
Bhat (2005) [2]	Rapid diagnostic test or enzyme immunoassay, isolation of virus in tissue-cell culture, direct or indirect immunofluorescent-antibody staining, RT-PCR analysis, or immunohistochemistry.
Broor (2014) [3]	RT-PCR
Budge (2014) [4]	Real-time monoplex RT-PCR analysis of nasal swabs.
Cox (2012) [5 a,b]	Viral culture, immunofluorescence antibody staining, RT-PCR, or rapid diagnostic test.
Dawood (2010) [6 b]	Viral culture, direct or indirect fluorescent antibody staining, rapid antigen test, or RT-PCR.
Griffin (2004) [7 c]	Viral culture or RT-PCR.
Grijalva (2006) [8 b,c]	Viral culture or RT-PCR.
Grijalva (2007) [9 b,c]	Viral culture or RT-PCR.
Iwane (2004) [10 c]	Viral culture or RT-PCR.
Ji (2010) [11]	Fluorescent monoclonal antibody assay.
Libster (2010) [12]	RT-PCR
Madhi (2014) [13]	RT-PCR
Montes (2005) [14]	RT-PCR
Nasreen (2014) [15]	Real-time RT-PCR analysis of nasopharyngeal swabs.
Nelson (2014) [16]	Immunofluorescence (IF) test and/or conventional viral culture in one of the 12 Hong Kong hospitals with pediatric patients (Prince of Wales Hospital). In the other 11 hospitals, infants with influenza were identified using diagnostic codes in a hospitalization database. Incidence rates were adjusted for over- and under-diagnosis based on the comparison of diagnostic codes with laboratory data in the one surveillance hospital in this study (Prince of Wales Hospital).
Poehling (2006) [17 c]	Two consecutive positive RT-PCRs or a positive viral culture.
Poehling (2013) [18 c]	Two consecutive positive RT-PCRs or a positive viral culture.
Proff (2009) [19]	Viral culture, RT-PCR, or direct immunofluorescent antibody (DFA) staining, or rapid diagnostic tests.
Silvennoinen (2011) [20]	Influenza A or B antigens in nasopharyngeal aspirates by one-incubation, monoclonal time-resolved fluoroimmunoassay, viral culture, or rapid diagnostic test.
Stein (2010) [21]	RT-PCR
Yu (2013) [22]	RT-PCR

RT-PCR: reverse-transcriptase polymerase chain reaction

Table S2. Incidence estimates of laboratory-confirmed influenza hospitalizations among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate (95% CI)	Adjustment
Ampofo (2006) [1]	July 2001 to June 2004	65	25,710	25.3 per 10,000 population (16.1–37.5)	None
Broor (2014) [3]	August 2009 to July 2011	-- [a]	-- [a]	17.8 per 10,000 population (6.3–51.9)	Adjusted for missed hospitalizations at non-study hospitals by dividing the unadjusted incidence by the proportion of hospitalizations among area residents occurring at study facilities.
Cox (2012) [5]	2008–2009	188	156,129	12.0 per 10,000 population (10.4–13.9 [b])	None
	2009–2010	328	162,376 [b]	20.2 per 10,000 population (18.1–22.5 [b])	None
Dawood (2010) [6]	2003–2004	357	120,608 [b]	29.6 per 10,000 population (26.7–32.8 [b])	None
	2004–2005	166	129,688 [b]	12.8 per 10,000 population (11.0–14.9 [b])	
	2005–2006	205	169,421 [b]	12.1 per 10,000 population (10.5–13.8 [b])	
	2006–2007	141	151,613 [b]	9.3 per 10,000 population (7.9–10.9 [b])	
	2007–2008	252	155,556 [b]	16.2 per 10,000 population (14.3–18.3 [b])	
Griffin (2004) [7]	2000–2001 to 2003–2004	-- [a]	-- [a]	43.0 per 10,000 population [c,d]	None
Grijalva (2006) [8]	2003–2004	37	4,056	91.2 per 10,000 population (67.0–145.0)	None
Grijalva (2007) [9]	2004–2005	63	14,368	43.8 per 10,000 population (38.9–52.1)	None
Iwane (2004) [10]	2000–2001	21 [b]	8,591	24.0 per 10,000 population (10.0–38.0)	None
Ji (2010) [11]	2007	15	24,261	6.18 per 10,000 population (3.1–9.3)	None

	2008	15	23,886	6.3 per 10,000 population (3.1–9.5)	
Libster (2010) [12]	May 2009 to July 2009	83	41,180	20.2 per 10,000 population (16.2–24.2 [b])	None
Madhi (2014) [13]	2011–2012	1	1,023	9.8 per 10,000 population (0.49–48.2 [b])	None
Montes (2005) [14]	2001–2002	9	1765 [b]	51.0 per 10,000 population (24.9–93.6 [b])	None
	2002–2003	0	1820 [b]	0	
	2003–2004	13	1781 [b]	73.0 per 10,000 population (40.6–121.7 [b])	
	July 2001 to June 2004 [e]	22	5366 [b]	41.0 per 10,000 population (26.4–61.1 [b])	
Nasreen (2014) [15]	June 2010 to October 2010	0	1,264	0	None
Nelson (2014) [16]	April 2005 to March 2011 (0 to <2 months)	-- [a]	-- [a]	65.6 per 10,000 person-years	Adjustment for over- and under-diagnosis of influenza.
	April 2005 to March 2011 (2 to <6 months)	-- [a]	-- [a]	184.5 per 10,000 person-years	
Poehling (2006) [17]	2000–2001	20	8,333 [b]	24.0 per 10,000 population (10.0–39.0)	Rate adjusted by multiplying the influenza burden for each age group and study year by age-specific rate of acute respiratory tract infection or fever estimated from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). The numerator of the rate was weighted for both the days of surveillance and the proportion of eligible children enrolled.
	2001–2002	37	8,605 [b]	43.0 per 10,000 population (22.0–66.0)	
	2002–2003	20	8,696 [b]	23.0 per 10,000 population (9.0–38.0)	
	2003–2004	103	14,306 [b]	72.0 per 10,000 population (53.0–92.0)	
	2000–2001 to 2003–2004 [e]	180	40,000 [b]	45.0 per 10,000 population (34.0–55.0)	
Poehling (2013) [18]	2004–2005	-- [a]	-- [a]	34.0 per 10,000 population (25.0–45.0)	
	2005–2006	-- [a]	-- [a]	24.0 per 10,000 population (10.0–40.0)	
	2006–2007	-- [a]	-- [a]	20.0 per 10,000 population (9.0–33.0)	

	2007–2008	-- [a]	-- [a]	43.0 per 10,000 population (25.0–63.0)	
	2008–2009	-- [a]	-- [a]	16.0 per 10,000 population (7.0–26.0)	
	2004–2005 to 2008–2009 [e]	96	35,556 [b]	27.0 per 10,000 population (21.0–33.0)	
Proff (2009) [19]	2004–2005	64	34,483 [b]	18.6 per 10,000 population (14.4–23.6 [b])	None
	2005–2006	81	34,527 [b]	23.5 per 10,000 population (18.8–29.0 [b])	
	2006–2007	39	34,884 [b]	11.2 per 10,000 population (8.1–15.1 [b])	
	2007–2008	79	35,049 [b]	22.5 per 10,000 population (18.0–27.9 [b])	
Silvennoinen (2011) [20]	July 1988 to June 2004	88	31,884 [b]	27.6 per 10,000 population (22.0–33.6)	None
Stein (2010) [21]	July 12, 2009 to December 24, 2009	30	9,375 [b]	32.0 per 10,000 population (22.0–45.1) [f]	None
Yu (2013) [22]	April 2010 to April 2012	156	6,240 [b]	250.0 per 10,000 population (213.0–292.0) [b,e]	Adjusted for the size of the resident population in the two study districts and the age-specific proportion of all influenza-associated hospitalized patients at the four surveillance hospitals.

[a] Not reported in original study and insufficient information to compute.
[b] Computed by review authors.
[c] 95% confidence intervals were not provided and cannot be computed due to insufficient information reported in the original study.
[d] Mean across four influenza seasons.
[e] Pooled across influenza seasons.
[f] For infants under three months of age.

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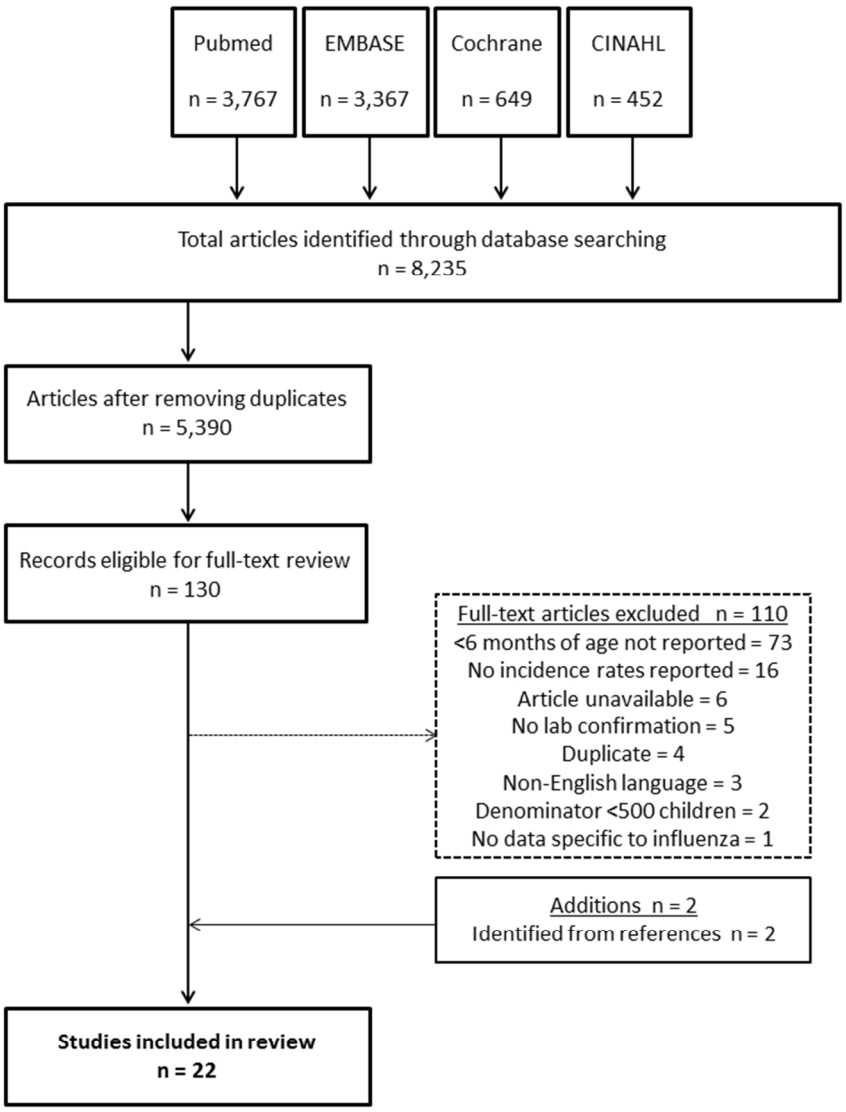

Figure 1

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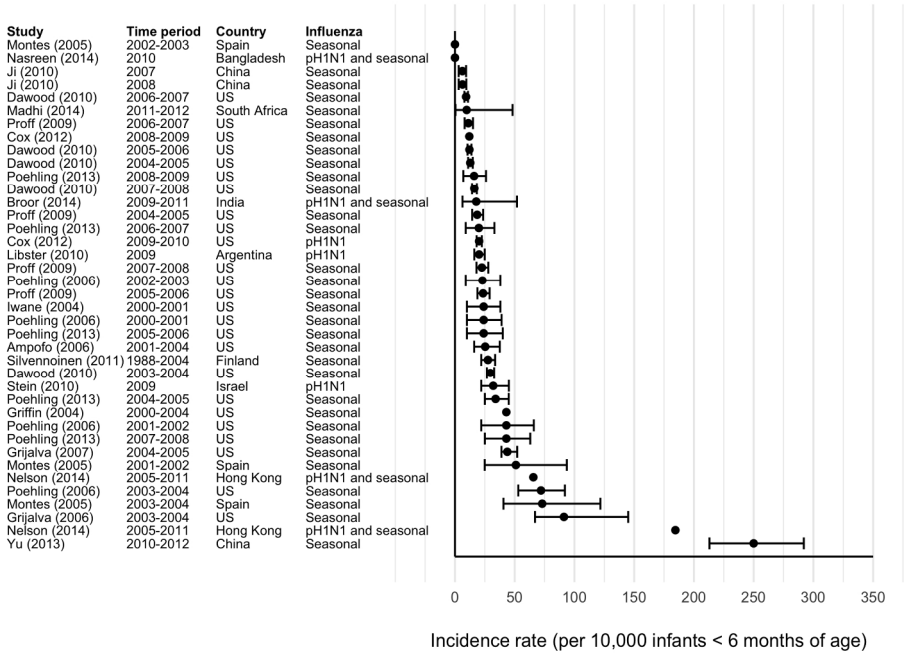

Figure 2A

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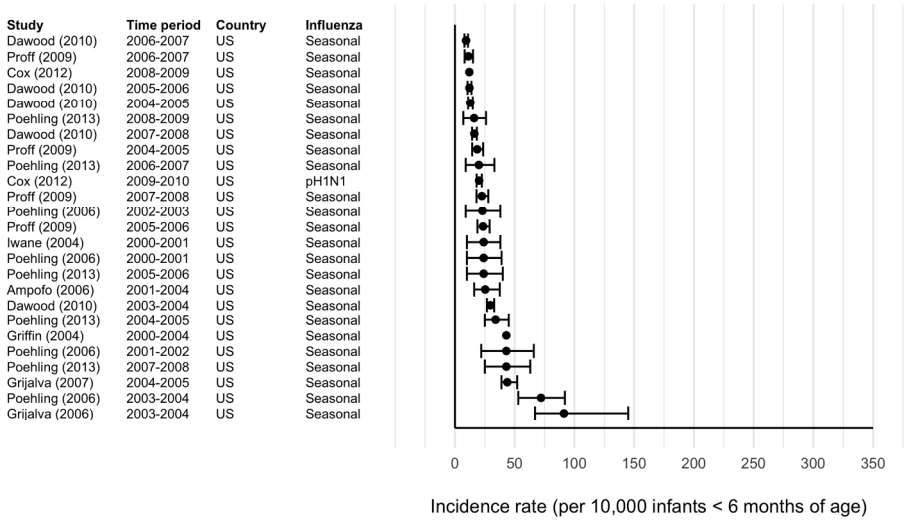

Figure 2B

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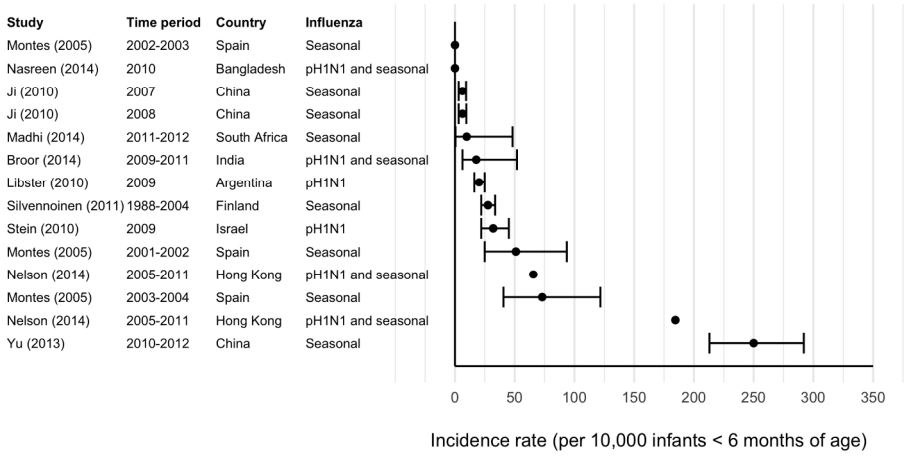

Figure 2C

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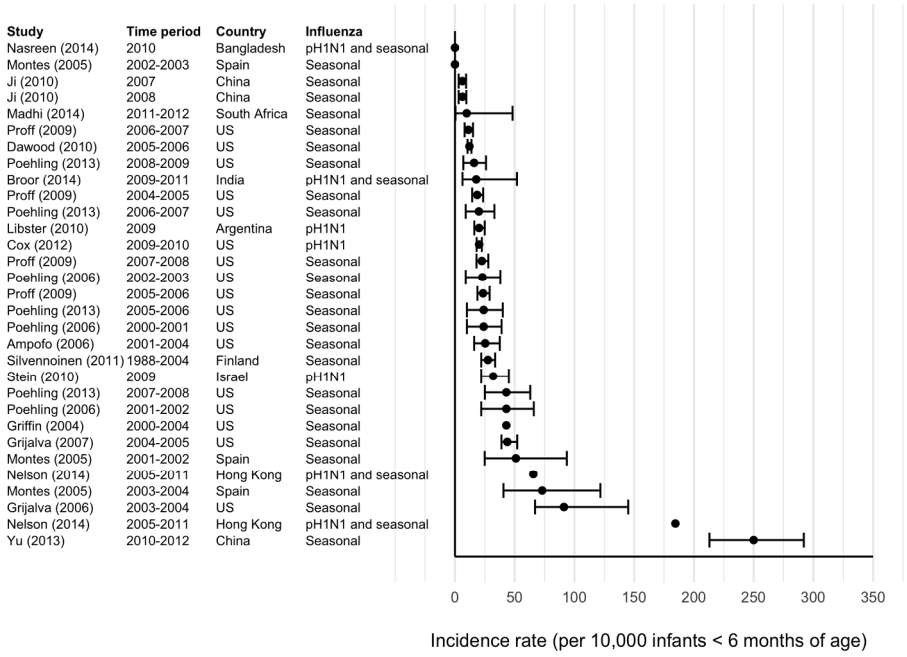

Figure 2D

793x529mm (72 x 72 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2-5; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Incidence of laboratory-confirmed influenza disease among infants under six months of age: A systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016526.R1
Article Type:	Research
Date Submitted by the Author:	02-Jun-2017
Complete List of Authors:	Fell, Deshayne; Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada; University of Ottawa, School of Epidemiology, Public Health and Preventive Medicine Johnson, Jeanene Mor, Zohar; Ministry of Health, Tel Avvi Department of Health Katz, Mark; Medical School for International Health and Department of Health Systems Management, Ben Gurion University in the Negev Skidmore, Becky; Independent Information Specialist Neuzil, KM; PATH, Ortiz, Justin; Organisation mondiale de la Sante, Initiative for Vaccine Research Bhat, Niranjan ; Center for Vaccine Innovation and Access, PATH
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Immunology (including allergy), Global health, Infectious diseases, Paediatrics
Keywords:	Influenza, Hospitalization, Infant, Systematic review

Incidence of laboratory-confirmed influenza disease among infants under six months of age: A systematic review

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Article Type: Research Article

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ABSTRACT (291 words)

Objectives: The aim of this systematic review was to assess incidence rates of laboratory-confirmed influenza (LCI) outcomes among infants under six months of age.

Design: Systematic literature search and review of indexed studies in PubMed, Embase, the Cochrane Library, and CINAHL Plus from inception to April 19, 2017.

Setting: Population-based estimates from community or hospital settings.

Participants: Infants under six months of age.

Primary and secondary outcome measures: LCI illness in ambulatory care settings, LCI hospitalization, LCI intensive care unit admission and LCI death. Only studies with population-based incidence data were included.

Results: We identified 27 primary studies, eleven of which were from the United States (US), four were from other non-US high-income settings, and the remainder were from lower-middle- or upper-middle-income countries. Most studies (n=23) assessed incidence of LCI hospitalization, but meta-analysis to pool study-specific rates was not possible due to high statistical and methodological heterogeneity. Among US studies, the reported incidence of LCI hospitalization ranged from 9.3 to 91.2 per 10,000 infants under six months for seasonal influenza, while the only US-based estimate for pandemic H1N1 influenza was 20.2 per 10,000 infants. Reported rates for LCI hospitalization for seasonal influenza from other countries ranged from 6.2 to 73.0 per 10,000 infants under six months, with the exception of one study with an estimated rate of 250 per 10,000 infants. No events were reported in five of the nine studies that evaluated LCI death among infants under six months.

Conclusion: Our review of published studies found limited data on LCI outcomes for infants under six months, particularly from non-US settings. Globally representative and reliable

incidence data are necessary to fully evaluate influenza disease burden and the potential impact of maternal influenza immunization programs on morbidity and mortality in young infants.

Strengths and limitations of this study

- This review of laboratory-confirmed, population-based estimates of influenza incidence highlights the relative lack of studies that specifically report influenza outcomes among infants under the age of six months.
- The majority of data identified in this review originate from the United States, deriving primarily from just two influenza surveillance systems, posing challenges for estimating the impact of maternal influenza immunization programs on infant influenza outcomes, particularly for low- and middle-income countries.
- We were unable to perform any meta-analyses due to high methodological and statistical heterogeneity.

Keywords: Influenza, Hospitalization, Infant, Systematic review

INTRODUCTION

The influenza virus is a common pathogen identified in young children with acute lower respiratory infections, such as pneumonia and bronchiolitis,[1] globally accounting for approximately 10% of all respiratory hospitalizations in children under 18 years[2] and approximately 3% of post-neonatal deaths.[3] Influenza virus infection can also manifest in various other conditions including seizures, wheezing, croup, otitis media, and occasionally encephalitis and encephalopathy,[4–7] and it can progress to secondary bacterial pneumonias or exacerbate underlying chronic medical conditions.

Infants under six months of age are considered to be at high risk for severe influenza and associated complications due to documented high rates of influenza-associated hospitalization[8–12] and mortality.[7] However, since influenza vaccines are not licensed for use in this age group due to poor immunogenic responses to the vaccine,[13] protection of newborns and young infants from influenza virus infection and related complications requires alternate strategies.[14] One such strategy is immunization of pregnant women with influenza vaccine, which has been shown to reduce influenza virus infection among young infants through transplacental transfer of maternal anti-influenza antibodies.[15–17]

A 2011 systematic review and meta-analysis by Nair et al.[1] estimated the global incidence of influenza outcomes among children under the age of five years and concluded that influenza in young children results in significant utilization of health services, particularly among infants younger than one year. However, age-specific estimates for infants under six months were not reported.[1] There is a paucity of published data on incidence of influenza outcomes among

children in this younger age group,[14] yet these data are necessary for informing evidence-based decision-making regarding vaccination programs, provision of appropriate health services, and prioritizing future research. In 2014, the World Health Organization (WHO) formed a working group[18] to systematically review the evidence and estimate incidence rates of laboratory-confirmed influenza outcomes among infants less than six months of age.

METHODS

In consultation with the WHO influenza working group,[18] we developed a systematic review protocol (available on request). This manuscript was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[19]

Search strategy and study selection

Our search strategy was developed by an experienced medical information specialist based on the review protocol (available from author on request) and informed by the approach used by Nair et al. in their systematic review of the global influenza burden among young children.[1] We searched PubMed, Embase, the Cochrane Library, and CINAHL Plus with Full Text from inception to April 19, 2017. Our strategies utilized a combination of controlled vocabulary (e.g., "Influenza, Human", "Infant Mortality", "Incidence") and keywords (e.g., influenza, neonate, rate). No language or date restrictions were applied but animal-only and opinion pieces (e.g., comments, editorials, interviews) were removed from the initial search results where possible. No unpublished data were pursued or included. Specific details regarding the search strategies appear in Supplementary Appendix 1.

We used Reference Manager Version 12 to download our search results and remove duplicates. Abstracts were then exported to Abstrackr (http://abstrackr.cebm.brown.edu/) for screening and data abstraction. Two teams of two reviewers independently screened all titles and abstracts to identify potentially relevant articles for full-text review. Disagreements between reviewers were resolved through discussion and consensus. The same two teams of reviewers carried out full-text screening to identify studies that met all the inclusion and exclusion criteria for data extraction and quality assessment. While extracting data, the reviewers also examined the reference lists to identify potentially relevant articles that may have been missed during screening.

We included studies that reported original data on population-based incidence rates for the following laboratory-confirmed influenza (LCI) outcomes among infants under six months of age: LCI illness in ambulatory care settings, LCI hospitalization, LCI intensive care unit (ICU) admission, and LCI death. We excluded studies that did not ascertain LCI outcomes either throughout at least one full influenza season in geographic settings with defined seasonality, or otherwise for at least one full year. We also excluded studies if influenza was not examined as a primary outcome, but rather as a co-infection in a study population identified on the basis of another infectious disease (e.g., influenza co-infection in a cohort of hospitalized measles cases[20]). Finally, studies that used a case definition that was not clearly defined or consistently applied, and those that were not population based or had a population denominator of fewer than 500 infants under six months of age were excluded. We included data from the comparator group of any randomized controlled trials (RCT) on influenza immunization during pregnancy if the study otherwise met our inclusion criteria.

Data extraction and quality assessment

Data from each included study were abstracted by one of two reviewers using a standardized data extraction form which was first pilot-tested to ensure a high level of agreement between reviewers. We extracted the following, where available, from each study: author; publication year; study design; study country; study population and size; age ranges studied; subject selection criteria; length of surveillance period and influenza season (particularly specifying the 2009–2010 pandemic versus other seasons); circulating influenza virus strains; definition and type of outcomes included in study; methods for ascertaining cases (e.g., active versus passive surveillance); criteria used for influenza testing; laboratory assay used to confirm influenza diagnosis; and influenza vaccination coverage in pregnant women in locations where the studies were conducted. We also extracted information, where available, on the numerator and denominator for each incidence rate; any statistical analyses performed, including variables used to compute adjusted rates; crude and adjusted incidence rates for each outcome with 95% confidence intervals (CI) or other measures of variance; and any sensitivity analyses presented in the paper. Study authors were contacted as needed to clarify data or methods. Two independent reviewers evaluated the quality of each study. Since all included studies were case series or surveillance studies that did not include comparative analyses, we used a modification of the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Descriptive/Case Series to assess individual study quality.[21] This checklist assesses four items: clearly defined case inclusion criteria, objective assessments of exposure and outcome, and sufficient follow-up time for outcome ascertainment. In addition, we assessed the quality of evidence across studies using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation

(GRADE) framework.[22,23] For each outcome, we determined a GRADE rating of high quality, moderate quality, low quality, or very low quality for each outcome according to criteria such as study design and limitations, inconsistency in study findings, and imprecision.[22,23]

Data synthesis and analysis

We qualitatively summarized individual study characteristics in descriptive tables. For each outcome, we extracted the incidence rates and 95% CIs as reported by the primary study when they were provided, and otherwise computed them using raw study data where possible. We estimated the numerator or denominator values when an unadjusted incidence rate was reported along with only one of the other two data points. We interpreted incidence rates (computed using person-time denominators for infants under six months) and incidence proportions (computed using the estimated size of the population of infants under six months) as approximately equivalent. No attempt was made to mathematically convert one to the other since most studies that reported an incidence proportion used the total number of infants under the age of one year and divided in half, which would approximate six months of person-time follow-up assuming a static population with no losses to follow-up. We used Stata SE software version 12 (Stata-Corp LP, College Station, TX, USA) to generate pooled incidence estimates for LCI hospitalization via random effects meta-analyses[24] and the I^2 statistic to quantitatively assess statistical heterogeneity.[25] Pooled incidence estimates were not reported when statistical heterogeneity was high (i.e., I^2 >75%); however, qualitatively, we explored sources of heterogeneity in sub-groups to augment our interpretation. *A priori*, we hypothesized that heterogeneity would likely arise due to differences in pandemic versus seasonal influenza, study population, case ascertainment

methods, and study quality. We generated forest plots using the R package "ggplot2" (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study selection

We identified 9,298 records through our initial electronic literature searches; following de-duplication, 5,998 went through initial title and abstract screening. We identified 150 potentially relevant articles and excluded 125 after full-text review, leaving 25. Most manuscripts (81/125; 65%) were excluded because they lacked age-specific data on infants under six months. During full-text screening, we added two articles that had originally been excluded by our systematic query but were subsequently identified through a hand search of reference lists.[16,26] This brought the total number of primary studies included in our review to 27 (Figure 1).

Study characteristics

Nearly half (11/27) of the studies originated from the United States,[7–9,26–33] and the remainder were from lower-middle-income (n=5),[11,17,34–36] upper-middle-income (n=7),[16,37–42] and other non-US high-income settings (n=4)[43–46] (Table 1). There were no studies from low-income countries. Twenty-three studies assessed LCI hospitalization, [8,9,11,16,17,26–33,35,36,38–41,43–46]six studies assessed LCI illness in ambulatory care settings,[9,16,17,34,37,42] seven studies reported LCI ICU admission,[9,26,32,39,40,45,46] and nine assessed LCI deaths[7,11,16,17,26,28,35,40,44] (Table 1). All studies were published in 2004 or later and reported data from influenza seasons between 2000 and 2014. Two studies exclusively reported influenza outcomes from the 2009 H1N1 pandemic time period,[40,46] six reported data from the 2009 pandemic time period along with other influenza

seasons,[27,35–37,43,44] and the remainder reported LCI outcomes from seasonal influenza epidemics. Most studies used reverse transcription-polymerase chain reaction (RT-PCR) laboratory testing methods, either alone or in combination with other methods, to confirm influenza from patient samples (Supplementary Table S1). Four of the 25 non-randomized trials included in this review[39,41,44,45] provided some contextual information on uptake of maternal influenza immunization in their study population, but none provided specific rates (Supplementary Table S2). We were able to obtain additional clarifying data from four[16,27,40,42] of six studies by contacting study authors. Only two studies received a score lower than 4/4 on the modified JBI Critical Appraisal Checklist — one such study did not assess all influenza outcomes using objective criteria[44] and the other did not clearly document the case definition.[46] Applying the modified GRADE assessment,[23] the quality of evidence for incidence rates of LCI hospitalization of infants under six months of age was deemed to be moderate, while the quality of evidence for the other three outcomes was considered low (Supplementary Appendix 2). In large part, this determination was based on high heterogeneity in incidence rates across studies, partly due to variability in surveillance methodologies and methods used to compute rates. Moreover, other than hospitalization, the number of studies reporting data for the other outcomes of interest was small.

Laboratory-confirmed influenza illness in ambulatory care settings

Six studies, two of which were from lower or lower-middle-income countries, assessed LCI illness in ambulatory care settings[9,16,17,34,37,42] (Table 2). Five of the studies used RT-PCR to confirm influenza virus infection, and one used either RT-PCR or viral culture[9] (Supplementary Table S1). In a community-based prospective cohort study conducted between 2009 and 2011 in

the Cajamarca region of Peru, researchers conducted active household surveillance to identify infants with symptoms of acute respiratory illness for confirmatory influenza laboratory testing. In this study, the adjusted incidence of LCI illness among infants less than six months of age was 35 per 100 person-years of follow-up (95% CI: 26–48).[37] Using similar active surveillance methods, the RCT from South Africa reported an incidence of LCI illness among infants born to non-HIV infected women in the placebo group of 3.6 per 100 infants (95% CI: 2.6–5.0),[16] and the RCT from Mali reported an incidence of 8.3 per 100 person-years among infants in the control arm.[17] In a study conducted over three influenza seasons in the Suzhou District of China, the incidence of LCI illness among infants under six months ranged from 2.3 per 100 in 2013–2014 to 2.9 per 100 in 2012–2013.[42] Finally, data from the New Vaccine Surveillance Network (NVSN), a population-based active sentinel surveillance program operating in three regions of the United States (Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York), estimated a rate of LCI illness based on outpatient clinic visits among infants under six months of 2.8 per 100 infants (95% CI: 0.7–11.1) in 2002–2003 and 5.9 per 100 infants (95% CI: 2.8–12.8) in 2003–2004.[9] We did not consider statistical meta-analysis of this outcome due to the variable geographic settings and methodologies employed by the studies. For instance, the latter NVSN study estimated incidence rates from population-based surveillance of outpatient clinic visits,[9] while the study from Peru utilized community-based surveillance including a household component,[37] and the two RCTs employed active surveillance with weekly contact with study participants.[16,17]

Laboratory-confirmed influenza hospitalization

Graphical and tabular summaries of individual estimates originating from the 23 studies that reported incidence rates of LCI hospitalization can be found in Figure 2 and Supplementary Table S3. Ten of the 23 studies originated from the United States; six of those reported data from one of two population-based active surveillance programs: the Emerging Infections Program (EIP)[27,28] or the NVSN.[8,9,29,32] Two additional US studies led by Grijalva et al. reported estimates using capture-recapture methods based on surveillance data from both the EIP and NVSN systems,[30,31] and the remaining two US studies reported data from separate systems.[26,33] In the United States, estimated rates of LCI hospitalization of infants less than six months of age during seasonal epidemics varied from a low of 9.3 per 10,000 infants (95% CI: 7.9–10.9) in 2006–2007[28] to a high of 91.2 per 10,000 infants (95% CI: 67–145)[30] in 2003–2004. The only US-based estimate for the 2009 pandemic H1N1 time period was 20.2 per 10,000 infants (95% CI: 18.1–22.5).[27]

The 13 non-US studies (four from high-income countries, six from upper-middle-income countries, two from lower-middle-income countries, and one from a low-income country) reported similar LCI hospitalization rates for seasonal influenza. Most incidence rates for seasonal influenza ranged from 6.2 per 10,000 infants (95% CI: 3.1–9.3) in China in 2007[39] to 73.0 per 10,000 infants (95% CI: 40.6–121.7) in Spain in 2003–2004.[11] However, a higher estimated rate was reported from one post-pandemic study of seasonal influenza from China (250 per 10,000 infants under six months in 2010–2011, 95% CI: 213–292[41]). The highest estimate from non-US based studies from the 2009 pandemic H1N1 influenza time period was 259 per 10,000 person-years (95% CI: 97.0–689) in Kenya.[36]

Although 10 studies from the United States presented incidence rates of LCI hospitalization of infants under six months, there was overlap in a number of seasons among the eight studies utilizing data from the EIP and NVSN surveillance programs (Table 3). For instance, two studies reported the same rate from the NVSN system for the 2000–2001 season (24.0 per 10,000 infants),[9,32] and similar combined season rates for 2000–2004 from the NVSN system (reported as 43.0 per 10,000 infants[29] and 45.0 per 10,000 infants[9]). In addition, estimates are available from both the EIP and the NVSN for several years. In such instances, incidence rates from the NVSN system were consistently higher in magnitude than the EIP estimates. Moreover, in two studies, Grijalva et al. combined data from the EIP and NVSN surveillance systems using a capture-recapture methodology[30,31] — a surveillance method that attempts to estimate the extent of under-ascertainment of cases using information from two or more data sources.[47] This methodology yielded a higher combined incidence rate of LCI hospitalization than was provided by either system alone.[30,31] For instance, in 2003–2004, which was a more severe influenza season, individual EIP and NVSN estimates were 29.6 per 10,000 infants (95% CI: 26.7–32.8)[28] and 72.0 per 10,000 infants (95% CI: 53.0–92.0),[9] respectively. Using the combined data from both systems, the revised estimate was 91.2 per 10,000 infants (95% CI: 67.0–145.0).[30]

Laboratory-confirmed influenza ICU admission

LCI ICU admission rates for infants under six months are available from seven studies[9,26,32,39,40,45,46] (Table 4). However, all rates shown in Table 4 were computed by review authors, either due to non-reporting in the original study[9,22,28,33,34,37] or due to graphical presentation of rates in a figure only.[46] Estimated rates of LCI ICU admission for seasonal influenza ranged from a low of 0.5 per 10,000 infants (95% CI: 0.8–16.5) between 2000–2001

and 2003–2004 in the Salt Lake City area of the United States[9] to a high of 3.5 per 10,000 between 2001 and 2004 in the surveillance counties covered by the NVSN (95% CI: 1.7–6.4).[26] The absolute number of LCI ICU admissions of infants under six months was very low in all study populations (from a low of zero[32] to a high of 12 admissions[40]). Two studies were conducted during the 2009 H1N1 pandemic time period — in Argentina, Libster et al. reported a rate of LCI ICU admission of 2.9 per 10,000 infants (95% CI: 1.6–5.0)[40] and in Israel, Stein et al. reported a similar rate of 2.5 per 10,000 infants (95% CI: 0.79–6.0).[46]

Laboratory-confirmed influenza death

Nine studies included LCI death among infants under six months of age as an outcome.[7,11,16,17,26,28,35,40,44] In six of the nine study populations, surveillance for LCI deaths was conducted, but none were identified[11,16,26,35,44] (Table 5). Bhat et al. reported data from enhanced national-level surveillance of pediatric LCI deaths in the United States during the 2003–2004 season.[7] In this study, there were 18 deaths of infants under six months of age, corresponding to a rate of 0.88 per 100,000 infants (95% CI: 0.52–1.39), which was the highest among all pediatric age groups up to 18 years. In a smaller US surveillance study using data from the EIP system operating in 10 states, three influenza deaths of infants under six months were recorded during 2003–2004 to 2007–2008 combined, with a corresponding rate of 0.41 per 100,000 person-years (95% CI: 0.11–1.12).[28] Among all nine studies, the highest rate of LCI deaths in infants was reported in Buenos Aires, Argentina, for the 2009 pandemic H1N1 time period; two deaths were recorded, and the LCI mortality rate was 5 per 100,000 infants (95% CI: 0.82–16.1).[40]

DISCUSSION

In this systematic review, we provide a summary of published data up to April 2017 regarding the incidence of laboratory-confirmed influenza outcomes among infants under six months of age. Our review of 27 studies covering 14 influenza seasons demonstrates a relatively wide range of estimates in incidence rates for several LCI outcomes in this age group. This broad distribution is likely associated with biological variability of influenza clinical disease and epidemiology and host immunity, as well as methodological factors of the studies themselves, including differences in care provider practices for influenza testing and hospital admission. In particular, estimates of rates for LCI hospitalizations, the most frequently reported and best described outcome among these studies, ranged 10-fold, from 9.3 to 91.2 per 10,000 infants, within the United States alone, and varied even more widely in other settings. The incidence of LCI hospitalizations was generally higher during the 2009 pandemic H1N1 time period (20 per 10,000 infants[40] to 259[36] per 10,000 person-years) than during seasonal influenza years, though few estimates from the H1N1 pandemic time period were available. Our work also highlights the relative lack of studies that specifically report influenza outcomes in this vulnerable age group and the limited information included in studies that do include such findings. LCI outcomes other than hospitalization, such as intensive care unit admission and death, were even less commonly assessed and varied markedly in the level of detail described. Moreover, the majority of data identified in this review come from the United States, deriving primarily from just two influenza surveillance systems, indicating the constrained geographic coverage of the collected datasets. These limitations pose challenges for estimating the potential impact of maternal influenza immunization programs on infant influenza outcomes, particularly for low- and middle-income countries.

Our review methodology utilized a comprehensive search strategy that emphasized high sensitivity to capture a broad set of articles for screening. We subsequently restricted our review to laboratory-confirmed, population-based estimates of influenza incidence, ensuring greater consistency and stability of rates across studies. Our review also benefits from a number of strengths regarding the original studies identified through our search. First, the majority of the data come from well-established surveillance systems that cover several seasons and include additional evaluations (e.g., capture-recapture methods[30,31]) to confirm the validity of their findings. This consistency adds to the stability of the range of estimates reported here and provides a better understanding of the effects of seasonal variation on annual burden estimates. Second, the included studies generally obtained high scores in the quality assessment tool providing some assurance that they met at least minimum quality criteria.

Nevertheless, there are several important limitations. Among the primary studies, the different surveillance methodologies (e.g., passive versus active surveillance; different sensitivity of diagnostic tests; recruitment only in a subset of days per week; different denominators or methods to calculate incidence rates; surveillance only during part of the year; rate adjustment for various factors) contributed to the heterogeneity of the results. Moreover, some studies reported only a small number of seasons or a limited geographic area which may not provide a fully representative assessment of typical influenza incidence. Although none of the non-randomized studies specifically reported the uptake of maternal influenza immunization in their study population, the majority were either studies from the United States during pre-2009 pandemic seasons when rates were low,[48] or were from settings without recommendations for

influenza immunization during pregnancy; consequently, this was unlikely to be an important contributor to the heterogeneity in incidence rates. We were unable to include several studies that aggregated data from infants under six months within larger age strata, thus not reporting data specific to this policy-relevant age group. Future surveillance studies should report data for infants under six months, even if only as supplementary data, to facilitate future pooling and meta-analyses. The reports themselves were incomplete at times, lacking numerator data, denominator data or precision estimates, precluding the ability to perform meta-analysis. Even with full reporting of the data, key factors may have influenced the accuracy and completeness of specific surveillance approaches. Importantly, Grijalva et al.[30,31] demonstrated that the two US surveillance systems each underestimate the incidence of LCI hospitalizations. In both 2003–2004 and 2004–2005, the incidence of LCI hospitalization was higher using the combined capture-recapture methodology[47] than when estimated using either NVSN or EIP data alone. Finally, several of the US-based studies described overlapping seasons across multiple reports, thus contributing to a risk of some duplicate reporting.

Although we evaluated studies that included a narrower age range compared to the review by Nair et al.,[1] our results are generally consistent with the findings presented in that review, which reported rates of severe acute lower respiratory infection (corresponding to influenza hospitalization) ranging from 10 to 170 per 10,000 person-years among infants under one year of age. These consistent findings support the overall interpretation that influenza has a significant role in early infant respiratory morbidity. Of note, the incidence rates reported for influenza hospitalization in the control arms of the randomized clinical trials included in this review[16,17] were at the lower end of the range of estimates (one infant LCI hospitalization in each trial,

corresponding to a rate of 9.8 per 10,000 infants in South Africa [personal communication: M Nunes, 7 Dec 2016], and 10.8 per 10,000 person-years in Mali [personal communication: M Tapia, 15 Dec 2016]). These low rates compared with other estimates could be due to the epidemiologic characteristics of the particular influenza seasons or due to the close observation of subjects and opportunity for treatment and follow-up afforded by the active surveillance in the trials. Using prospective active surveillance methods, these two trials likely provide the best estimates of the incidence of LCI illness in an ambulatory setting among infants under six months: 3.6 per 100 infants[16] and 8.3 per 100 person-years of follow up.[17] Another recent trial of maternal influenza immunization in Nepal, published subsequent to our literature search, documented an incidence rate of LCI illness in an ambulatory setting of 18.1 per 100 person-years of follow-up among infants in the placebo group.[49]

In conclusion, our systematic review demonstrates that existing data on laboratory-confirmed influenza outcomes among infants under six months of age are sparse, of varying quality, and heavily weighted toward high-income populations. More research is needed in key regions to obtain a more globally representative picture of the incidence of influenza outcomes among young infants. In particular, estimates are required from the low- and low-middle-income countries of Asia and Africa where, in absolute numbers, the majority of cases occur. Higher quality data will be essential in order to allow global and country-level policy-makers to make evidence-based decisions that appropriately prioritize interventions such as maternal influenza immunization for reducing influenza disease in young infants who are, themselves, not eligible for influenza vaccination.

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Funding: This work was supported by the Bill & Melinda Gates Foundation through the World Health Organization. The research was coordinated by PATH. Drs. Fell and Katz received financial support from the World Health Organization's Initiative for Vaccine Research. The authors also acknowledge the Centers for Disease Control and Prevention (CDC), which provides financial support to the World Health Organization Initiative for Vaccine Research (U50 CK000431).

Disclaimer: Justin R. Ortiz is an employee of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

Competing interests: The authors have no conflicts to declare.

Data sharing statement: The data set is available on request from the corresponding author.

Acknowledgments: We acknowledge members of the WHO Taskforce to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling, a working group of the WHO Initiative for Vaccine Research, for their contributions through early discussions about this study. We are grateful to Glen Zinck (PATH) for his help with project organization, to Dr. Corinne Riddell (McGill University) for her assistance with producing Forest plots, and to Laura Walsh (University of Ottawa) for her assistance with updating the data extraction. We additionally thank Dr. Kevin Pottie (University of Ottawa), Dr. Michael Gravett (University of Washington)

and Dr. Dayre McNally (University of Ottawa) for their thoughtful reviews of an earlier version of this manuscript.

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Table 1. Characteristics of the primary studies and laboratory-confirmed influenza (LCI) outcomes assessed

First author (Year)	Location	World Bank country income group [d]	World Health Organization Region [e]	Study design	Time period	Pandemic or seasonal influenza	Reported LCI outcomes			
							LCI illness in ambulatory care settings	LCI hospitalization	LCI ICU admission	LCI death
Ali (2016) [34]	Sindh Province, Pakistan	Lower middle income	South-East Asia Region	Surveillance	October 2011 to June 2014	Seasonal	✔			
Ampofo (2006) [26]	Salt Lake City, Utah, United States	High income	Region of the Americas	Retrospective cohort	July 2001 to June 2004	Seasonal		✔	✔	✔
Bennet (2016) [43]	Stockholm, Sweden	High income	European Region	Retrospective cohort	1998–1999 to 2013–2014	Pandemic H1N1 and seasonal		✔		
Bhat (2005) [7]	United States	High income	Region of the Americas	Surveillance	September 2003 to May 2004	Seasonal				✔
Broor (2014) [35]	Haryana State, India	Lower middle income	South-East Asia Region	Surveillance	August 2009 to July 2011	Pandemic H1N1 and seasonal		✔		✔
Budge (2014) [37]	Department of Cajamarca, Peru	Upper middle income	Region of the Americas	Prospective cohort	May 2009 to September 2011	Pandemic H1N1 and seasonal	✔			
Cohen (2016) [38]	Gauteng Province, KwaZulu-Natal Province, Mpumalanga Province, South Africa	Upper middle income	African Region	Surveillance	January 2010 to December 2013	Seasonal		✔		
Cox (2012) [27] [a,b]	United States	High income	Region of the Americas	Surveillance (EIP)	April 2008 to April 2010	Pandemic H1N1 and seasonal		✔		
Dawood (2010) [28] [b]	United States	High income	Region of the Americas	Surveillance (EIP)	2003–2004 to 2007–2008	Seasonal		✔		✔
Griffin (2004) [29] [c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001 to 2003–2004	Seasonal		✔		
Grijalva (2006) [30] [b,c]	Davidson County, Tennessee, United States	High income	Region of the Americas	Surveillance (NVSN and EIP capture-recapture study)	2003–2004	Seasonal		✔		
Grijalva (2007) [31] [b,c]	Davidson County, Tennessee;	High income	Region of the Americas	Surveillance (NVSN and EIP capture-	2004–2005	Seasonal		✔		

	Hamilton County, Ohio; and Monroe County, New York, United States			recapture study)						
Iwane (2004) [32] [c]	Davidson County, Tennessee; Monroe County, New York; United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001	Seasonal		✔	✔	
Ji (2010) [39]	Jiangsu province, China	Upper middle income	Western Pacific Region	Surveillance	Jan 2007 to December 2008	Seasonal		✔	✔	
Libster (2010) [40]	Buenos Aires, Argentina	Upper middle income	Region of the Americas	Case series	May 2009 to July 2009	Pandemic H1N1		✔	✔	✔
Madhi (2014) [16]	Soweto, South Africa	Upper middle income	African Region	Randomized controlled trial (RCT)	2011 to 2012	Seasonal	✔	✔		✔
McMorrow (2015) [36]	Nairobi and Lwak, Kenya	Lower middle income	African Region	Surveillance	January 2008 to December 2012	Pandemic H1N1 and seasonal		✔		
Montes (2005) [11]	Regions of Basque Country, Spain	Upper middle income	European Region	Retrospective cohort	July 2001 to June 2004	Seasonal		✔		✔
Nelson (2014) [44]	Hong Kong (China)	High income	Western Pacific Region	Retrospective cohort	April 2005 to March 2011	Pandemic H1N1 and seasonal		✔		✔
Poehling (2006) [9] [c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2000–2001 to 2003–2004	Seasonal	✔	✔	✔	
Poehling (2013) [8] [c]	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	High income	Region of the Americas	Surveillance (NVSN)	2004–2005 to 2008–2009	Seasonal		✔		
Proff (2009) [33]	Colorado, United States	High income	Region of the Americas	Surveillance	2004 to 2008 (October 1 to May 31 annually)	Seasonal		✔		
Silvennoinen (2011) [45]	Finland	High income	European Region	Retrospective cohort	July 1988 to June 2004	Seasonal		✔	✔	

Stein (2010) [46]	Israel	High income	European Region	Prospective cohort	July 12, 2009 to December 24, 2009	Pandemic H1N1		✔	✔	
Tapia (2016) [17]	Bamako, Mali	Low income	African Region	Randomized controlled trial (RCT)	September 12, 2011 to January 28, 2014	Seasonal	✔	✔		✔
Yu (2013) [41]	Jingzhou City, Hubei Province, China	Upper middle income	Western Pacific Region	Surveillance	April 2010 to April 2012	Seasonal		✔		
Zhang (2016) [42]	Suzhou District, China	Upper middle income	Western Pacific Region	Surveillance	April 2011 to March 2014	Seasonal	✔			
Total = 27 studies							**6**	**23**	**7**	**9**

[a] Although the study objective was to report data from the 2009 H1N1 influenza pandemic, the reported incidence rates from other years for comparison. As the incidence rates from 2008–2009 have not been reported elsewhere, they have been included.
[b] Emerging Infections Program (EIP).
[c] New Vaccine Surveillance Network (NVSN). Surveillance was conducted from November 1 through April 30 each year, but the time period was extended if influenza was detected earlier or ended later.
[d] World Bank. World Development Indicators. Accessed: 10 Jan 2017. Available at: http://data.worldbank.org/data-catalog/world-development-indicators
[e] World Health Organization. WHO regional offices. Accessed: 10 Jan 2017. Available at: http://www.who.int/about/regions/en/

Table 2. Incidence estimates of laboratory-confirmed influenza illness in ambulatory care settings among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate per 100 (95% CI)	Adjustment
Ali (2016) [34]	October 2011 to June 2014	3 [a]	399 [b]	0.75 per 100 person-years (0.0-1.6)	None
Budge (2014) [37]	May 2009 to September 2011	-- [c]	-- [c]	35 per 100 person-years (26-48)	Rate adjusted for clustering at the individual child level due to multiple episodes.
Madhi (2014) [16]	2011 to 2012	37	1,023	3.6 per 100 population (2.6-5.0)	None
Poehling (2006) [9]	2002–2003 to 2003–2004 [d]	-- [c]	-- [c]	2002–2003: 2.8 per 100 population (0.7-11.1) 2003–2004: 5.9 per 100 population (2.8-12.8)	Rate adjusted by multiplying the influenza burden for each age group and study year by age-specific rate of acute respiratory tract infection or fever estimated from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS).
Tapia (2016) [17]	September 12, 2011 to January 28, 2014	77	927 [e]	8.3 per 100 person-years (6.6-10.3) [e]	None
Zhang (2016) [42]	April 2011 to March 2014	420 [f]	11,057	2011–2012: 5.7 per 100 population (3.6-8.3)	Adjusted for the age-specific proportion of all influenza-associated ILI out-patient visits at the surveillance hospital.
		487 [f]	12,393	2012–2013: 7.9 per 100 population (2.8-14.1)	
		252 [f]	13,674	2013–2014: 2.3 per 100 population (1.2-3.6)	
		1,160 [f]	37,124	2011–2014: 4.9 per 100 population (2.4-7.9)	

[a] Influenza B only.
[b] Number of person-years contributed by 692 infants.
[c] Not reported in original study and insufficient information to compute.
[d] Rates based on number of outpatient clinic visits attributable to influenza in 2002–2003 to 2003–2004 only.
[e] Number of person-years contributed by 2,041 infants. Rate and 95% CI derived by converting person-days to person-years.
[f] Age-specific numerators estimated by multiplying the number of ILI visits by the proportion of total influenza ILI.

Table 3. Incidence estimates of laboratory-confirmed influenza hospitalization among infants under six months of age from US-based influenza surveillance systems

Influenza season reported	Surveillance system		
	EIP Rate per 10,000 population (95% CI)	NVSN Rate per 10,000 population (95% CI)	EIP and NVSN combined Rate per 10,000 population (95% CI)
Individual seasons			
2000–2001		24.0 (10.0–38.0) [32]	
		24.0 (10.0–39.0) [9]	
2001–2002		43.0 (22.0–66.0) [9]	
2002–2003		23.0 (9.0–38.0) [9]	
2003–2004	29.6 (26.7–32.8) [28]	72.0 (53.0–92.0) [9]	91.2 (67.0–145.0) [a 30]
2004–2005	12.8 (11.0–14.9) [28]	34.0 (25.0–45.0) [8]	43.8 (38.9–52.1) [b 31]
2005–2006	12.1 (10.5–13.8) [28]	24.0 (10.0–40.0) [8]	
2006–2007	9.3 (7.9–10.9) [28]	20.0 (9.0–33.0) [8]	
2007–2008	16.2 (14.3–18.3) [28]	43.0 (25.0–63.0) [8]	
2008–2009	12.0 [27]	16.0 (7.0–26.0) [8]	
2009–2010 (H1N1 pandemic)	20.2 (18.1–22.5) [27]		
Combined seasons			
2000–2004		43.0 [29]	
		45.0 (34.0–55.0) [9]	
2004–2009		27.0 (21.0–33.0) [9]	

EIP: Emerging Infections Program; NVSN: New Vaccine Surveillance Network

[a] Individual estimates: EIP=34.5 per 10,000; NVSN=66.6 per 10,000.

[b] Individual estimates: EIP=17.4 per 10,000; NVSN=29.9 per 10,000.

Table 4. Incidence estimates of laboratory-confirmed influenza ICU admission among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate per 10,000 (95% CI)	Adjustment
Ampofo (2006) [26]	July 2001 to June 2004	9 [a]	25,710	3.5 per 10,000 population (1.7–6.4) [a]	None
Iwane (2004) [32]	2000–2001	0	8,591	0	None
Ji (2010) [39]	Jan 2007 to December 2008	3	48,147 [a]	0.62 per 10,000 person-years (1.6–17.0) [a]	None
Libster (2010) [40]	May 2009 to July 2009	12	41,000	2.9 per 10,000 population (1.6–5.0) [a]	None
Poehling (2006) [9]	2000–2001 to 2003–2004	2	40,000	0.5 per 10,000 population (0.8–16.5) [a]	None
Silvennoinen (2011) [45]	July 1988 to June 2004	5	31,884	1.6 per 10,000 population 0.6–3.5) [a]	None
Stein (2010) [46]	July 12, 2009 to December 24, 2009	4	16,000 [a]	2.5 per 10,000 population [b]	None

[a] Estimated by review authors from information reported in original study..
[b] Estimated from Figure 2 in original study.[46]

Table 5. Incidence estimates of laboratory-confirmed influenza death among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate per 100,000 (95% CI)	Adjustment
Ampofo (2006) [26]	July 2001 to June 2004	0	25,710	0	None
Bhat (2005) [7]	September 2003 to May 2004	18	-- [a]	0.88 per 100,000 population (0.52–1.39)	None
Broor (2014) [35]	August 2009 to July 2011	0	-- [a]	0	None
Dawood (2010) [28]	2003–2004 to 2007–2008	3	726,886 [b]	0.41 per 100,000 person-years (0.11–1.12) [b]	None
Libster (2010) [40]	May 2009 to July 2009	2	41,000	5 per 100,000 population (0.82–16.1) [b]	None
Madhi (2014) [16]	2011 to 2012	0	1,023	0	None
Montes (2005) [11]	July 2001 to June 2004	0	5,366	0	None
Nelson (2014) [44]	April 2005 to March 2011	0	-- [a]	0	None
Tapia (2016) [17]	September 12, 2011 to January 28, 2014	0	927 [c]	0	None

[a] Not reported in original study and insufficient information to compute.
[b] Estimated by review authors from information reported in original study.
[c] Number of person-years contributed by 2,041 infants.

Figure legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing selection of studies

Figure 2. Incidence estimates of laboratory-confirmed influenza (LCI) hospitalization among infants under six months of age [a,b]

[a] Heterogeneity I^2: 100%
[b] All estimates can be found in Supplementary Table S3.

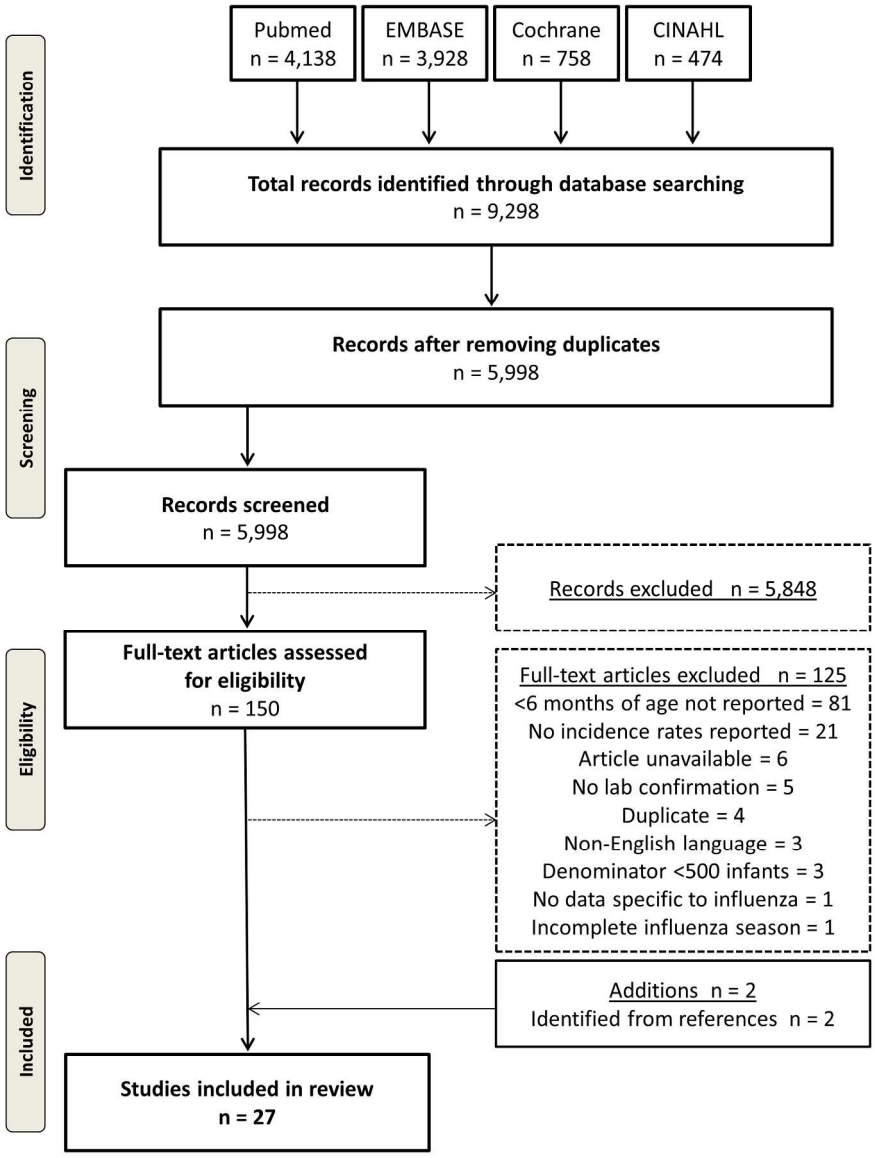

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing selection of studies

190x254mm (300 x 300 DPI)

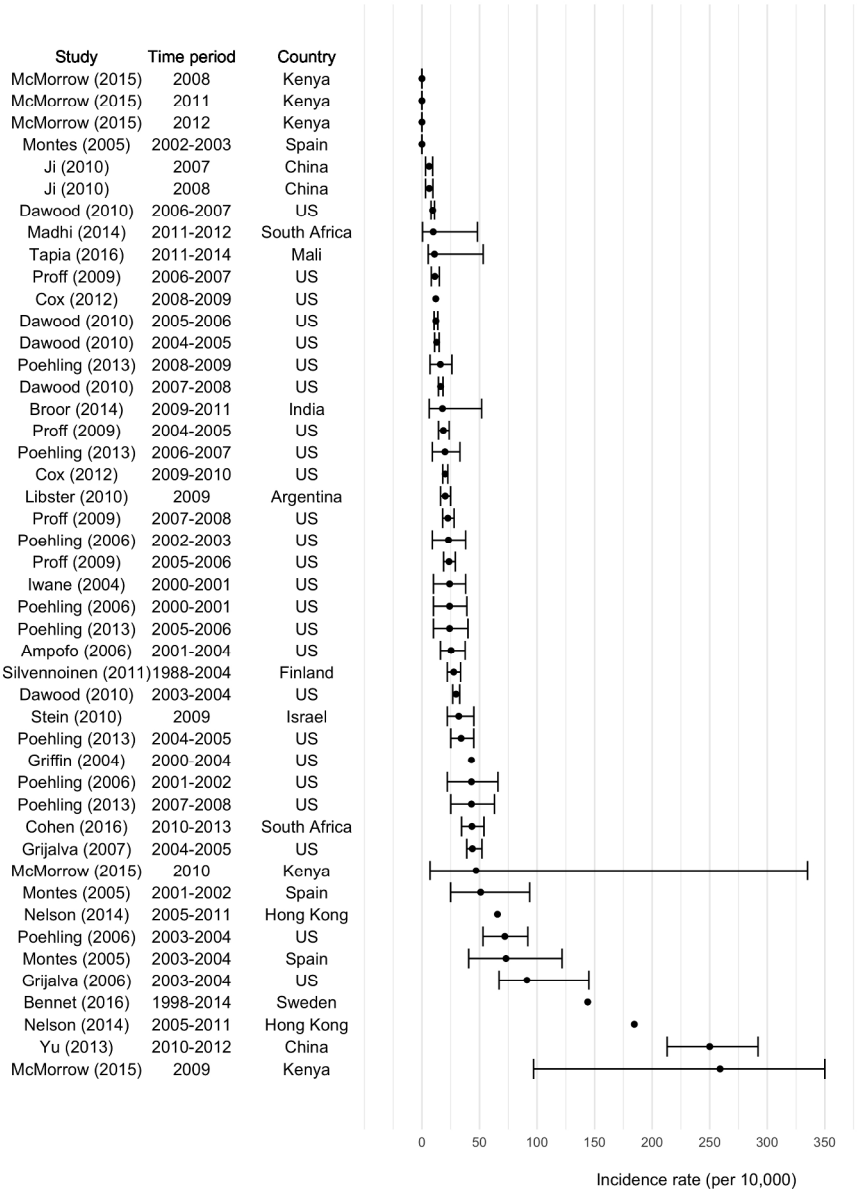

Figure 2. Incidence estimates of laboratory-confirmed influenza (LCI) hospitalization among infants under six months of age

215x279mm (300 x 300 DPI)

Table S1. Methods of laboratory testing

First author (Year)	Method of laboratory testing
Ali (2016) [1]	RT-PCR
Ampofo (2006) [2]	7-valent direct fluorescent antibody (DFA) staining (Simufluor respiratory screen).
Bennet (2016) [3]	Immunofluorescence and viral isolation prior to October 2007, RT-PCR for the remainder of the study period.
Bhat (2005) [4]	Rapid diagnostic test or enzyme immunoassay, isolation of virus in tissue-cell culture, direct or indirect immunofluorescent-antibody staining, RT-PCR analysis, or immunohistochemistry.
Broor (2014) [5]	RT-PCR
Budge (2014) [6]	Real-time monoplex RT-PCR analysis of nasal swabs.
Cohen (2016) [7]	RT-PCR
Cox (2012) [8 a,b]	Viral culture, immunofluorescence antibody staining, RT-PCR, or rapid diagnostic test.
Dawood (2010) [9 b]	Viral culture, direct or indirect fluorescent antibody staining, rapid antigen test, or RT-PCR.
Griffin (2004) [10 c]	Viral culture or RT-PCR.
Grijalva (2006) [11 b,c]	Viral culture or RT-PCR.
Grijalva (2007) [12 b,c]	Viral culture or RT-PCR.
Iwane (2004) [13 c]	Viral culture or RT-PCR.
Ji (2010) [14]	Fluorescent monoclonal antibody assay.
Libster (2010) [15]	RT-PCR
Madhi (2014) [16]	RT-PCR
McMorrow (2015) [17]	RT-PCR
Montes (2005) [18]	RT-PCR
Nelson (2014) [19]	Immunofluorescence (IF) test and/or conventional viral culture in one of the 12 Hong Kong hospitals with pediatric patients (Prince of Wales Hospital). In the other 11 hospitals, infants with influenza were identified using diagnostic codes in a hospitalization database. Incidence rates were adjusted for over- and under-diagnosis based on the comparison of diagnostic codes with laboratory data in the one surveillance hospital in this study (Prince of Wales Hospital).
Poehling (2006) [20 c]	Two consecutive positive RT-PCRs or a positive viral culture.
Poehling (2013) [21 c]	Two consecutive positive RT-PCRs or a positive viral culture.
Proff (2009) [22]	Viral culture, RT-PCR, or direct immunofluorescent antibody (DFA) staining, or rapid diagnostic tests.
Silvennoinen (2011) [23]	Influenza A or B antigens in nasopharyngeal aspirates by one-incubation, monoclonal time-resolved fluoroimmunoassay, viral culture, or rapid diagnostic test.

Stein (2010) [24]	RT-PCR
Tapia (2016) [25]	RT-PCR
Yu (2013) [26]	RT-PCR
Zhang (2016) [27]	RT-PCR

RT-PCR: reverse-transcriptase polymerase chain reaction

Table S2. Information reported on influenza vaccination coverage in pregnant women in locations where the studies included were conducted

First author (Year)	Text from article on influenza vaccination coverage in pregnant women	Location	Time period	Pandemic or seasonal influenza
Ali (2016) [1]	No information provided in text.	Sindh Province, Pakistan	October 2011 to June 2014	Seasonal
Ampofo (2006) [2]	No information provided in text.	Salt Lake City, Utah, United States	July 2001 to June 2004	Seasonal
Bennett (2016) [3]	No information provided in text.	Stockholm, Sweden	1998–1999 to 2013–2014	Pandemic H1N1 and seasonal
Bhat (2005) [4]	No information provided in text.	United States	September 2003 to May 2004	Seasonal
Broor (2014) [5]	No information provided in text.	Haryana State, India	August 2009 to July 2011	Pandemic H1N1 and seasonal
Budge (2014) [6]	No information provided in text.	Department of Cajamarca, Peru	May 2009 to September 2011	Pandemic H1N1 and seasonal
Cohen (2016) [7]	No information provided in text.	Gauteng Province, KwaZulu-Natal Province, Mpumalanga Province, South Africa	January 2010 to December 2013	Seasonal
Cox (2012) [8]	No information provided in text.	United States	April 2008 to April 2010	Pandemic H1N1 and seasonal
Dawood (2010) [9]	No information provided in text.	United States	2003–2004 to 2007–2008	Seasonal
Griffin (2004) [10]	No information provided in text.	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	2000–2001 to 2003–2004	Seasonal
Grijalva (2006) [11]	No information provided in text.	Davidson County, Tennessee, United States	2003–2004	Seasonal
Grijalva (2007) [12]	No information provided in text.	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	2004–2005	Seasonal
Iwane (2004) [13]	No information provided in text.	Davidson County,	2000–2001	Seasonal

		Tennessee; Monroe County, New York; United States		
Ji (2010) [14]	"Influenza vaccination is not routinely recommended in China and immunization of children is uncommon."	Jiangsu province, China	Jan 2007 to December 2008	Seasonal
Libster (2010) [15]	No information provided in text.	Buenos Aires, Argentina	May 2009 to July 2009	Pandemic H1N1
Madhi (2014) [16]	This was an RCT of influenza vaccination of pregnant women in South Africa. Only data from the HIV-uninfected comparator group were included in this systematic review.	Soweto, South Africa	2011 to 2012	Seasonal
McMorrow (2015) [17]	No information provided in text.	Nairobi and Lwak, Kenya	January 2008 to December 2012	Pandemic H1N1 and seasonal
Montes (2005) [18]	No information provided in text.	Regions of Basque Country, Spain	July 2001 to June 2004	Seasonal
Nelson (2014) [19]	"The vaccination uptake rate among pregnant women in Hong Kong is low in general, and ranged between 1.7 and 4.9% from various studies reported during this period."	Hong Kong (China)	April 2005 to March 2011	Pandemic H1N1 and seasonal
Poehling (2006) [28]	No information provided in text.	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	2000–2001 to 2003–2004	Seasonal
Poehling (2013) [21]	No information provided in text.	Davidson County, Tennessee; Hamilton County, Ohio; and Monroe County, New York, United States	2004–2005 to 2008–2009	Seasonal
Proff (2009) [22]	No information provided in text.	Colorado, United States	2004 to 2008 (October 1 to May 31 annually)	Seasonal
Silvennoinen (2011) [23]	"Immunization of pregnant women is an alternative approach to protect young infants along with their mothers, but so far the	Finland	July 1988 to June 2004	Seasonal

	immunization rates of pregnant women against seasonal influenza have remained relatively low."			
Stein (2010) [24]	No information provided in text.	Israel	July 12, 2009 to December 24, 2009	Pandemic H1N1
Tapia (2016) [25]	This was an RCT of influenza vaccination of pregnant women in Mali. Only data from the comparator group were included in this systematic review. Influenza vaccine was not part of the national immunization program at the time the trial was conducted.	Bamako, Mali	September 12, 2011 to January 28, 2014	Seasonal
Yu (2013) [26]	"Seasonal influenza vaccination is not included in the national immunization program, and individuals must purchase it themselves. China CDC currently recommends annual influenza vaccination for persons with chronic illness, pregnant women, individuals aged <5 or ≥60 years old, health care workers, and close contacts of high-risk individuals, an estimated population of 570 million. China does not currently have the capacity to produce this much influenza vaccine."	Jingzhou City, Hubei Province, China	April 2010 to April 2012	Seasonal
Zhang (2016) [27]	No information provided in text.	Suzhou District, China	April 2011 to March 2014	Seasonal

Table S3. Incidence estimates of laboratory-confirmed influenza hospitalizations among infants under six months of age

First author (Year)	Time period	Number of cases	Denominator	Rate per 10,000 (95% CI)	Adjustment
Ampofo (2006) [2]	July 2001 to June 2004	65	25,710	25.3 per 10,000 population (16.1–37.5)	None
Bennet (2016) [3]	1998–1999 to 2013–2014	-- [a]	-- [a]	144 per 10,000 population [b]	None
Broor (2014) [5]	August 2009 to July 2011	-- [a]	-- [a]	17.8 per 10,000 population (6.3–51.9)	Adjusted for missed hospitalizations at non-study hospitals by dividing the unadjusted incidence by the proportion of hospitalizations among area residents occurring at study facilities.
Cohen (2016) [7]	January 2010 to December 2013	-- [a]	-- [a]	43.4 per 10,000 population (34.4–53.9) [c]	Adjusted for non-enrollment on weekends and due to refusal. Adjusted SARI case numbers were then multiplied by the age- and HIV exposure status–specific detection rate for influenza.
Cox (2012) [8]	2008–2009	188	156,129	12.0 per 10,000 population (10.4–13.9 [d])	None
	2009–2010	328	162,376 [b]	20.2 per 10,000 population (18.1–22.5 [d])	None
Dawood (2010) [9]	2003–2004	357	120,608 [b]	29.6 per 10,000 population (26.7–32.8 [d])	None
	2004–2005	166	129,688 [b]	12.8 per 10,000 population (11.0–14.9 [d])	
	2005–2006	205	169,421 [b]	12.1 per 10,000 population (10.5–13.8 [d])	
	2006–2007	141	151,613 [b]	9.3 per 10,000 population (7.9–10.9 [d])	
	2007–2008	252	155,556 [b]	16.2 per 10,000 population	

				(14.3–18.3 [d])	
Griffin (2004) [10]	2000–2001 to 2003–2004	-- [a]	-- [a]	43.0 per 10,000 population [e,f]	None
Grijalva (2006) [11]	2003–2004	37	4,056	91.2 per 10,000 population (67.0–145.0)	None
Grijalva (2007) [12]	2004–2005	63	14,368	43.8 per 10,000 population (38.9–52.1)	None
Iwane (2004) [13]	2000–2001	21 [d]	8,591	24.0 per 10,000 population (10.0–38.0)	None
Ji (2010) [14]	2007	15	24,261	6.2 per 10,000 population (3.1–9.3)	None
	2008	15	23,886	6.3 per 10,000 population (3.1–9.5)	
Libster (2010) [15]	May 2009 to July 2009	83	41,180	20.2 per 10,000 population (16.2–24.2 [d])	None
Madhi (2014) [16]	2011–2012	1[g]	1,023	9.8 per 10,000 population (0.49–48.2[d]) [h]	None
McMorrow (2015) [17]	2008	-- [a]	-- [a]	0	Rates adjusted by the proportion influenza positive among hospitalized children meeting the acute lower respiratory tract illness (ALRI) case definition to all hospitalized children who met the ALRI case definition but did not have a laboratory result/sample collected.
	2009	-- [a]	-- [a]	259 per 10,000 person-years (97–689)	
	2010	-- [a]	-- [a]	47 per 10,000 person-years (7–335)	
	2011	-- [a]	-- [a]	0	
	2012	-- [a]	-- [a]	0	
	January 2008 to December 2012	-- [a]	-- [a]	76 per 10,000 person-years (32–182)	
Montes (2005) [18]	2001–2002	9	1765 [d]	51.0 per 10,000 population (24.9–93.6 [d])	None
	2002–2003	0	1820 [d]	0	
	2003–2004	13	1781 [d]	73.0 per 10,000 population (40.6–121.7 [d])	
	July 2001 to June 2004 [e]	22	5366 [d]	41.0 per 10,000 population (26.4–61.1 [d])	

Nelson (2014) [19]	April 2005 to March 2011 (0 to <2 months)	-- [a]	-- [a]	65.6 per 10,000 person-years	Adjustment for over- and under-diagnosis of influenza.
	April 2005 to March 2011 (2 to <6 months)	-- [a]	-- [a]	184.5 per 10,000 person-years	
Poehling (2006) [20]	2000–2001	20	8,333 [d]	24.0 per 10,000 population (10.0–39.0)	Rate adjusted by multiplying the influenza burden for each age group and study year by age-specific rate of acute respiratory tract infection or fever estimated from the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS).
	2001–2002	37	8,605 [d]	43.0 per 10,000 population (22.0–66.0)	
	2002–2003	20	8,696 [d]	23.0 per 10,000 population (9.0–38.0)	
	2003–2004	103	14,306 [d]	72.0 per 10,000 population (53.0–92.0)	
	2000–2001 to 2003–2004 [e]	180	40,000 [d]	45.0 per 10,000 population (34.0–55.0)	
Poehling (2013) [21]	2004–2005	-- [a]	-- [a]	34.0 per 10,000 population (25.0–45.0)	The numerator of the rate was weighted for both the days of surveillance and the proportion of eligible children enrolled.
	2005–2006	-- [a]	-- [a]	24.0 per 10,000 population (10.0–40.0)	
	2006–2007	-- [a]	-- [a]	20.0 per 10,000 population (9.0–33.0)	
	2007–2008	-- [a]	-- [a]	43.0 per 10,000 population (25.0–63.0)	
	2008–2009	-- [a]	-- [a]	16.0 per 10,000 population (7.0–26.0)	
	2004–2005 to 2008–2009 [e]	96	35,556 [d]	27.0 per 10,000 population (21.0–33.0)	
Proff (2009) [22]	2004–2005	64	34,483 [d]	18.6 per 10,000 population (14.4–23.6 [d])	None
	2005–2006	81	34,527 [d]	23.5 per 10,000 population (18.8–29.0 [d])	
	2006–2007	39	34,884 [d]	11.2 per 10,000 population (8.1–15.1 [d])	
	2007–2008	79	35,049 [d]	22.5 per 10,000 population (18.0–27.9 [b])	

Silvennoinen (2011) [23]	July 1988 to June 2004	88	31,884 [d]	27.6 per 10,000 population (22.0–33.6)	None
Stein (2010) [24]	July 12, 2009 to December 24, 2009	30	9,375 [d]	32.0 per 10,000 population (22.0–45.1) [i]	None
Tapia (2016) [25]	September 12, 2011 to January 28, 2014	1 [j]	927 [k]	10.9 per 10,000 person-years (5.4–53.2) [h]	None
Yu (2013) [26]	April 2010 to April 2012	156	6,240 [d]	250.0 per 10,000 population (213.0–292.0) [d,l]	Adjusted for the size of the resident population in the two study districts and the age-specific proportion of all influenza-associated hospitalized patients at the four surveillance hospitals.

[a] Not reported in original study and insufficient information to compute.
[b] Rate shown is a median across individual season rates. The range was: 69 per 10,000 population to 331 per 10,000 population.
[c] Among HIV unexposed and uninfected infants.
[d] Computed by review authors.
[e] 95% confidence intervals were not provided and cannot be computed due to insufficient information reported in the original study.[f] Mean across four influenza seasons
[g] Number of influenza hospitalizations among infants in the control arm. Personal communication: M Nunes, 7 Dec 2016
[h] Rate computed by review authors among infants in the control arm.
[i] For infants under three months of age.
[j] Number of influenza hospitalizations among infants in the control arm. Personal communication: M Tapia, 15 Dec 2016.
[k] Number of person-years contributed by 2,041 infants.
[l] Pooled across influenza seasons.

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Supplementary Appendix 1

Incidence of influenza disease among infants under six months of age: A systematic review
Final Strategies
2015 Sep 25

PubMed
Search Name: Paediatric Influenza - Incidence

Search	Query	Items found
#72	Search #69 NOT (#70 OR #71)	3767
#71	Search letter [pt] NOT (randomized controlled trial [tiab] AND letter [pt])	889583
#70	Search comment [pt] OR editorial [pt] OR interview [pt]	924773
#69	Search #67 NOT #68	3789
#68	Search Animals [mesh] NOT (Animals [mesh] AND Humans [mesh])	4044914
#67	Search #37 OR #44 OR #56 OR #66	3805
#66	Search #29 AND #65	2846
#65	Search #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	2081824
#64	Search ecological study [tw] OR ecological studies [tw]	3166
#63	Search case-control [tw] OR case-base [tw] OR case-based [tw] OR case-comparison [tw] OR case-compeer [tw] OR case-referent [tw] OR case-referrent [tw]	233343
#62	Search Case-Control Studies [mesh]	727356
#61	Search population study [tw] OR population studies [tw] OR population-based study [tw] OR population-based studies [tw] OR population analys* [tw] OR population-based analys* [tw]	36835
#60	Search followup study [tw] OR followup studies [tw] OR follow up study [tw] OR follow up studies [tw]	539346
#59	Search longitudinal [tw] OR prospective [tw] OR retrospective [tw]	1337855
#58	Search cohort [tw] OR cohorts [tw]	402430
#57	Search Cohort Studies [mesh]	1447931
#56	Search #29 AND #55	250
#55	Search #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54	402882
#54	Search control group [tw] OR control groups [tw]	323436
#53	Search Control Groups [mesh]	1452
#52	Search interrupted time series [tw]	1332
#51	Search Interrupted Time Series Analysis [mesh]	77
#50	Search controlled study [tw] OR controlled studies [tw]	50430
#49	Search Historically Controlled Study [mesh]	27
#48	Search "controlled before and after" [tw] OR "controlled before after" [tw]	659
#47	Search Controlled Before-After Studies [mesh]	54

Search	Query	Items found
#46	Search nRCT [tw] OR nRCTs [tw] OR non-RCT [tw] OR non-RCTs [tw]	382
#45	Search nonrandom* [tw] OR non-random* [tw] OR quasi-random* [tw] OR quasi-experiment* [tw]	38100
#44	Search #29 AND #43	1072
#43	Search #38 OR #39 OR #40 OR #41 OR #42	1089159
#42	Search trial [ti]	142809
#41	Search single blind* [tw] OR double blind* [tw] OR triple blind* [tw] OR single mask* [tw] OR double mask* [tw] OR triple mask* [tw] OR single dumm* [tw] OR double dumm* [tw] OR triple dumm* [tw]	189591
#40	Search randomised [tw] OR randomized [tw] OR randomly [tw] OR RCT [tw] OR RCTs [tw] OR placebo* [tw]	841995
#39	Search "clinical trials as topic" [mesh]	289409
#38	Search controlled clinical trial [pt] OR randomized controlled trial [pt]	480668
#37	Search #29 AND #36	236
#36	Search #30 OR #31 OR #32 OR #33 OR #34 OR #35	286635
#35	Search "The Cochrane database of systematic reviews"[Journal] OR "evidence report/technology assessment summary"[Journal] OR "evidence report/technology assessment"[Journal]	11600
#34	Search meta-review* [tw] OR meta-overview* [tw] OR meta-synthes* [tw] OR "review of reviews" [tw]	566
#33	Search meta-analy* [tw] OR metanaly* [tw] OR metaanaly* [tw] OR met analy* [tw] OR integrative research [tw] OR integrative review* [tw] OR integrative overview* [tw] OR research integration [tw] OR research overview* [tw] OR collaborative review* [tw]	107088
#32	Search "meta-analysis as topic" [mesh]	14167
#31	Search meta analysis [pt]	57196
#30	Search systematic [sb]	261834
#29	Search #14 AND #28	10001
#28	Search #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	5398968
#27	Search Influenza, Human/ep [mesh]	15598
#26	Search DALY [tw] OR DALYs [tw]	1575
#25	Search "disability-adjusted" [tw] AND (year [tw] or years [tw])	1705
#24	Search burden [tw] OR burdens [tw] OR death [tw] OR deaths [tw] OR epidemiolog* [tw] OR incidence [tw] OR frequenc* [tw] OR morbidit* [tw] OR mortalit* [tw] OR occurrence* [tw] OR occurence* [tw] OR outbreak* [tw] OR prevalen* [tw] OR rate [tw] OR rates [tw] OR surveillance* [tw]	5398606
#23	Search Survival Rate [mesh]	132546
#22	Search Perinatal Mortality [mesh]	982
#21	Search Infant Mortality [mesh]	25188

Search	Query	Items found
#20	Search Hospital Mortality [mesh]	25731
#19	Search Cause of Death [mesh]	37174
#18	Search Mortality [mesh:noexp]	35224
#17	Search Morbidity [mesh]	396299
#16	Search Prevalence [mesh]	205729
#15	Search Incidence [mesh]	187146
#14	Search #6 AND #13	16201
#13	Search #7 OR #8 OR #9 OR #10 OR #11 OR #12	1653415
#12	Search ("1 month" [tw] OR "2 month" [tw] OR "2 months" [tw] OR "3 month" [tw] OR "3 months" [tw] OR "4 month" [tw] OR "4 months" [tw] OR "5 month" [tw] OR "5 months" [tw] OR "6 month" [tw] OR "6 months" [tw]) AND (age [tw] or aged [tw] OR ages [tw] OR old [tw])	386006
#11	Search ("one month" [tw] OR "two month" [tw] OR "two months" [tw] OR "three month" [tw] OR "three months" [tw] OR "four month" [tw] OR "four months" [tw] OR "five month" [tw] OR "five months" [tw] OR "six month" [tw] OR "six months" [tw]) AND (age [tw] or aged [tw] OR ages [tw] OR old [tw])	100127
#10	Search SGA [tw] OR LBW [tw] OR VLBW [tw]	10273
#9	Search neonat* [tw] OR newborn* [tw]	711217
#8	Search infant [tw] OR infants [tw] OR infancy [tw] OR baby [tw] OR babies [tw]	1081815
#7	Search Infant [mesh]	961979
#6	Search #1 OR #2 OR #3 OR #4 OR #5	108939
#5	Search H1N1 [tw] OR PH1N1 [tw] OR H3N2 [tw] OR AH1N1 [tw] OR AH3N2 [tw]	18776
#4	Search Influenza B Virus [mesh]	3184
#3	Search Influenza A Virus [mesh]	34136
#2	Search (influenza* [tw] OR flu [tw] OR grippe [tw])	108774
#1	Search Influenza, Human [mesh]	37849

Embase

Search Name: Paediatric Influenza - Incidence
Database: Embase Classic+Embase <1947 to 2015 September 24>
Search Strategy:
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1 influenza/ (56566)
2 exp Influenza virus A/ (36192)
3 exp Influenza virus B/ (5289)
4 pandemic influenza/ (3749)
5 seasonal influenza/ (3413)
6 (influenza* or flu or grippe).ti,ab,kw. (126039)
7 (H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2).ti,ab,kw. (20337)
8 or/1-7 (143389)
9 infant/ (584948)
10 (infant or infants or infancy or baby or babies).ti,ab,kw. (497405)
11 newborn/ (525200)
12 (neonat* or newborn*).ti,ab,kw. (415750)
13 (SGA or LBW or VLBW).ti,ab,kw. (14351)
14 ((one or two or three or four or five or six) adj (month or months) adj3 (age or aged or ages or old)).ti,ab,kw. (14881)
15 (("1 month" or "2 month" or "2 months" or "3 month" or "3 months" or "4 month" or "4 months" or "5 month" or "5 months" or "6 month" or "6 months") adj3 (age or aged or ages or old)).ti,ab,kw. (74046)
16 or/9-15 (1314942)
17 8 and 16 (13606)
18 incidence/ (237278)
19 prevalence/ (450891)
20 exp disease surveillance/ (15135)
21 Infection rate/ (19900)
22 morbidity/ (256072)
23 newborn morbidity/ (6013)
24 mortality/ (625197)
25 infant mortality/ (22660)
26 newborn mortality/ (10384)
27 "cause of death"/ (84993)
28 survival rate/ (176633)
29 (burden or burdens or death or deaths or epidemiolog* or incidence or frequenc* or morbidit* or mortalit* or occurrence* or occurence* or outbreak* or prevalen* or rate or rates or surveillance*).ti,ab,kw. (6043641)
30 influenza/ep (10380)
31 exp Influenza virus A/ep (201)
32 exp Influenza virus B/ep (18)
33 pandemic influenza/ep (612)
34 seasonal influenza/ep (343)
35 ("disability-adjusted" adj2 (year or years)).ti,ab,kw. (1990)
36 (DALY or DALYs).ti,ab,kw. (2091)
37 or/18-36 (6386442)

38 17 and 37 (7967)
39 meta-analysis/ (99125)
40 "systematic review"/ (95683)
41 "meta analysis (topic)"/ (22361)
42 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).ti,ab,kw. (111122)
43 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews").ti,ab,kw. (122272)
44 (cochrane or health technology assessment or evidence report).jw. (13908)
45 or/39-44 (263998)
46 38 and 45 (113)
47 randomized controlled trial/ or controlled clinical trial/ (524987)
48 exp "clinical trial (topic)"/ (164463)
49 (randomi#ed or randomly or RCT$1 or placebo*).ti,ab,kw. (928458)
50 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).ti,ab,kw. (184212)
51 trial.ti. (194717)
52 or/47-51 (1319714)
53 38 and 52 (744)
54 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).ti,ab,kw. (45795)
55 (nRCT or nRCTs or non-RCT$1).ti,ab,kw. (525)
56 (control* adj3 ("before and after" or "before after")).ti,ab,kw. (3869)
57 time series analysis/ (16042)
58 (time series adj3 interrupt*).ti,ab,kw. (1544)
59 controlled study/ (4737075)
60 (control* adj2 stud$3).ti,ab,kw. (221552)
61 control group/ (93065)
62 (control$ adj2 group$1).ti,ab,kw. (501642)
63 or/54-62 (5098022)
64 38 and 63 (1961)
65 cohort analysis/ (216857)
66 cohort.ti,ab,kw. (463216)
67 retrospective study/ (427824)
68 longitudinal study/ (82291)
69 prospective study/ (308661)
70 (longitudinal or prospective or retrospective).ti,ab,kw. (1180818)
71 follow up/ (983556)
72 ((followup or follow-up) adj (study or studies)).ti,ab,kw. (57996)
73 population research/ (74829)
74 ((population or population-based) adj (study or studies or analys#s)).ti,ab,kw. (17929)
75 exp case control study/ (106570)
76 (case-control* or case-base or case-based or case-comparison or case-compeer or case-referent or case-referrent).ti,ab,kw. (118283)
77 (ecological adj (study or studies)).ti,ab,kw. (3591)
78 or/65-77 (2608918)
79 38 and 78 (2060)
80 46 or 53 or 64 or 79 (3472)

81 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (22291007)
82 exp humans/ or exp human experimentation/ or exp human experiment/ (16544866)
83 81 not 82 (5747166)
84 80 not 83 (3382)
85 editorial.pt. (491119)
86 letter.pt. not (letter.pt. and randomized controlled trial/) (904244)
87 84 not (85 or 86) (3367)

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Cochrane Library

Search Name: Paediatric Influenza - Incidence
Date Run: 25/09/15 12:51:27.541
Description: WHO - 2015 Sep 25 - Final

ID	Search	Hits
#1	[mh "Influenza Human"]	1393
#2	(influenza* or flu or grippe):ti,ab,kw	6146
#3	[mh "Influenza A Virus"]	740
#4	[mh "Influenza B Virus"]	229
#5	(H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2):ti,ab,kw	855
#6	{or #1-#5}	6149
#7	[mh Infant]	13442
#8	(infant or infants or infancy or baby or babies):ti,ab,kw	40394
#9	(neonat* or newborn*):ti,ab,kw	22224
#10	(SGA or LBW or VLBW):ti,ab,kw	1208
#11	(((one or two or three or four or five or six) next (month or months)) near/3 (age or aged or ages or old)):ti,ab,kw	508
#12	(((1 or 2 or 3 or 4 or 5 or 6) next (month or months)) near/3 (age or aged or ages or old)):ti,ab,kw	3138
#13	{or #7-#12}	46302
#14	#6 and #13	1231
#15	[mh Incidence]	8037
#16	[mh Prevalence]	4006
#17	[mh Morbidity]	12265
#18	[mh ^Mortality]	505
#19	[mh "Cause of Death"]	1200
#20	[mh "Hospital Mortality "]	1103
#21	[mh "Infant Mortality"]	505
#22	[mh "Perinatal Mortality"]	65
#23	[mh "Survival Rate"]	8500
#24	(burden or burdens or death or deaths or epidemiolog* or frequenc* or incidence or morbidit* or mortalit* or occurrence* or occurence* or outbreak* or prevalen* or rate or rates or surveillance*):ti,ab,kw	292711
#25	[mh "Influenza, Human"/ep]	247
#26	("disability-adjusted" near/2 (year or years)):ti,ab,kw	40
#27	(DALY or DALYs):ti,ab,kw	42
#28	{or #15-#27}	292792
#29	#14 and #28	649

DSR - 12
DARE - 3
CENTRAL – 608
HTA – 5
NHS EED – 21

CINAHL Plus with Full Text

Search Name: Paediatric Influenza - Incidence

#	Query	Limiters/Expanders	Results
S70	S67 NOT (S68 OR S69)	Search modes - Boolean/Phrase	452
S69	PT Letter NOT (PT Letter AND PT randomized controlled trial)	Search modes - Boolean/Phrase	209,408
S68	PT comment OR PT editorial OR PT interview	Search modes - Boolean/Phrase	221,414
S67	S65 NOT S66	Search modes - Boolean/Phrase	454
S66	(MH "Animals+") NOT ((MH "Animals+") AND (MH "Human"))	Search modes - Boolean/Phrase	58,476
S65	S33 OR S40 OR S52 OR S64	Search modes - Boolean/Phrase	454
S64	S27 AND S63	Search modes - Boolean/Phrase	376
S63	S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62	Search modes - Boolean/Phrase	495,947
S62	TI (ecological W1 (study or studies)) OR AB (ecological W1 (study or studies))	Search modes - Boolean/Phrase	484
S61	(MH "Ecological Research")	Search modes - Boolean/Phrase	617
S60	TI ((case W1 control*) or "case-base" or "case-based" or "case-comparison" or "case-compeer" or "case-referent" or "case-referrent") OR AB ((case W1 control*) or "case-base" or "case-based" or "case-comparison" or "case-compeer" or "case-referent" or "case-referrent")	Search modes - Boolean/Phrase	16,368
S59	(MH "Case Control Studies+")	Search modes - Boolean/Phrase	53,567
S58	TI ((population or "population-based") W1 (study or studies or analys*)) OR AB ((population or "population-based") W1 (study or studies or analys*))	Search modes - Boolean/Phrase	13,246
S57	TI ((followup or "follow-up") W1 (study or studies)) OR AB ((followup or "follow-up") W1 (study or studies))	Search modes - Boolean/Phrase	6,843
S56	TI (longitudinal or prospective or retrospective) OR AB (longitudinal or prospective or retrospective)	Search modes - Boolean/Phrase	153,687
S55	(MH "Retrospective Design")	Search modes - Boolean/Phrase	143,341
S54	TI (cohort or cohorts) OR AB (cohort or cohorts)	Search modes -	72,938

		Boolean/Phrase	
S53	(MH "Prospective Studies+")	Search modes - Boolean/Phrase	274,540
S52	S27 AND S51	Search modes - Boolean/Phrase	52
S51	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50	Search modes - Boolean/Phrase	92,060
S50	(MH "Pretest-Posttest Control Group Design")	Search modes - Boolean/Phrase	458
S49	TI (control* N2 (group or groups)) OR AB (control* N2 (group or groups))	Search modes - Boolean/Phrase	45,568
S48	(MH "Control Group")	Search modes - Boolean/Phrase	6,585
S47	TI (control* N2 (study or studies)) OR AB (control* N2 (study or studies))	Search modes - Boolean/Phrase	33,851
S46	TI time series N3 interrupt* OR AB time series N3 interrupt*	Search modes - Boolean/Phrase	594
S45	(MH "Quasi-Experimental Studies+")	Search modes - Boolean/Phrase	9,154
S44	TI (control* N3 ("before and after" or "before after")) OR AB (control* N3 ("before and after" or "before after"))	Search modes - Boolean/Phrase	851
S43	TI (nRCT or nRCTs or (non W1 RCT) or (non W1 RCTs)) OR AB (nRCT or nRCTs or (non W1 RCT) or (non W1 RCTs))	Search modes - Boolean/Phrase	127
S42	TI (nonrandom* or (non W1 random*) or (quasi W1 random*) or (quasi W1 experiment*)) OR AB (nonrandom* or (non W1 random*) or (quasi W1 random*) or (quasi W1 experiment*))	Search modes - Boolean/Phrase	9,890
S41	(MH "Nonrandomized Trials")	Search modes - Boolean/Phrase	190
S40	S27 AND S39	Search modes - Boolean/Phrase	90
S39	S34 OR S35 OR S36 OR S37 OR S38	Search modes - Boolean/Phrase	269,666
S38	TI trial	Search modes - Boolean/Phrase	54,873
S37	TI ((singl* or doubl* or trebl* or tripl*) W1 (mask* or blind* or dumm*)) OR AB ((singl* or doubl* or trebl* or tripl*) W1 (mask* or blind* or dumm*))	Search modes - Boolean/Phrase	22,455
S36	TI (randomized or randomised or randomly or RCT or RCTs or placebo*) OR AB (randomized or randomised or randomly or RCT	Search modes - Boolean/Phrase	145,346

	or RCTs or placebo*)		
S35	(MH "Clinical Trials+")	Search modes - Boolean/Phrase	192,364
S34	PT randomized controlled trial	Search modes - Boolean/Phrase	53,623
S33	S27 AND S32	Search modes - Boolean/Phrase	22
S32	S28 OR S29 OR S30 OR S31	Search modes - Boolean/Phrase	80,899
S31	TI ((systematic W1 review*) or (systematic W1 overview*) or ("evidence-based" W1 review*) or ("evidence-based" W1 overview*) or (evidence N3 (review* or overview*)) or (meta W1 review*) or (meta W1 overview*) or (meta W1 synthes*) or "review of reviews") OR AB ((systematic W1 review*) or (systematic W1 overview*) or ("evidence-based" W1 review*) or ("evidence-based" W1 overview*) or (evidence N3 (review* or overview*)) or (meta W1 review*) or (meta W1 overview*) or (meta W1 synthes*) or "review of reviews")	Search modes - Boolean/Phrase	48,222
S30	TI ((meta W1 analy*) or metanaly* or metaanaly* or (met W1 analy*) or (integrative W1 research) or (integrative W1 review*) or (integrative W1 overview*) or (research W1 integration) or (research W1 overview*) or (collaborative W1 review*)) OR AB ((meta W1 analy*) or metanaly* or metaanaly* or (met W1 analy*) or (integrative W1 research) or (integrative W1 review*) or (integrative W1 overview*) or (research W1 integration) or (research W1 overview*) or (collaborative W1 review*))	Search modes - Boolean/Phrase	27,188
S29	(MH "Meta Analysis") OR (MH "Meta Synthesis")	Search modes - Boolean/Phrase	23,728
S28	(MH "Systematic Review")	Search modes - Boolean/Phrase	34,365
S27	S14 AND S26	Search modes - Boolean/Phrase	1,303
S26	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	Search modes - Boolean/Phrase	575,777
S25	(MH "Influenza, Human+/EP")	Search modes - Boolean/Phrase	2,173
S24	TI (DALY OR DALYs) OR AB (DALY OR DALYs)	Search modes - Boolean/Phrase	338
S23	TI ("disability-adjusted" W2 (year or years)) OR AB ("disability-adjusted" W2 (year or years))	Search modes - Boolean/Phrase	314
S22	TI (burden OR burdens OR death OR deaths OR epidemiolog* OR	Search modes -	518,824

	incidence OR frequenc* OR morbidit* OR mortalit* OR occurrence* OR occurence* OR outbreak* OR prevalen* OR rate OR rates OR surveillance*) OR AB (burden OR burdens OR death OR deaths OR epidemiolog* OR incidence OR frequenc* OR morbidit* OR mortalit* OR occurrence* OR occurence* OR outbreak* OR prevalen* OR rate OR rates OR surveillance*)	Boolean/Phrase	
S21	(MH "Infant Mortality")	Search modes - Boolean/Phrase	5,927
S20	(MH "Hospital Mortality")	Search modes - Boolean/Phrase	9,665
S19	(MH "Cause of Death")	Search modes - Boolean/Phrase	8,401
S18	(MH "Mortality")	Search modes - Boolean/Phrase	17,533
S17	(MH "Morbidity+")	Search modes - Boolean/Phrase	96,224
S16	(MH "Prevalence")	Search modes - Boolean/Phrase	54,979
S15	(MH "Incidence")	Search modes - Boolean/Phrase	40,248
S14	S6 AND S13	Search modes - Boolean/Phrase	2,251
S13	S7 OR S8 OR S9 OR S10 OR S11 OR S12	Search modes - Boolean/Phrase	210,074
S12	TI (((1 or 2 or 3 or 4 or 5 or 6) W1 (month or months)) N3 (age or aged or ages or old)) OR AB (((1 or 2 or 3 or 4 or 5 or 6) W1 (month or months)) N3 (age or aged or ages or old))	Search modes - Boolean/Phrase	5,423
S11	TI (((one or two or three or four or five or six) W1 (month or months)) N3 (age or aged or ages or old)) OR AB (((one or two or three or four or five or six) W1 (month or months)) N3 (age or aged or ages or old))	Search modes - Boolean/Phrase	961
S10	TI (SGA OR LBW OR VLBW) OR AB (SGA OR LBW OR VLBW)	Search modes - Boolean/Phrase	2,175
S9	TI (neonat* OR newborn*) OR AB (neonat* OR newborn*)	Search modes - Boolean/Phrase	42,737
S8	TI (infant OR infants OR infancy OR baby OR babies) OR AB (infant OR infants OR infancy OR baby OR babies)	Search modes - Boolean/Phrase	70,500
S7	(MH "Infant+")	Search modes - Boolean/Phrase	175,001
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes -	18,305

		Boolean/Phrase	
S5	TI ((H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2) OR AB ((H1N1 or PH1N1 or H3N2 or AH1N1 or AH3N2)	Search modes - Boolean/Phrase	3,569
S4	MH "Influenza B Virus"	Search modes - Boolean/Phrase	202
S3	MH "Influenza A Virus+"	Search modes - Boolean/Phrase	4,040
S2	TI (influenza* or flu or grippe) OR AB (influenza* or flu or grippe)	Search modes - Boolean/Phrase	16,391
S1	MH "Influenza, Human+"	Search modes - Boolean/Phrase	5,660

Supplementary Appendix 2. Application of modified GRADE evaluation[1,2] for systematic literature review of the incidence of laboratory-confirmed influenza (LCI) outcomes among infants under six months of age

Table 1. GRADE evaluation for studies reporting laboratory-confirmed influenza (LCI) illness in ambulatory settings among infants under six months of age

Profile of individual studies		**Comments**
Number of studies Number of estimates	6 9	
Lowest estimate (95% confidence interval)	0.75 per 100 person-years (95% CI: 0.0–1.6)	▪ Sindh Province, Pakistan ▪ October 2011 to June 2014
Highest estimate (95% confidence interval)	35 per 100 person-years (95% CI: 26–48)	▪ Department of Cajamarca, Peru ▪ May 2009 to September 2011
GRADE assessment [a]		**Comments**
Phase of investigation	Level 2 (high)	▪ Two randomized controlled trials and four observational studies
GRADE criteria (based on narrative review, not meta-analysis)		
Study limitations: ▪ **Downgrade by -1** if most evidence is from studies with moderate or unclear risk of bias for most bias domains (serious limitations). ▪ **Downgrade by -2** if most evidence is from studies with high risk of bias for almost all bias domains (very serious limitations).		▪ No change.
Inconsistency: unexplained heterogeneity or variability in results across studies ▪ **Downgrade by -1** when estimates of the risk factor association with the outcome vary in direction (for example, some effects appear protective whereas others show risk) and the confidence intervals show no, or minimal overlap.	-1	▪ Qualitatively high heterogeneity in results across studies, likely due to differences in influenza season characteristics as well as different surveillance methodologies. ▪ **Downgrade by 1.**
Indirectness: the study sample, the prognostic factor, and/or the		▪ No change.

outcome in the primary studies do not accurately reflect the review question ▪ **Downgrade by -1** when: (1) the final sample only represents a subset of the population of interest; (2) when the complete breadth of the prognostic factor that is being considered in the review question is not well represented in the available studies; or (3) when the outcome that is being considered in the review question is not broadly represented.		
Imprecision: ▪ **Downgrade by -1** if the evidence is generated by a few studies involving a small number of participants and most of the studies provide imprecise results. ▪ For narrative summary: Within-study imprecision: (1) sample size justification is not provided and there are less than 10 outcome events for each prognostic variable (for dichotomous outcomes), and (2) no precision in the estimation of the effect size within each primary study. Across study imprecision: there are few studies and small number of participants across studies.	-1	▪ There are only 6 studies in total, and a relatively small number of cases in several of the studies. ▪ **Downgrade by 1.**
Publication bias: ▪ **Downgrade by -1** unless the value of the risk/protective factor in predicting the outcome has been repetitively investigated, ideally by phase 2 and 3 studies.		▪ No change.
Moderate/large effect size: ▪ **Upgrade by +1** if moderate or large similar effect is reported by most studies.		▪ No change.
Dose effect: ▪ **Upgrade by +1** if possible gradient exists within and between primary studies.	N/A	▪ No change.
GRADE: OVERALL QUALITY OF EVIDENCE **(+, very low; ++, low; +++, moderate; ++++, high)**	++ **Low**	

[a] Based on Huguet et al.[2] adaptation of GRADE evaluation framework.[1]

Table 2. GRADE evaluation for studies reporting laboratory-confirmed influenza (LCI) hospitalization among infants under six months of age

Profile of individual studies		**Comments**
Number of studies Number of estimates	23 46	
Lowest estimate (95% confidence interval)	0	▪ Jiangsu province, China ▪ 2007
Highest estimate (95% confidence interval)	259 per 10,000 person-years (95% CI: 97–689)	▪ Nairobi and Lwak, Kenya ▪ 2009
GRADE assessment [a]		**Comments**
Phase of investigation	Level 2 (high)	▪ Two randomized controlled trials and 21 observational studies
GRADE criteria (based on narrative review, not meta-analysis)		
Study limitations: ▪ **Downgrade by -1** if most evidence is from studies with moderate or unclear risk of bias for most bias domains (serious limitations). ▪ **Downgrade by -2** if most evidence is from studies with high risk of bias for almost all bias domains (very serious limitations).		▪ No change.
Inconsistency: unexplained heterogeneity or variability in results across studies ▪ **Downgrade by -1** when estimates of the risk factor association with the outcome vary in direction (for example, some effects appear protective whereas others show risk) and the confidence intervals show no, or minimal overlap.	-1	▪ Qualitatively high heterogeneity in results across studies, likely due to differences in influenza season characteristics as well as different surveillance methodologies. ▪ **Downgrade by 1.**
Indirectness: the study sample, the prognostic factor, and/or the outcome in the primary studies do not accurately reflect the review question ▪ **Downgrade by -1** when: (1) the final sample only represents a subset of the population of interest; (2) when the complete breadth of the prognostic factor that is being considered in the review question is not well represented in the available studies;		▪ No change.

or (3) when the outcome that is being considered in the review question is not broadly represented.		
Imprecision: ▪ **Downgrade by -1** if the evidence is generated by a few studies involving a small number of participants and most of the studies provide imprecise results. ▪ For narrative summary: Within-study imprecision: (1) sample size justification is not provided and there are less than 10 outcome events for each prognostic variable (for dichotomous outcomes), and (2) no precision in the estimation of the effect size within each primary study. Across study imprecision: there are few studies and small number of participants across studies.		▪ No change.
Publication bias: ▪ **Downgrade by -1** unless the value of the risk/protective factor in predicting the outcome has been repetitively investigated, ideally by phase 2 and 3 studies.		▪ No change.
Moderate/large effect size: ▪ **Upgrade by +1** if moderate or large similar effect is reported by most studies.		▪ No change.
Dose effect: ▪ **Upgrade by +1** if possible gradient exists within and between primary studies.	N/A	▪ No change.
GRADE: OVERALL QUALITY OF EVIDENCE **(+, very low; ++, low; +++, moderate; ++++, high)**	+++ **Moderate**	

[a] Based on Huguet et al.[2] adaptation of GRADE evaluation framework.[1]

Table 3. GRADE evaluation for studies reporting laboratory-confirmed influenza (LCI) ICU admission among infants under six months of age

Profile of individual studies		**Comments**
Number of studies Number of estimates	7 7	
Lowest estimate (95% confidence interval)	0	▪ Davidson County, Tennessee; Monroe County, New York, United States ▪ 2000-2001
Highest estimate (95% confidence interval)	3.5 per 10,000 population (95% CI: 1.7–6.4)	▪ Salt Lake City, Utah, United States ▪ July 2011 to June 2004
GRADE assessment [a]		**Comments**
Phase of investigation	Level 2 (high)	▪ All were observational studies
GRADE criteria (based on narrative review, not meta-analysis)		
Study limitations: ▪ **Downgrade by -1** if most evidence is from studies with moderate or unclear risk of bias for most bias domains (serious limitations). ▪ **Downgrade by -2** if most evidence is from studies with high risk of bias for almost all bias domains (very serious limitations).		▪ No change.
Inconsistency: unexplained heterogeneity or variability in results across studies ▪ **Downgrade by -1** when estimates of the risk factor association with the outcome vary in direction (for example, some effects appear protective whereas others show risk) and the confidence intervals show no, or minimal overlap.	-1	▪ Qualitatively high heterogeneity in results across studies, likely due to differences in influenza season characteristics as well as different surveillance methodologies. ▪ **Downgrade by 1.**
Indirectness: the study sample, the prognostic factor, and/or the outcome in the primary studies do not accurately reflect the review question ▪ **Downgrade by -1** when: (1) the final sample only represents a subset of the population of interest; (2) when the complete breadth of the prognostic factor that is being considered in the		▪ No change.

review question is not well represented in the available studies; or (3) when the outcome that is being considered in the review question is not broadly represented.		
Imprecision: ▪ **Downgrade by -1** if the evidence is generated by a few studies involving a small number of participants and most of the studies provide imprecise results. ▪ For narrative summary: Within-study imprecision: (1) sample size justification is not provided and there are less than 10 outcome events for each prognostic variable (for dichotomous outcomes), and (2) no precision in the estimation of the effect size within each primary study. Across study imprecision: there are few studies and small number of participants across studies.	-1	▪ There are only 7 studies in total, and a small number of cases in each of the studies leading to wide confidence intervals around the incidence estimates. ▪ **Downgrade by 1.**
Publication bias: ▪ **Downgrade by -1** unless the value of the risk/protective factor in predicting the outcome has been repetitively investigated, ideally by phase 2 and 3 studies.		▪ No change.
Moderate/large effect size: ▪ **Upgrade by +1** if moderate or large similar effect is reported by most studies.		▪ No change.
Dose effect: ▪ **Upgrade by +1** if possible gradient exists within and between primary studies.	N/A	▪ No change.
GRADE: OVERALL QUALITY OF EVIDENCE **(+, very low; ++, low; +++, moderate; ++++, high)**	++ **Low**	

[a] Based on Huguet et al.[2] adaptation of GRADE evaluation framework.[1]

Table 4. GRADE evaluation for studies reporting laboratory-confirmed influenza (LCI) death among infants under six months of age

Profile of individual studies		**Comments**
Number of studies Number of estimates	9 9	
Lowest estimate (95% confidence interval)	0	▪ Surveillance for LCI deaths was conducted, but no deaths were ascertained in six of the nine studies.
Highest estimate (95% confidence interval)	5 per 100,000 population (95% CI: 0.82-16.1)	▪ Buenos Aires, Argentina ▪ May 2009 to July 2009
GRADE assessment [a]		**Comments**
Phase of investigation	Level 2 (high)	▪ Two randomized controlled trials and seven observational studies
GRADE criteria (based on narrative review, not meta-analysis)		
Study limitations: ▪ **Downgrade by -1** if most evidence is from studies with moderate or unclear risk of bias for most bias domains (serious limitations). ▪ **Downgrade by -2** if most evidence is from studies with high risk of bias for almost all bias domains (very serious limitations).		▪ No change.
Inconsistency: unexplained heterogeneity or variability in results across studies ▪ **Downgrade by -1** when estimates of the risk factor association with the outcome vary in direction (for example, some effects appear protective whereas others show risk) and the confidence intervals show no, or minimal overlap.	-1	▪ Qualitatively high heterogeneity in results across studies, likely due to differences in influenza season characteristics as well as different surveillance methodologies. ▪ **Downgrade by 1.**
Indirectness: the study sample, the prognostic factor, and/or the outcome in the primary studies do not accurately reflect the review question ▪ **Downgrade by -1** when: (1) the final sample only represents a subset of the population of interest; (2) when the complete breadth of the prognostic factor that is being considered in the review question is not well represented in the available studies;		▪ No change.

or (3) when the outcome that is being considered in the review question is not broadly represented.		
Imprecision: ▪ **Downgrade by -1** if the evidence is generated by a few studies involving a small number of participants and most of the studies provide imprecise results. ▪ For narrative summary: Within-study imprecision: (1) sample size justification is not provided and there are less than 10 outcome events for each prognostic variable (for dichotomous outcomes), and (2) no precision in the estimation of the effect size within each primary study. Across study imprecision: there are few studies and small number of participants across studies.	-1	▪ There are only nine studies in total, and no cases of LCI deaths among infants under six months of age were ascertained in six of the nine studies. ▪ **Downgrade by 1.**
Publication bias: ▪ **Downgrade by -1** unless the value of the risk/protective factor in predicting the outcome has been repetitively investigated, ideally by phase 2 and 3 studies.		▪ No change.
Moderate/large effect size: ▪ **Upgrade by +1** if moderate or large similar effect is reported by most studies.		▪ No change.
Dose effect: ▪ **Upgrade by +1** if possible gradient exists within and between primary studies.	N/A	▪ No change.
GRADE: OVERALL QUALITY OF EVIDENCE **(+, very low; ++, low; +++, moderate; ++++, high)**	++ **Low**	

[a] Based on Huguet et al.[2] adaptation of GRADE evaluation framework.[1]

References

1. Guyatt G, Oxman AD, Akl E a, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026.
2. Huguet A, Hayden JA, Stinson J, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. *Syst Rev*. 2013;2:71. doi:10.1186/2046-4053-2-71.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10; Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2-5; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

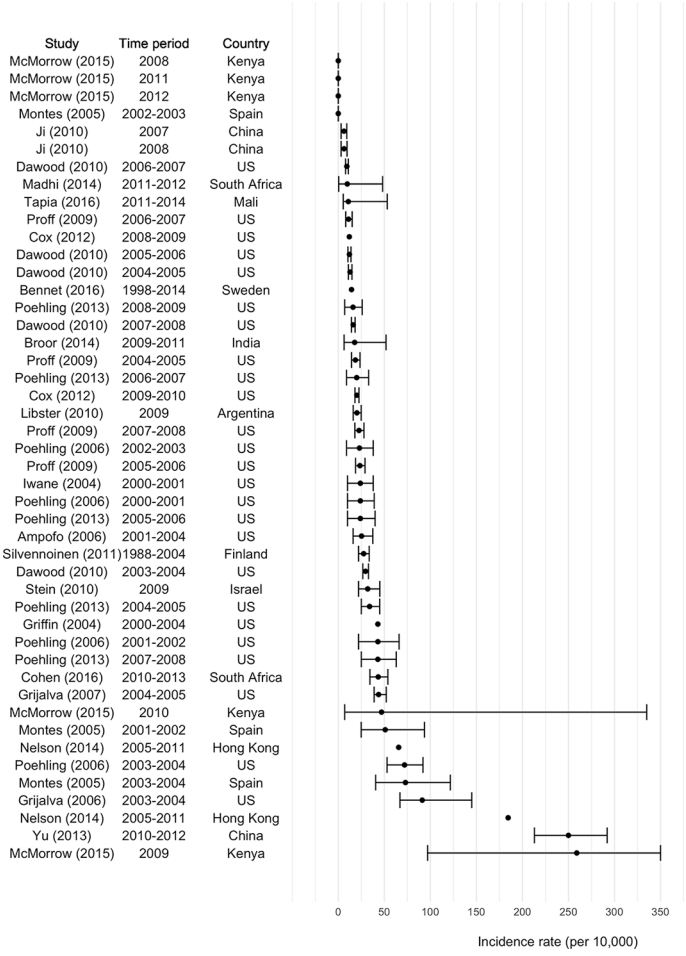
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

Correction: *Incidence of laboratory-confirmed influenza disease among infants under 6 months of age: a systematic review*

Fell DB, Johnson J, Mor Z, *et al*. Incidence of laboratory-confirmed influenza disease among infants under 6 months of age: a systematic review. *BMJ Open* 2017;7:e016526. doi: 10.1136/bmjopen-2017-016526

In figure 2 and online supplementary table 3 , Bennet (2016) are reported to have found an influenza incidence of 144 per 10 000 in infants younger than six months; however, the correct figure is a median yearly incidence 1998–2014 of 144 per 10^5 in this age group, which equals 14.4 per 10 000. This correct figure is among the lowest in similar settings, and considerably reduces the variability of reported incidences.
The corrected figure 2 is shown below:



A corrected version of the supplementary table is available here: revised supplementary table 3.

BMJ Open 2018;**8**:e016526corr1. doi:10.1136/bmjopen-2017-016526corr1