Effectiveness of influenza vaccination in preventing hospitalisation due to influenza in children: a systematic review and meta-analysis

Nicki L Boddington[a]*, Isabelle Pearson[a], Heather Whitaker[b], Punam Mangtani[c$], Richard G Pebody[a$]

a. Immunisation and Countermeasures Department, Public Health England, UK
b. Statistics, Modelling and Economics Department, Public Health England, UK
c. Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK

*Corresponding author: nicki.boddington@phe.gov.uk, Immunisation and Countermeasures Department, Public Health England, 61 Colindale Avenue, London, NW9 5EQ, UK, +44 0208 327 7000

Alternative author: punam.mangtani@lshtm.ac.uk, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

[$]Joint last authors

Key words: Vaccine effectiveness, children, hospitalisation, influenza, systematic review

Running title: Influenza vaccine effectiveness in children

Key points: This study provides a complete and up-to-date review of the literature and highlights that influenza vaccination provides good protection against any influenza-associated hospitalisation in children and provides continued support for annual vaccination in children. Effectiveness varies by subtype and vaccine type.

Abstract

This systematic review assesses the literature for estimates of influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalisation in children.

Studies of any design to 08 June 2020 were included if the outcome was hospitalisation, participants were 17 years old or less and influenza infection was laboratory-confirmed.

A random-effects meta-analysis of 37 studies that used a test-negative design gave a pooled seasonal IVE against hospitalisation of 53.3% (47.2-58.8) for any influenza. IVE was higher against influenza A/H1N1pdm09 (68.7%, 56.9-77.2) and lowest against influenza A/H3N2 (35.8%, 23.4-46.3). Estimates by vaccine type ranged from 44.3% (30.1-55.7) for LAIV to 68.9% (53.6-79.2) for inactivated vaccines. IVE estimates were higher in seasons when the circulating influenza strains were antigenically matched to vaccine strains (59.3%, 48.3-68.0).

Influenza vaccination gives moderate overall protection against influenza-associated hospitalisation in children supporting annual vaccination. IVE varies by influenza subtype and vaccine type.

Introduction

It is estimated that influenza causes 3-5 million severe infections annually (1). One of the groups at elevated risk of severe influenza illness are younger children, particularly younger children under two years, as well as children with chronic medical conditions (2).

Influenza vaccination remains the most effective method of preventing influenza illness in the population and reducing its burden. The World Health Organization (WHO) recommends annual influenza vaccination to individuals at increased risk of severe disease (disease resulting in hospitalisation or death) including healthy children aged 6 to 59 months (3). A number of countries have begun to adopt programmes to vaccinate children or are considering vaccination (4-6). Monitoring the effectiveness of the influenza vaccine in children is important both from an annual perspective to inform how well matched the vaccine might be to the main circulating strain and from a longer-term perspective to inform resource allocation including for future adoption in other settings. Globally there are two broad types of influenza vaccines available: inactivated influenza vaccines (IIV) and live-attenuated influenza vaccines (LAIV). In early randomised control trials (RCT) in high income settings LAIV was found to offer high protection to children, often higher than IIV (7-9), and with higher levels of acceptability than traditional injectable vaccines, LAIV has, in some countries, been preferentially recommended in children (10). However, vaccine-effectiveness studies post-licensure have shown mixed effectiveness of LAIV with estimates ranging from 0% to 57.6% (11-17).

One of the main study designs used to estimate influenza vaccine effectiveness (IVE) is the test-negative study design (TND). The method was first developed to measure IVE against medically-attended outcomes (18), however it has become increasingly used for hospital admissions with influenza (19, 20). Using this approach, the cases are those that fit the clinical case definition and test positive for influenza and those that meet the clinical case definition, but test negative are used as controls.

However, there are limitations to single season studies given the year-to-year variability of influenza, and thus meta-analyses of data from separate studies and over several seasons can be used to provide more robust VE estimates. A recent, industry sponsored, systematic review and meta-analysis of the effectiveness of influenza vaccination in preventing severe illness in children (6 months to 17 years old) found that influenza vaccination provided moderately good protection against influenza-associated hospitalisation of over 50% pooled over all seasons, but there was also considerable heterogeneity (21). The heterogeneity across studies especially given issues such as egg adaptation with influenza A/H3N2 or blunting of LAIV effectiveness against influenza A/H1N1pdm09 (22, 23) suggest that further disaggregation by season, subtype and vaccine match would be useful to inform future vaccine use.

In this study we review and summarise the literature of all study types estimating IVE against laboratory-confirmed influenza-associated hospitalisation up to June 2020. We aim to provide updated estimates of overall IVE against laboratory-confirmed influenza-associated hospitalisations, and for the first time, by vaccine type (IIV and LAIV) as well asby influenza subtype and vaccine match.

Methods

We conducted a systematic review and meta-analysis of extracted IVE estimates. We restricted the meta-analysis to studies that used a TND to reduce heterogeneity due to study design across studies.

Search strategy and selection criteria

A search strategy was developed using the PICOST (population, intervention, comparison, outcome, situation and type of study) framework. All study designs were included except case series/reports and systematic/critical reviews.

Databases, search construct, screening and study selection

The following databases were used to conduct a comprehensive literature search: MEDLINE, Embase, Global Health, Web of Science and SCOPUS from inception to 02 May 2019 and updated on 08 June 2020. We developed a unique search strategy for each database, the main search terms included "influenza/flu", "immunisation/vaccination", "effectiveness" and "hospitalisation/intensive care/death" (full searches in Supplementary Material). No language restrictions were placed on the searches. Reference lists were searched to identify additional studies. The study protocol was registered on Prospero (CRD42019149315).

After removal of duplicates, two reviewers independently screened titles and abstracts of studies identified through the initial search. Identified studies were retrieved in full text and independently assessed for inclusion using an adapted Cochrane ERC data collection form. Any disagreements were solved by discussion.

Studies were considered eligible for inclusion if they met all the following criteria: (i) outcome was hospitalisation, (ii) study participants were children (17 years and less), (iii) influenza infection was laboratory confirmed (by any method).

The following studies were excluded: (i) studies conducted in an outpatient setting, (ii) studies containing exclusively adult data (or mixed adult and children data which could not be separated, or where estimates for children were non-estimable), (iii) interim estimates superseded by a final report, and (iv) studies that assessed the monovalent 2009 pandemic vaccine. Studies that assessed influenza VE against intensive care admission or death were also excluded due to the small number (n=2) that assessed these outcomes (24, 25).

Data collection and extraction

We used a structured electronic collection tool to extract data from the studies reviewed. For each article, one author extracted the information and another one checked the extracted data. When necessary corresponding authors were contacted for clarification of data.

Data analysis

TND studies were grouped by influenza season and we performed a random effects meta-analysis to estimate the IVE against any type of influenza-related hospitalisation in children.

Secondary analyses were carried out by stratifying the data by influenza type (influenza A and B), age group (less than 5 years old, 6-17 years old) and vaccine type (IIV, QIV, TIV, LAIV). Where possible influenza type A was further sub-grouped by subtype (A/H1N1pdm09 and A/H3N2) and influenza B by vaccine type (IIV, QIV, TIV, LAIV). A sensitivity analysis was undertaken, restricting the overall analysis to only studies which used molecular testing. Studies that used multiple types of tests were excluded.

Throughout the study VE estimates by individual influenza season were used in preference to multiple season estimates, including for sub-group analyses, unless only multiple season estimates were available.

For the VE estimates by season, estimates from the southern hemisphere were grouped with those from the subsequent northern hemisphere season, apart from in seasons when the vaccine compositions were different. In this case they were grouped with the previous northern hemisphere season estimates when the vaccine compositions matched.

Where given, adjusted VE estimates were included in the meta-analysis and no minimum criteria were established for adjustment.

Where studies specified vaccination status (i.e. partially or fully vaccinated) we used fully vaccinated VE estimates which was usually defined by authors as children vaccinated in line with the recommended vaccination schedule.

For the overall meta-analysis, estimates for any age groups within 6 months to 17 years were included. For the sub-group analysis by age, any estimate that fell within the age band of interest was included.

The analysis by vaccine match was restricted to studies that presented VE estimates against hospitalisation by single seasons. In the first instance, authors conclusions about the similarity

between circulating and vaccine strains were used. In the absence of this information, the WHO Weekly Epidemiological Records (WER) (26) and other relevant public health body websites were used to determine antigenic characterisation of circulating virus strains and the WHO recommendations on the composition of influenza virus vaccines (27). VE estimates by subtype were used if available otherwise overall VE estimates for all influenza were used. A match between the circulating strain and vaccine was considered if either all the vaccine components belonged to the same influenza A subtypes and B lineages, or if at least one vaccine strain was similar to the predominant virus circulating.

Heterogeneity among studies and subgroups was assessed using the χ^2 -based Q test (Cochran's Q) and the I^2 statistic. Studies were assessed for risk of bias using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool (28).

Stata v16.1 (Stata Corporation, College Station, TX) was used to perform the statistical analysis.

Results

After removing duplicates, we identified 2,592 potential studies. Following title and abstract screening, 305 studies were identified for full text review. Of these 262 were excluded leaving a total of 45 studies, of which 37 studies used the TND (Figure 1).

Six studies used a non-TND and are summarised in Table 1. Four were case-control studies (29-32), one used the screening method (33) and one was a prospective, non-randomised observational study (34) (Table 1). Excluding the case-control study by Joshi *et al.,* (2012) (30), all non-TND studies showed good protection against influenza-associated hospitalisation with estimates ranging between 54% and 83%.

Among the 37 TND studies, the study years ranged from 2005/2006 to 2018/2019 (Table 2). The majority were from the Northern Hemisphere (n=26), 10 studies were from the Southern Hemisphere and there was one global study.

- Estimates of overall IVE against hospitalisation (by season) (Figure 2)

Thirty-four studies provided IVE estimates in children against any type of influenza-associated hospitalisation. Among them six studies provided estimates over multiple seasons (35-40). The overall pooled IVE against hospitalisation in children due to any influenza across the seasons was 53.3% (95% CI 47.2-58.8) with moderate heterogeneity (I^2 = 62.7%, p=0.000) (Figure 2). Heterogeneity by season was much lower than the overall heterogeneity, though it was still moderate to high across studies in the 2016/17 and 2018/19 seasons. In a sensitivity analysis, the overall results were similar (52% (95% CI 41.7, 60.5)) when restricted to studies which used molecular testing.

- Estimates of IVE against hospitalisation by type/subtype (Figure 3)

Twenty-two studies provided IVE estimates against influenza A hospitalisations (Figure 3). Overall IVE against influenza A hospitalisation was 58.0% (95% CI 49.8, 64.8) with moderate heterogeneity (I^2 = 62.1%, p=0.000). Eight studies assessed IVE against influenza A only which gave a IVE of 59.7% (95% CI 46.3, 69.8) with moderate heterogeneity (I^2 = 54.0%, p=0.043). Fourteen studies assessed subtype specific IVE. The IVE against influenza A/H1N1pdm09 was 68.7% (95% CI 56.9, 77.2), with moderate heterogeneity (I^2 = 65.87%, p=0.001) and against influenza A/H3N2 was 35.8% (95% CI 23.4, 46.3), with low heterogeneity (I^2 = 0%, p=0.893).

Nineteen studies provided IVE estimates against influenza B hospitalisation (Supplement Figure 1). Overall IVE against influenza B hospitalisation was 47.6% (95% CI 38.0, 55.7) with low heterogeneity (I^2 = 17.9%, p=0.346).

- Estimates of IVE against hospitalisation by vaccine type (Figure 4)

Thirty-five studies provided IVE estimates against influenza-associated hospitalisation by vaccine type (Figure 4). For LAIV, based on a small number of studies (n=3), IVE was 44.3% (95% CI 30.1, 55.7). IVE for inactivated influenza vaccine was 67.1% (95% CI 53.5, 76.8). For TIV specifically the IVE was 47.5% (95% CI 39.5, 54.4) and for QIV 50.2% (10.7, 72.3). For influenza B specifically, the IVE estimate for

quadrivalent vaccine was higher, 48.0% (95% CI -7.9, 74.9), than the trivalent vaccine with an IVE of 42.9% (95% CI 25.1, 56.5) although with wide and overlapping confidence intervals (Supplement Figure 1).

- Estimates of IVE against hospitalisation by age group (Supplement Figure 2+3)

Fifteen studies provided IVE estimates against influenza-associated hospitalisation in children aged 6 months to 5 years. The pooled VE estimate was 61.7% (95% CI 54.1, 68.1) with moderate heterogeneity (I^2 = 58.6%, p=0.000). For children aged 6 years to 17 years, influenza VE was 51.7% (95% CI 42.9, 59.1) with low heterogeneity (I^2 = 0.66%, p=0.8567).

- Estimates of IVE against hospitalisation by vaccine match (Figure 5)

Information on whether the vaccine matched the circulating virus strains during the study periods were ascertained for twenty studies. IVE estimates were highest in seasons where the circulating influenza strains were antigenically matched to those strains included in the vaccine (IVE=59.3%, 95% CI 48.3-68.0), and in seasons where there was a mixed match with the vaccine (IVE= 58.4%, 95% CI 34.0-73.7) i.e. good match for some but not all the circulating strains. In seasons when there was a mismatch between circulating and vaccine strains, IVE was 33.6% (95% CI -2.4-57.0).

- Risk of bias assessments

Studies were either assessed as having moderate (n=37) or severe risk of bias (n=16). Most studies appeared to provide useful evidence although biases inherent with non-randomised studies remained such as selection bias. Generally, this is lower in TND studies since cases and controls are selected from a population of persons presenting with a defined set of symptoms, and in this review, these persons were hospitalised, reducing the scope for ascertainment bias. In two studies however controls were not hospitalised, introducing more serious risk of bias. A further source of bias was the lack of adjustment for underlying medical conditions in the analysis.

Discussion

In this paper we present an updated and independent review of the literature on the effectiveness of influenza vaccination in preventing hospitalisations due to influenza in children. The review includes all study designs to provide a more complete picture of the evidence. We also present the results of an updated meta-analysis that provides pooled estimates of IVE against influenza-associated hospitalisation in children by vaccine type, influenza type/subtype, age group and vaccine match.

Overall, we found that influenza vaccination provided good protection against any influenza-associated hospitalisation in children aged 6 months to 17 years old (53.2%, 95% CI 47.1-58.6). Overall heterogeneity was present but reduced when the data was split by season. This is unsurprising given the variability in the main circulating strains and vaccine match each season, as well as antigenic changes that might require attention such as egg-adaptation (22). The meta-analysis was restricted to TND studies and excluded ICU admissions and deaths to reduce heterogeneity.

To the best of our knowledge, this is the first study that looks at the effectiveness of influenza vaccination in preventing hospitalisation in children by vaccine type and vaccine match. The IVE estimates by vaccine type ranged from 44.3% (95% CI 30.1-55.7) for LAIV to 68.9% (53.6-79.2) for IIV although the results were not statistically different. Whilst early RCTs suggested that LAIV may have superior efficacy compared with IIV in children (7-9), more recent observational studies have shown mixed effectiveness of LAIV against medically-attended influenza in children, particularly against influenza A(H1N1)pdm09 (11-17, 41, 42). Effectiveness estimates have also varied geographically with studies from the United States showing low LAIV effectiveness during the 2013-2016 seasons (12-14, 41, 43, 44). Hypothesised reasons for the recent lower LAIV estimates include a reduction in fitness in the vaccine strain (45), problems with vaccine production (46), mismatch between vaccine and circulating strains, or negative interference (10). Further studies are required to assess the difference of effectiveness between LAIV and IIV against more severe outcomes including hospitalisations in children.

By influenza type, IVE was slightly higher against influenza A compared to influenza B although the confidence intervals overlapped and by influenza A subtype, IVE was slightly higher against influenza A/H1N1pdm09 compared with influenza A/H3N2. Poor VE has often been seen against influenza A(H3N2), including against severe influenza in adults (47). This is thought to be related vaccine mismatch as well as to egg adaptation of A(H3N2) vaccine viruses during the vaccine production process (22, 48).

By age, IVE was higher in younger children, 6 months to 5 years, compared to those 6 years to 17 years although the confidence intervals overlapped. IVE estimates were also higher in seasons where the circulating influenza strains were antigenically matched to the vaccine strains and in seasons where there was a mixed match with the vaccine.

The majority of studies used molecular testing, specifically RT-PCR, for influenza confirmation. Overall IVE estimates were similar when restricted to studies using only molecular tests. Molecular diagnostic tests are highly sensitive and specific for detecting influenza viruses (49). Other methods, such as rapid antigen tests, are often found to be less sensitive and/or specific and can lead to biased VE estimates (49, 50).

Other sources of bias, common to many studies included in the review, was the lack of inclusion of underlying medical conditions as a confounder in their analyses. This is an important confounder since many underlying conditions can increase the risk of hospitalisation for respiratory symptoms, as well as being indications for vaccination (20).

The IVE estimates of this study are consistent with, although slightly lower than, a similar meta-analysis of IVE against hospitalisation in children carried out up to November 2019 (21). This study identified 28 studies compared with the 37 studies included in this meta-analysis. This study did not assess IVE by vaccine type. Our estimates were generally lower, although we had smaller confidence intervals and thus greater precision around our estimates. In contrast, our estimates were higher than a similar meta-analysis of IVE against hospitalisation in adults rather than children (47). The authors

in this study showed that vaccination provided moderate protection against influenza-associated hospitalisation (47).

Meta-analyses of studies reporting IVE against medically-attended influenza illness using the TND show a consistent pattern in terms of higher VE against A(H1N1)pdm09 and lowest against A(H3N2) (51, 52). This is in-line with the conclusions from a meta-analysis that inpatient and outpatient IVE estimates were consistent with each other most of the time (19).

The meta-analysis was limited by the number of observations for some sub-group analyses such as influenza B lineage-specific IVE estimates and we did not look at prior vaccination or the effect of full versus partial vaccination. Previous studies in the outpatient setting have shown the potential benefit of full vaccination, particularly in younger children (under 5 years), which can be considered as two doses in children aged 6 months to 8 years depending on past vaccination status (53-56). Whilst we did restrict the meta-analysis to TND studies, we did not apply any further restriction to other methodological features. Only a small number of studies included in this review reported the match between the vaccine and the antigenic characterisation of circulating virus strains. We therefore made use of WHO publications and other relevant public health body websites.

In conclusion, this study demonstrates that influenza vaccination offers moderate protection against any influenza-associated hospitalisation in children aged 6 months to 17 years old. It also highlights variable protection over seasons as well as by influenza type/subtype and vaccine type although further evidence is required.

Funding and Conflicts of interest

There are no funding sources to declare or conflicts of interests from any authors.

References

1. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health technology assessment. 2003;7(35):iii-iv, xi-xiii, 1-170.
2. Neuzil KM, Zhu Y, Griffin MR, Edwards KM, Thompson JM, Tollefson SJ, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. J Infect Diseases. 2002;185(2):147-52.
3. World Health Organization. Vaccines against influenza WHO position paper - November 2012. Releve epidemiologique hebdomadaire. 2012;87(47):461-76.
4. Mereckiene J, Cotter S, D'Ancona F, Giambi C, Nicoll A, Levy-Bruhl D, et al. Differences in national influenza vaccination policies across the European Union, Norway and Iceland 2008-2009. EuroSurveillance. 2010;15(44).
5. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR.53(RR06):1-40.
6. Canadian Paediatric Society. Vaccine recommendations for children and youth for the 2020/2021 influenza season 2020 [20 October 2020]. Available from: https://www.cps.ca/en/documents/position/vaccine-recommendations-2020-2021-influenza-season.
7. Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. NEJM. 1998;338(20):1405-12.
8. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. NEJM. 2007;356(7):685-96.
9. Ashkenazi S, Vertruyen A, Arístegui J, Esposito S, McKeith DD, Klemola T, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006;25(10):870-9.
10. Matrajt L, Halloran ME, Antia R. Successes and Failures of the Live-attenuated Influenza Vaccine: Can We Do Better? Clin Infect Dis. 2020;70(6):1029-37.
11. King JP, McLean HQ, Meece JK, Levine MZ, Spencer SM, Flannery B, et al. Vaccine failure and serologic response to live attenuated and inactivated influenza vaccines in children during the 2013-2014 season. Vaccine. 2018;36(9):1214-9.
12. Gaglani M, Pruszynski J, Murthy K, Clipper L, Robertson A, Reis M, et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013-2014 in the United States. J Infect Dis. 2016;213(10):1546-56.
13. Jackson ML, Chung JR, Jackson LA, Phillips CH, Benoit J, Monto AS, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. NEJM. 2017;377(6):534-43.
14. McLean HQ, Caspard H, Griffin MR, Poehling KA, Gaglani M, Belongia EA, et al. Effectiveness of live attenuated influenza vaccine and inactivated influenza vaccine in children during the 2014-2015 season. Vaccine. 2017;35(20):2685-93.
15. Nohynek H, Baum U, Syrjänen R, Ikonen N, Sundman J, Jokinen J. Effectiveness of the live attenuated and the inactivated influenza vaccine in two-year-olds - a nationwide cohort study Finland, influenza season 2015/16. EuroSurveillance. 2016;21(38).
16. Pebody R, Warburton F, Andrews N, Ellis J, von Wissmann B, Robertson C, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. EuroSurveillance. 2015;20(36).
17. Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. EuroSurveillance. 2016;21(38).

18. Skowronski DM, Masaro C, Kwindt TL, Mak A, Petric M, Li Y, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: results from the 2005-2006 season of dual A and B vaccine mismatch in Canada. Vaccine. 2007;25(15):2842-51.
19. Feng S, Cowling BJ, Sullivan SG. Influenza vaccine effectiveness by test-negative design - Comparison of inpatient and outpatient settings. Vaccine. 2016;34(14):1672-9.
20. Foppa IM, Ferdinands JM, Chaves SS, Haber MJ, Reynolds SB, Flannery B, et al. The case test-negative design for studies of the effectiveness of influenza vaccine in inpatient settings. Int J Epidemiol. 2016;45(6):2052-9.
21. Kalligeros M, Shehadeh F, Mylona EK, Dapaah-Afriyie C, van Aalst R, Chit A, et al. Influenza vaccine effectiveness against influenza-associated hospitalization in children: A systematic review and meta-analysis. Vaccine. 2020;38(14):2893-903.
22. Belongia EA, McLean HQ. Influenza Vaccine Effectiveness: Defining the H3N2 Problem. Clin Infect Dis. 2019;69(10):1817-23.
23. Penttinen PM, Friede MH. Decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines: an observational bias or a technical challenge? EuroSurveillance. 2016;21(38).
24. Ferdinands JM, Olsho LEW, Agan AA, Bhat N, Sullivan RM, Hall M, et al. Effectiveness of Influenza Vaccine Against Life-threatening RT-PCR-confirmed Influenza Illness in US Children, 2010–2012. J Infect Diseases. 2014;210(5):674-83.
25. Flannery B, Reynolds SB, Blanton L, Santibanez TA, O'Halloran A, Lu PJ, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010-2014. Pediatrics. 2017;139(5).
26. World Health Organization. Weekly Epidemiological Record 2020 [Available from: https://www.who.int/wer/en/.
27. World Health Organization. WHO recommendations on the composition of influenza virus vaccines 2020 [21 October 2020]. Available from: https://www.who.int/influenza/vaccines/virus/recommendations/en/.
28. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
29. Dixon GA, Moore HC, Kelly H, Jacoby P, Carcione D, Williams S, et al. Lessons from the first year of the WAIVE study investigating the protective effect of influenza vaccine against laboratory-confirmed influenza in hospitalised children aged 6-59 months. Influenza Other Respir Viruses. 2010;4(4):231-4.
30. Joshi AY, Iyer VN, Hartz MF, Patel AM, Li JT. Effectiveness of trivalent inactivated influenza vaccine in influenza-related hospitalization in children: a case-control study. Allergy Asthma Proc. 2012;33(2):e23-7.
31. Wang CY, Chang YH, Huang LM, Chi H, Chiu NC, Chang LY, et al. Effects of influenza vaccine and sun exposure time against laboratory-confirmed influenza hospitalizations among young children during the 2012-13 to 2015-16 influenza seasons. Journal of microbiology, immunology, and infection. 2019;52(6):880-7.
32. Sugaya N, Shinjoh M, Nakata Y, Tsunematsu K, Yamaguchi Y, Komiyama O, et al. Three-season effectiveness of inactivated influenza vaccine in preventing influenza illness and hospitalization in children in Japan, 2013-2016. Vaccine. 2018;36(8):1063-71.
33. Pebody R, Sile B, Warburton F, Sinnathamby M, Tsang C, Zhao H, et al. Live attenuated influenza vaccine effectiveness against hospitalisation due to laboratory-confirmed influenza in children two to six years of age in England in the 2015/16 season. EuroSurveillance. 2017;22(4).
34. Katayose M, Hosoya M, Haneda T, Yamaguchi H, Kawasaki Y, Sato M, et al. The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons. Vaccine. 2011;29(9):1844-9.
35. Blyth CC, Cheng AC, Finucane C, Jacoby P, Effler PV, Smith DW, et al. The effectiveness of influenza vaccination in preventing hospitalisation in children in Western Australia. Vaccine. 2015;33(51):7239-44.

36. Buchan SA, Booth S, Scott AN, Simmonds KA, Svenson LW, Drews SJ, et al. Effectiveness of Live Attenuated vs Inactivated Influenza Vaccines in Children During the 2012-2013 Through 2015-2016 Influenza Seasons in Alberta, Canada: A Canadian Immunization Research Network (CIRN) Study. JAMA pediatrics. 2018;172(9):e181514.
37. Menniti-Ippolito F, Da Cas R, Traversa G, Santuccio C, Felicetti P, Tartaglia L, et al. Vaccine effectiveness against severe laboratory-confirmed influenza in children: results of two consecutive seasons in Italy. Vaccine. 2014;32(35):4466-70.
38. Staat MA, Griffin MR, Donauer S, Edwards KM, Szilagyi PG, Weinberg GA, et al. Vaccine effectiveness for laboratory-confirmed influenza in children 6-59 months of age, 2005-2007. Vaccine. 2011;29(48):9005-11.
39. Campbell AP, Ogokeh CE, McGowan C, Rha B, Selvarangan R, Staat MA, et al. 899. Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza in Children Hospitalized with Respiratory Illness in the United States, 2016–2017 and 2017–2018 Seasons. Open Forum Infect Dis. 2019;6(Suppl 2):S26-S7.
40. Sofia Arriola C, El Omeiri N, Azziz-Baumgartner E, Thompson MG, Sotomayor-Proschle V, Fasce RA, et al. Influenza vaccine effectiveness against hospitalizations in children and older adults-Data from South America, 2013-2017. A test negative design. Vaccine: X. 2019;3:100047.
41. Pebody R, McMenamin J, Nohynek H. Live attenuated influenza vaccine (LAIV): recent effectiveness results from the USA and implications for LAIV programmes elsewhere. Arch Dis Childh. 2018;103(1):101-5.
42. Caspard H, Mallory RM, Yu J, Ambrose CS. Live-Attenuated Influenza Vaccine Effectiveness in Children From 2009 to 2015-2016: A Systematic Review and Meta-Analysis. Open Forum Infect Dis. 2017;4(3):ofx111.
43. Poehling KA, Caspard H, Peters TR, Belongia EA, Congeni B, Gaglani M, et al. 2015-2016 Vaccine Effectiveness of Live Attenuated and Inactivated Influenza Vaccines in Children in the United States. Clin Infect Dis. 2018;66(5):665-72.
44. Zimmerman RK, Nowalk MP, Chung J, Jackson ML, Jackson LA, Petrie JG, et al. 2014-2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. Clin Infect Dis. 2016;63(12):1564-73.
45. Ambrose CS, Bright H, Mallory R. Letter to the editor: Potential causes of the decreased effectiveness of the influenza A(H1N1)pdm09 strain in live attenuated influenza vaccines. EuroSurveillance. 2016;21(45).
46. Caspard H, Coelingh KL, Mallory RM, Ambrose CS. Association of vaccine handling conditions with effectiveness of live attenuated influenza vaccine against H1N1pdm09 viruses in the United States. Vaccine. 2016;34(42):5066-72.
47. Rondy M, El Omeiri N, Thompson MG, Levêque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. J Infect. 2017;75(5):381-94.
48. Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci. 2017;114(47):12578-83.
49. World Health Organization. Evaluation of influenza vaccine effectiveness: a guide to the design and interpretation of observational studies Geneva2017 [Available from: https://apps.who.int/iris/bitstream/handle/10665/255203/9789241512121-eng.pdf;jsessionid=319A7D92519BFE97B99E05E2683B697E?sequence=1.
50. Jackson ML, Rothman KJ. Effects of imperfect test sensitivity and specificity on observational studies of influenza vaccine effectiveness. Vaccine. 2015;33(11):1313-6.
51. Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis. 2016;16(8):942-51.

52. Darvishian M, van den Heuvel ER, Bissielo A, Castilla J, Cohen C, Englund H, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. Lancet Respir Med. 2017;5(3):200-11.
53. Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2019-20 Influenza Season. MMWR. 2019;68(3):1-21.
54. Ritzwoller DP, Bridges CB, Shetterly S, Yamasaki K, Kolczak M, France EK. Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. Pediatrics. 2005;116(1):153-9.
55. Shuler CM, Iwamoto M, Bridges CB, Marin M, Neeman R, Gargiullo P, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. Pediatrics. 2007;119(3):e587-95.
56. Eisenberg KW, Szilagyi PG, Fairbrother G, Griffin MR, Staat M, Shone LP, et al. Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003-2004 and 2004-2005 influenza seasons. Pediatrics. 2008;122(5):911-9.

Tables and Figures

Table 1: Characteristics and overall vaccine effectiveness estimates of non-Test Negative Design (TND) studies identified in the systematic review

Author and year of publication	Country	Study design	Influenza season	Vaccine type	Diagnostic test used	Age groups	Clinical inclusion criteria	Vaccine ascertainment	Overall VE estimates against all influenza types (95% CI)
Dixon, 2010 (29)	Australia	Case-control	2008	TIV	Multiple	6 months – 59 months	Laboratory confirmed influenza for cases; acute non-ARI as controls	Parental report; validated by vaccine provided/Australian Childhood Immunisation Registry (for 87% of participants)	▪ 87% (-11, 98) (crude) ▪ 83% (-54, 98) (adjusted)
Joshi, 2012 (30)	United States	Case-control	1999-2006	TIV	Multiple	6 months – 18 years	Medically-attended influenza illness (cases laboratory confirmed influenza; controls laboratory confirmed influenza but not hospitalised)	Medical records	-267% (-740, -60) (OR = 3.67 (1.6, 8.4) (crude)
Katayose, 2011 (34)	Japan	Prospective, non-randomised, observational	2002/03 – 2007/08	TIV	Rapid tests	6 months – 5 years	ARI	Medical records	71% (59, 80) (against influenza A) (crude)
Pebody, 2017 (33)	England	Screening	2015/16	LAIV	RT-PCR	2 years – 6 years	Hospitalised, laboratory confirmed influenza for cases	Medical records	▪ 58.3% (38.8, 72.4) (crude) ▪ 54.5% (31.5, 68.4) (adjusted)
Wang, 2019 (31)	Taiwan	Case-control	2012/13 – 2015/16	Not stated	Multiple	6 months – 5 years	Hospitalised, laboratory confirmed influenza for cases;	Vaccination cards	57.3% (40.6, 69.4) (OR 0.427, 0.306-0.594) (adjusted)

							matched controls seeking medical services in same facility		
Sugaya, 2018 (32)	Japan	Case-control + TND*	2013/14 – 2015/16	QIV	Rapid tests	6 months – 15 years	ILI (cases laboratory confirmed influenza, controls were outpatients with ILI irrespective of whether they were positive/negative for influenza.	Multiple	45% (36, 54) (adjusted)

*results from the TND study reported in Table 2

Table 2: Characteristics of Test Negative Design (TND) studies identified in the systematic review and included in the meta-analysis

Author and year of publication	Country(ies)	Influenza season(s)	Vaccine type	Diagnostic test used	Clinical inclusion criteria	Vaccine ascertainment	Relevant child age group included	ROBINS-I Risk of Bias
Arriola, 2019	South America	2013 - 2017	Inactivated trivalent	RT-PCR	SARI	Multiple	6 months - 24 months	Moderate
Baselga-Moreno, 2019	Multiple	2016/17	Not stated	RT-PCR	ILI for patients >5 years	Multiple	0 months - 17 years	Severe
Bissielo, 2016	New Zealand	2015	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Moderate
Blyth, 2015	Australia	2008, 2010 - 2013	Inactivated trivalent	RT-PCR	ARI	Medical records	6 months - 17 years	Moderate
Blyth, 2016	Australia	2014	Inactivated trivalent	RT-PCR	ARI	Multiple	6 months - 15 years	Severe
Blyth, 2019	Australia	2017	Inactivated quadrivalent	RT-PCR	ARI	Multiple	6 months - 16 years	Moderate
Blyth, 2020	Australia	2018	Inactivated quadrivalent	RT-PCR	ARI	Multiple	6 months - 16 years	Moderate
Boddington, 2019	England	2015/16	Multiple	RT-PCR	Suspect influenza	Medical records	2 years - 16 years	Moderate
Buchan, 2017	Canada	2010/11 - 2013/14	TIV or LAIV	Multiple	Individuals hospitalised + respiratory specimen collected within 3 days of admission	Billing claims records	6 months - 59 months	Moderate
Buchan, 2018	Canada	2012/13 - 2015/16	LAIV or IIV	RT-PCR	Hospitalised + tested for influenza	Multiple	2 years - 17 years	Moderate
Campbell, 2019	US	2016/17, 2017/18	Not stated	Molecular assay	ARI	Multiple	6 months - 17 years	Moderate

Chiu, 2016	Hong Kong	2009/10 - 2013/14	Inactivated trivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Chiu, 2018a	Hong Kong	2016/17	Inactivated trivalent + quadrivalent	RT-PCR	ARI	Multiple	6 months - 17 years	Severe
Chiu, 2018b	Hong Kong	2017/18	Inactivated trivalent + quadrivalent	Multiple	ARI	Multiple	6 months - 17 years	Severe
Chiu, 2019	Hong Kong	2018/19	Inactivated trivalent + quadrivalent	RT-PCR	ARI	Multiple	6 months - 17 years	Severe
Chua, 2019	Hong Kong	2011 - 2019	Inactivated trivalent + quadrivalent	Multiple	ARI	Multiple	6 months - 8 years	Severe
Cowling, 2014	Hong Kong	2009 - 2012	Inactivated trivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Cowling, 2017	Hong Kong	2015/16	Inactivated trivalent + quadrivalent	Multiple	ARI	Parental report	6 months - 17 years	Severe
Feldstein, 2020	US	2015/16	Multiple	Molecular assay	ARI	Multiple	6 months - 17 years	Moderate
Feng, 2018	Hong Kong	2012 - 2016	Multiple	Multiple	ARI	Multiple	6 months - 17 years	Severe
Fowlkes, 2017	US	2013 - 2016	Multiple	RT-PCR	SARI	Vaccine register	6 months - 12 years	Moderate
Menniti-Ippolito, 2014	Italy	2011/12, 2012/13	Not stated	RT-PCR	ILI	Parental report	6 months - 16 years	Severe

Omeiri, 2018	Latin America	2013	Inactivated trivalent	RT-PCR	SARI	Multiple	6 months - 5 years	Moderate
Pebody, 2020	England	2018/19	LAIV + inactivated quadrivalen	RT-PCR	Hospitalised + tested for influenza	Medical records	2 years - 17 years	Moderate
Pierse, 2016	New Zealand	2014	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Moderate
Qin, 2016	China	2013/14, 2014/15	Inactivated trivalent	RT-PCR	Inpatients with diagnosis potentially associated with influenza + ILI for patients >5 years	Vaccine register	6 months - 17 years	Moderate
Segaloff, 2019	Israel	2015/16 - 2017/18	Inactivated trivalent	RT-PCR	Hospitalised + tested for influenza (as part of clinical care)	Medical records	6 months - 8 years	Severe
Shinjoh, 2015	Japan	2013/14	Inactivated trivalent	Rapid tests	Fever 38^{o}C or over	Medical records	6 months - 15 years	Severe
Shinjoh, 2018	Japan	2016/17	Inactivated quadrivalent	Rapid tests	Fever 38^{o}C or over	Multiple	6 months - 15 years	Moderate
Staat, 2011	US	2005/06, 2006/07	Inactivated trivalent	RT-PCR	ARI	Multiple	6 months - 59 months	Moderate
Sugaya, 2016	Japan	2014/15	Inactivated trivalent	Rapid tests	Fever 38^{o}C or more and cough and/or rhinorrhoea	Multiple	6 months - 15 years	Severe
Sugaya, 2018	Japan	2013/14 - 2015/16	Multiple	Rapid tests	Fever 38^{o}C or more and cough and/or rhinorrhoea	Multiple	6 months - 15 years	Moderate
Turner, 2014a	New Zealand	2013	Inactivated trivalent	RT-PCR	SARI	Self-report	6 months - 17 years	Severe
Turner, 2014b	New Zealand	2012	Inactivated trivalent	Multiple	SARI	Self-report	6 months - 17 years	Severe

Wang, 2016	China	2011/12	Not stated	RT-PCR	SARI	Vaccine register	6 months - 59 months	Moderate
Yeung, 2018	Hong Kong	2014/15, 2015/16	Multiple	Multiple	Febrile/respiratory-associated admissions	Multiple	6 months - 72 months	Severe
Zhang, 2017	China	2015/16	Inactivated trivalent	RT-PCR	Hospitalised with diagnosis from list of conditions	Vaccine register	6 month - 4 years	Moderate

Figure Legends

Figure 1: Flowchart of the selection of studies

Figure 2: Seasonal influenza vaccine effectiveness against any influenza hospitalisation by season

Figure 3: Influenza vaccine effectiveness estimates against hospitalisation by influenza A

Figure 4: Influenza vaccine effectiveness estimates against hospitalisation by vaccine type

Figure 5: Influenza vaccine effectiveness against hospitalisation in children by vaccine match

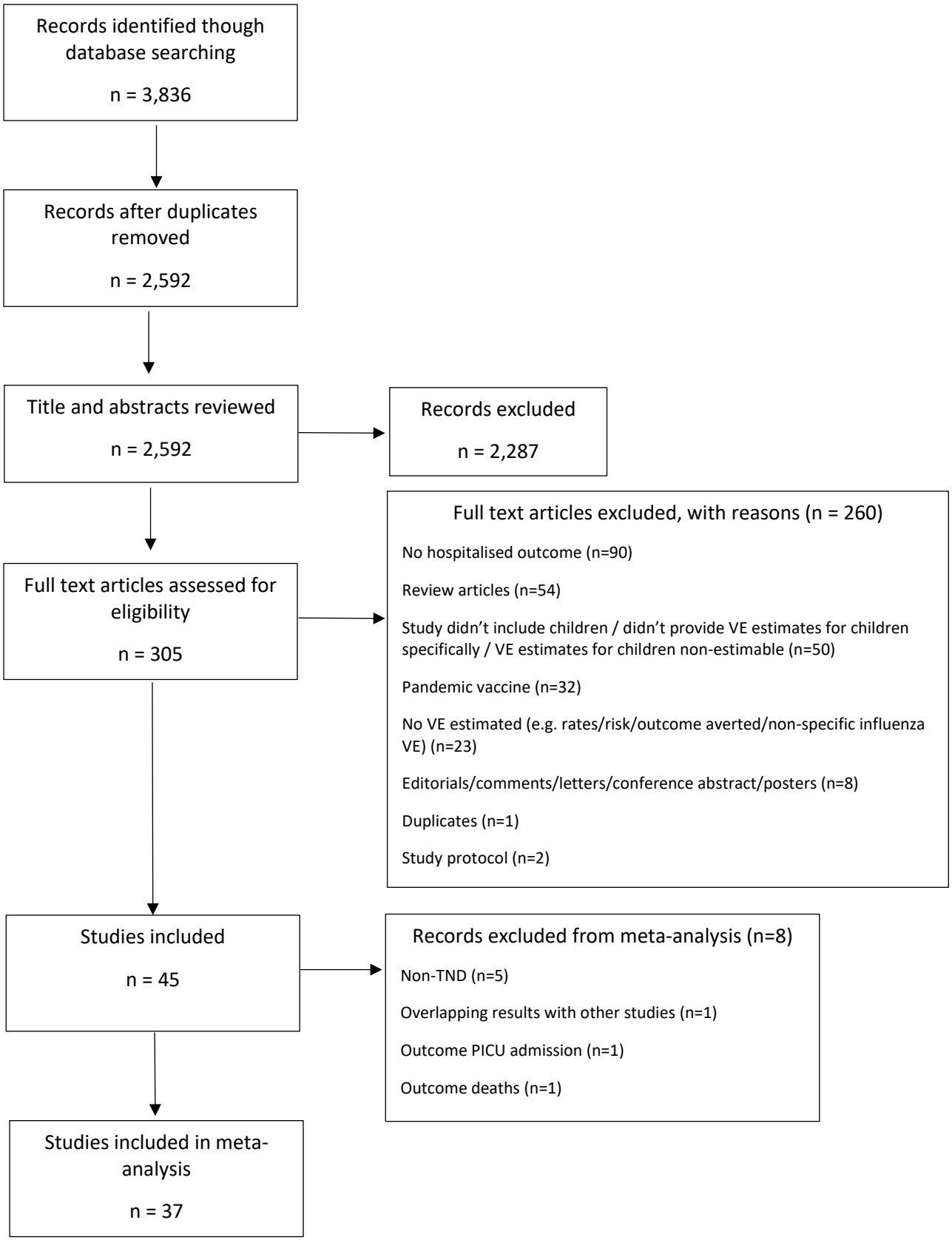

Figure 1: Flowchart of the selection of studies

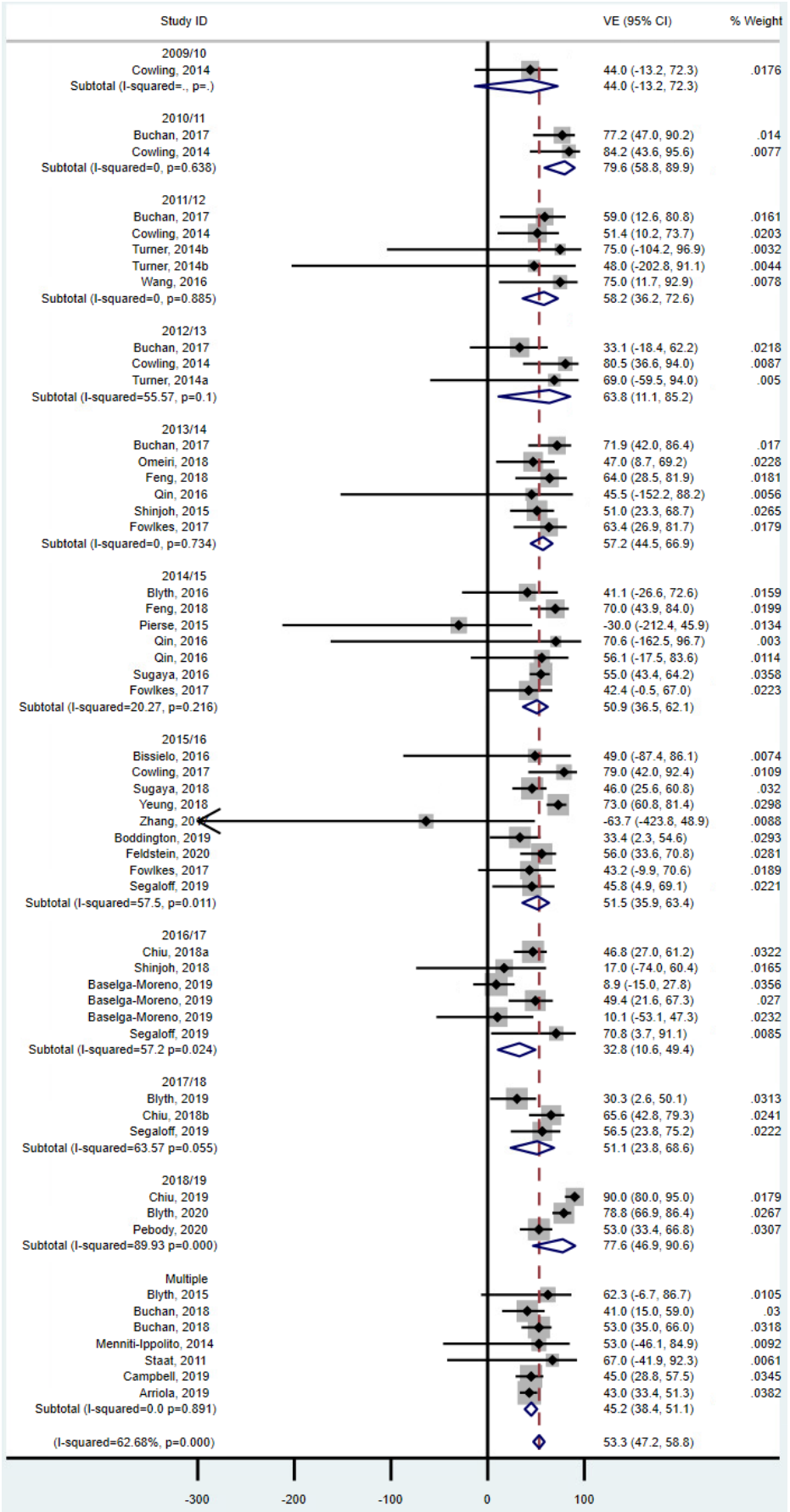

Figure 2: Seasonal influenza vaccine effectiveness against any influenza hospitalisation by season

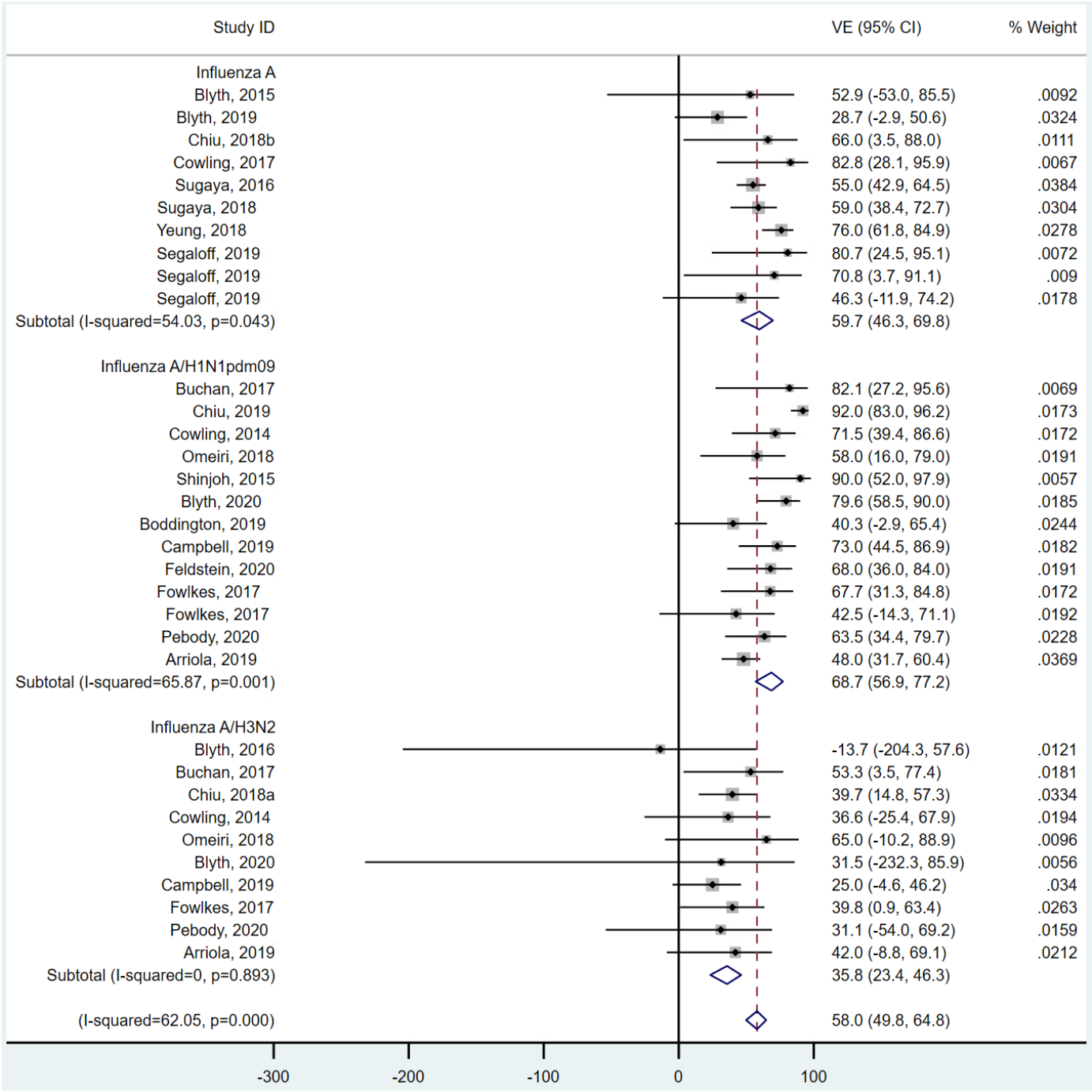

Figure 3: Influenza vaccine effectiveness estimates against hospitalisation by influenza A

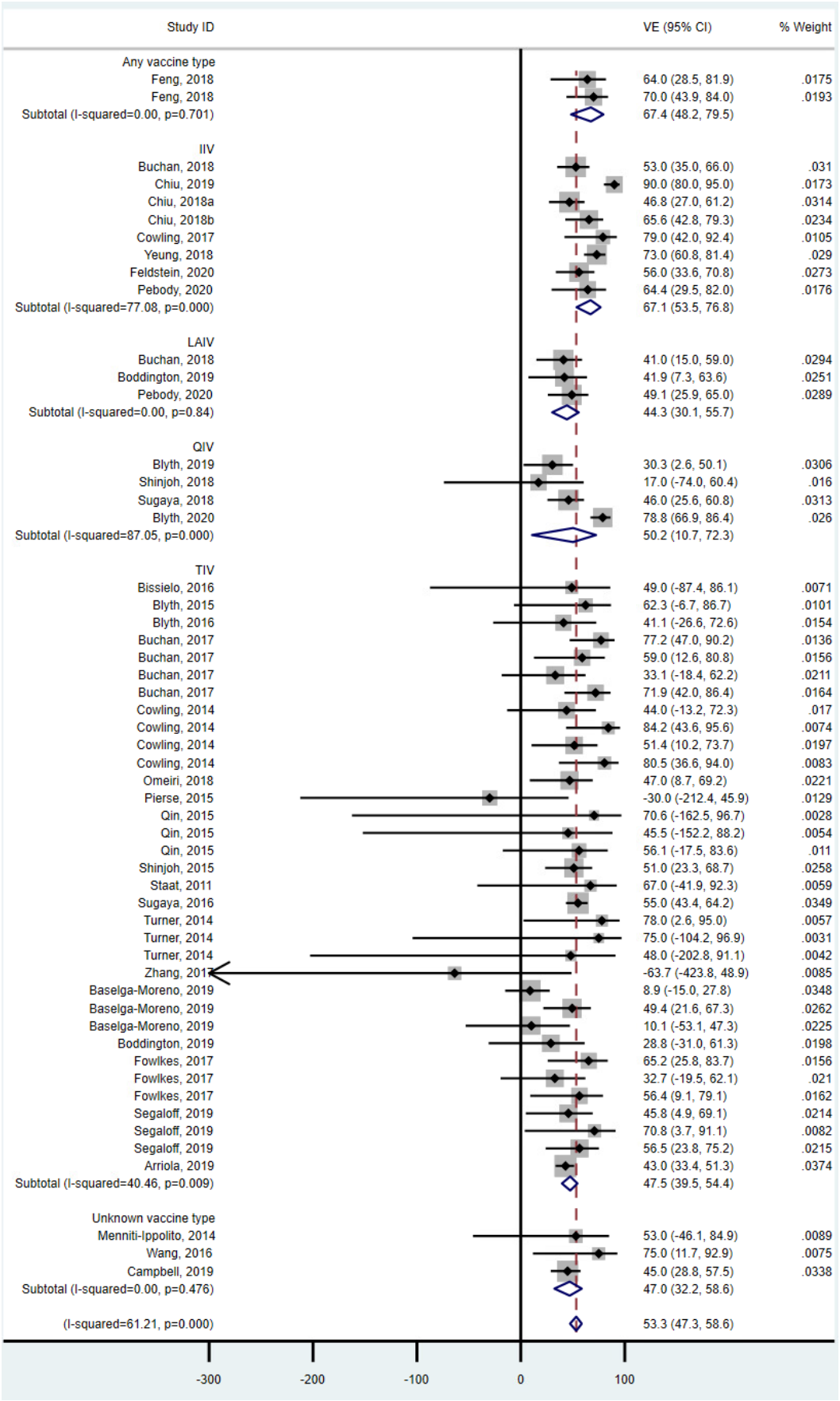

Figure 4: Influenza vaccine effectiveness estimates against hospitalisation by vaccine type

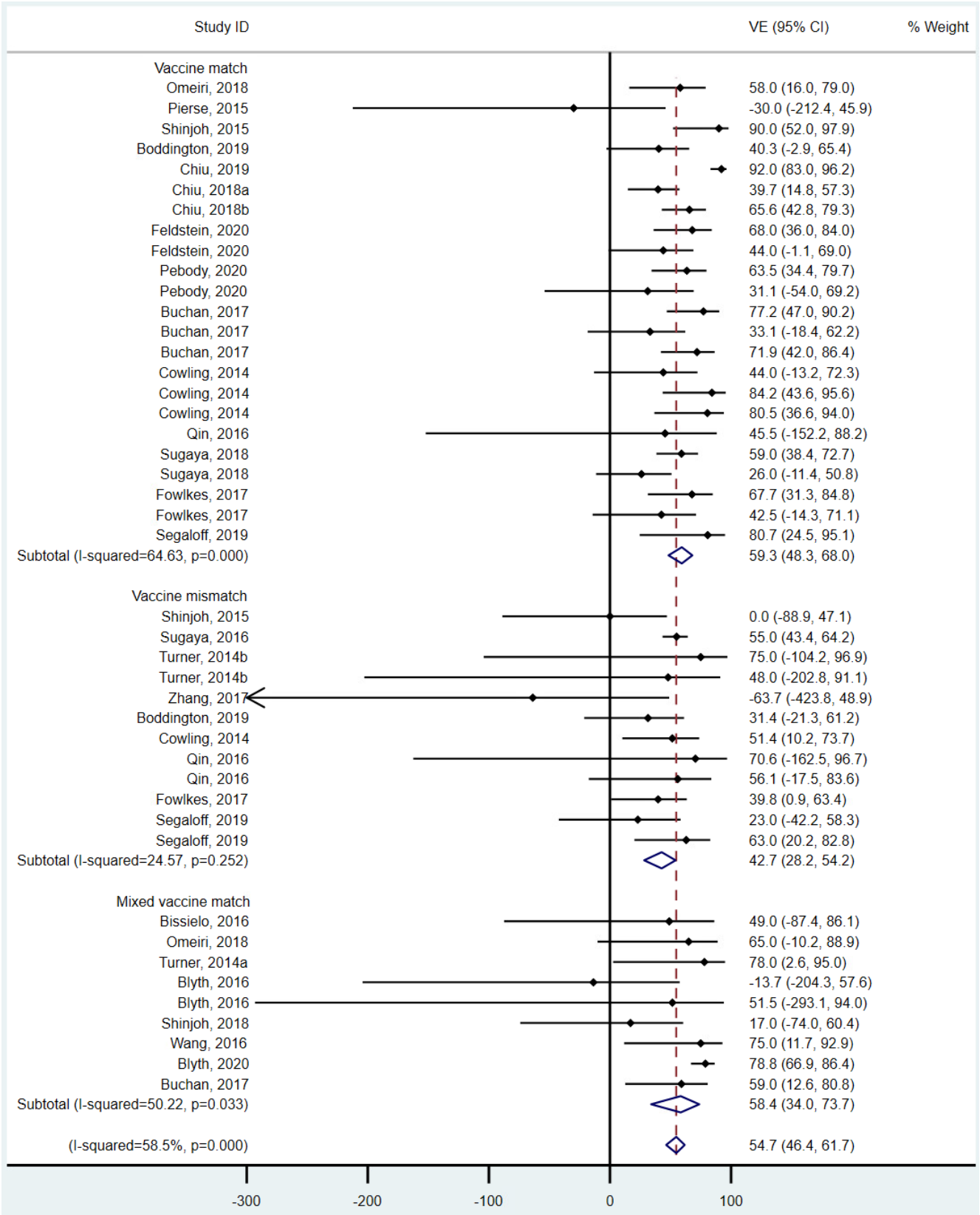

Figure 5: Influenza vaccine effectiveness against hospitalisation in children by vaccine match