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Review

Influenza vaccine effectiveness against influenza-associated hospitalization in children: A systematic review and meta-analysis

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ABSTRACT

Vaccination remains the most effective way to prevent influenza infection, albeit vaccine effectiveness (VE) varies by year. Compared to other age groups, children and elderly adults have the highest risk of developing influenza-related complications and requiring hospitalization. During the last years, "test negative design" (TND) studies have been implemented in order to estimate influenza VE. The aim of this systematic review and meta-analysis was to summarize the findings of TND studies reporting influenza VE against laboratory-confirmed influenza-related hospitalization in children aged 6 months to 17 years. We searched the PubMed and Embase databases and identified 2615 non-duplicate studies that required detailed review. Among them, 28 met our inclusion criteria and we performed a random-effects meta-analysis using adjusted VE estimates. In our primary analysis, influenza vaccine offered significant protection against any type influenza-related hospitalization (57.48%; 95% CI 49.46–65.49). When we examined influenza VE per type and strain, VE was higher against H1N1 (74.07%; 95% CI: 54.85–93.30) and influenza B (50.87%; 95% CI: 41.75–59.98), and moderate against H3N2 (40.77%; 95% CI: 25.65–55.89). Notably, influenza vaccination offered higher protection in children who were fully vaccinated (61.79%; 95% CI: 54.45–69.13), compared to those who were partially vaccinated (33.91%; 95% CI: 21.12 – 46.69). Also, influenza VE was high in children less than 5 years old (61.71%; 95% CI: 49.29–74.12) as well as in children 6–17 years old (54.37%; 95% CI: 35.14–73.60). In conclusion, in the pediatric population, influenza vaccination offered significant protection against influenza-related hospitalization and complete annual vaccination should be encouraged.

Contents

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1. Introduction

Influenza infection remains a major health burden for both adult and pediatric population. According to World Health Organization, there are an estimated 1 billion cases, of which 3 to 5 million are severe, resulting in 290,000–650,000 influenza-related respiratory deaths annually [1]. Compared to other age groups, children often face the greatest risk of influenza infection [2], while they also play a crucial role in introducing and spreading influenza virus in households and the community [3]. Of note, children younger than 5 years old, and particularly those younger than 2 years old, are at high risk of developing serious influenza-associated complications, including death and hospitalization [4]. Since 2010, CDC estimates that flu-related hospitalizations among children younger than 5 years ranged from 7000 to 26,000 [5].

Vaccination remains the most effective method to prevent influenza infection [6], albeit effectiveness may vary by season due to antigenic variability of seasonal influenza viruses and the degree of matching between influenza vaccine strains and circulating strains [7]. In this regard, assessments of influenza vaccine effectiveness (VE) by influenza surveillance networks around the globe provide useful information to public health policy makers and evaluate the impact of vaccination programs. During the recent years, a special type of case-control study, named "test-negative study design" (TND), has been increasingly used as the preferred method to report influenza VE [8,9]. Patients presenting with influenza-like illness are enrolled if they meet predetermined inclusion criteria and are then laboratory tested for influenza. Those who are laboratory confirmed with influenza infection serve as cases and those who test negative serve as controls [8,9].

Most commonly, TND studies are conducted in the ambulatory setting, and a meta-analysis by Belogna et al. yielded that influenza vaccination offers moderate protection against medically attended influenza in the pediatric population (56% against influenza B, 43% against H3N2 and 69% against H1N1) [10]. However, TND studies are increasingly implemented with inpatients as well, and their results seem to be representative of the protection against influenza-associated hospitalization [11]. A recent meta-analysis by Rondy et al. reported that influenza vaccination offered moderate protection against influenza-associated hospitalization in adults, with VE against any influenza type estimated at 41% (95% CI: 34–48) [12]. However, in the pediatric population, vaccination protocols as well as the disease impact is different than in adults and data cannot be extrapolated. Since there is no similar analysis that focuses on this population, in this study, we performed a meta-analysis of TND studies reporting influenza VE against influenza-associated hospitalizations in the pediatric population.

2. Methods

We performed this systematic review and meta-analysis in line with MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [13] and the complete checklist of reporting criteria can be found on Table S3.

2.1. Search strategy

We searched the PubMed and Embase databases from January 1st 2005 to November 15th 2019. We selected January 1st 2005 as our initial search date, since it has been previously reported [10] that the first study which utilized TND to estimate influenza vaccine effectiveness was published in 2005 [14]. For our literature search we used the following search term: (influenza OR flu) AND (vaccine OR vaccination) AND effectiveness AND (hospitalization OR hospitalisation).

2.2. Study selection

Two authors (MK and CDA) reviewed the titles and abstracts of all potentially eligible studies. Studies were considered eligible for inclusion if they met all of the following criteria: (i) used a TND to estimate vaccine effectiveness, (ii) contained data of hospitalized children, (iii) influenza infection was laboratory confirmed (no method restriction was imposed). We excluded the following studies: (i) studies conducted in an outpatient setting, (ii) studies containing exclusively adult data (or mixed pediatric and adult data that were not reported separately), (iii) interim reports superseded by a final report, (iv) studies using other design to report vaccine effectiveness, (v) studies published in languages other than English, (vi) studies assessing influenza VE against intensive care unit admission.

2.3. Outcomes of interest

Our primary outcome of interest was the effectiveness of influenza vaccine against laboratory confirmed influenza hospitalization in children, computed separately by influenza type (any type, H1N1pmd09, H3N2, Influenza B) and children age group (children younger children than 5 years old and children aged 6–17 years old). Our age sub classification was based on the fact that children younger than 5 years old, and especially those under 2 years old, are at higher risk for influenza complications, including hospitalization [4]. As secondary outcome we sought for the effectiveness of partial versus full vaccination against influenza hospitalization.

2.4. Data extraction and quality assessment

Screening, evaluation and data extraction from eligible studies was performed independently by two authors (MK and CDA). Discrepancies were resolved by a third reviewer (EM) and consensus. For each of the included studies the following information were extracted: author and publication year, study period, country and region, patient age group, clinical inclusion criteria, influenza

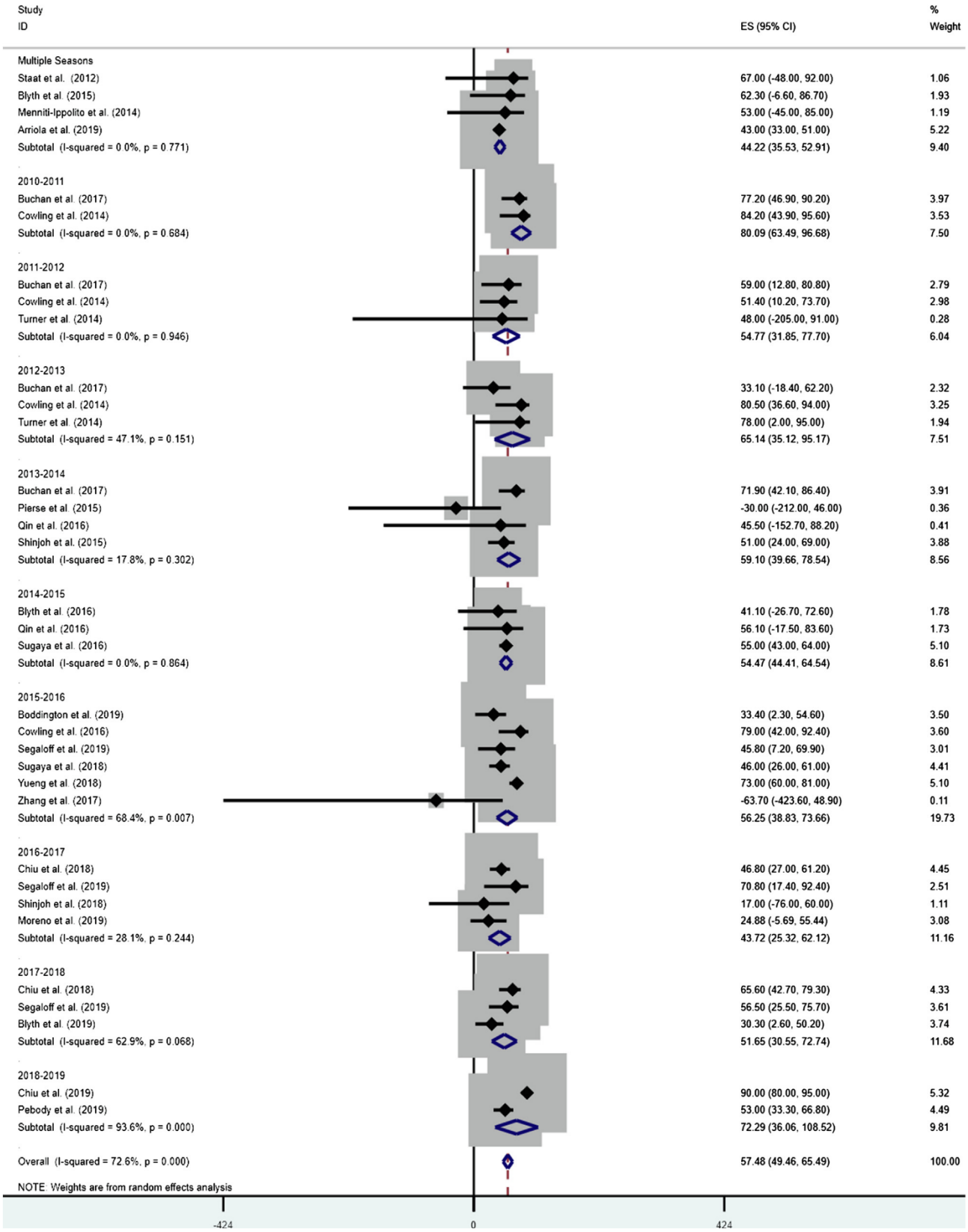

Fig. 1. Seasonal influenza vaccine effectiveness against any influenza hospitalization.

diagnostic test(s) used, vaccination ascertainment method, maximum days from symptoms onset to swab, vaccine type, the adjustment and matching variables used in each study, and the adjusted influenza vaccine effectiveness estimates of interest.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies [15]. The NOS is a star-based system and each study can receive a maximum of 9 stars (highest quality). Each study is judged based on three main domains: the selection of

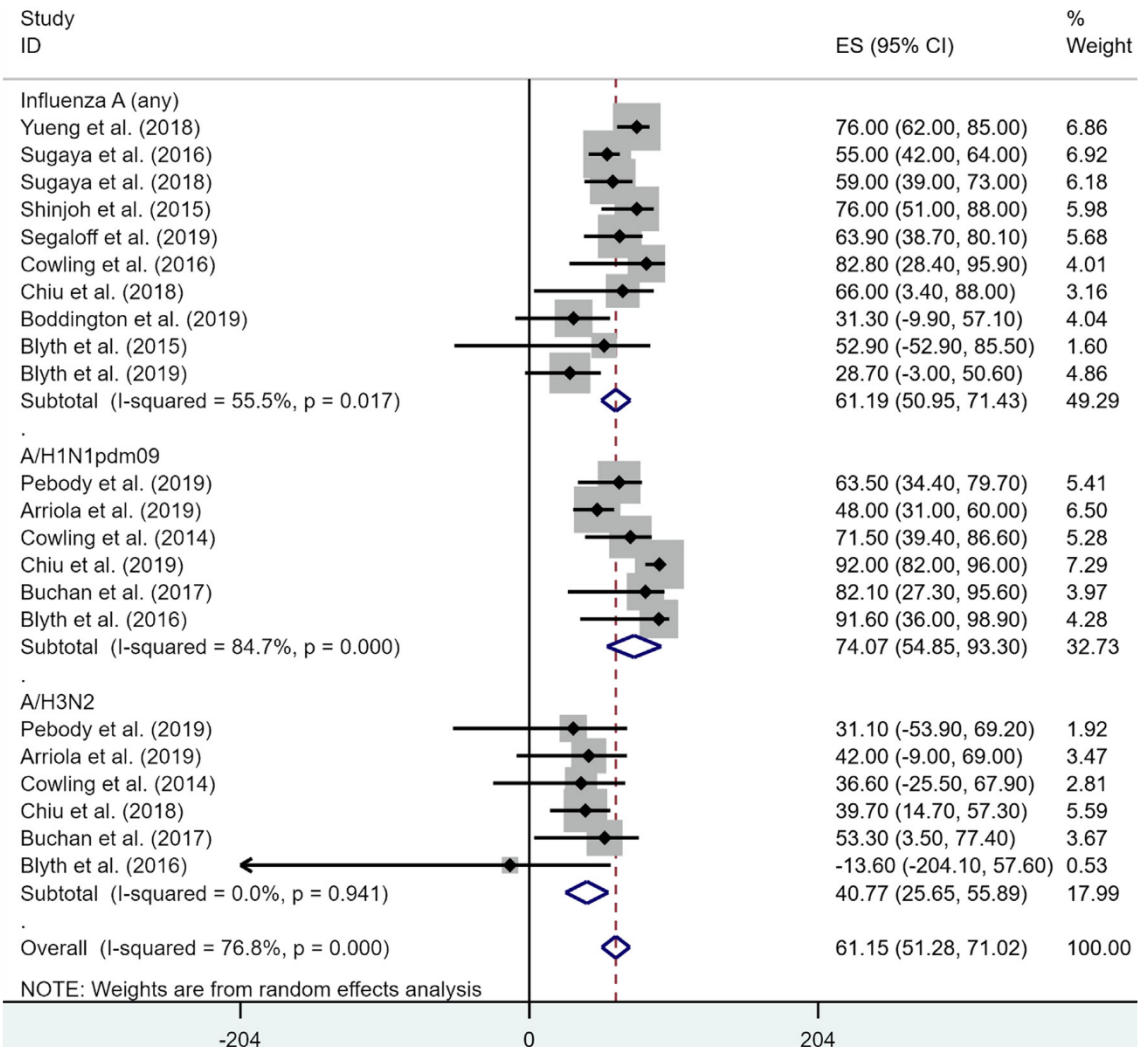

Fig. 2. Influenza vaccine effectiveness against type A influenza hospitalization.

the study groups (maximum 4 stars), the comparability of the study groups (maximum 2 stars), and the ascertainment of exposure or outcome of interest (maximum 3 stars).

2.5. Data synthesis and analysis

We grouped the included studies by influenza season and performed a random effects meta-analysis to estimate the effectiveness of the influenza vaccine against any type influenza-related hospitalization in children, using the DerSimonian and Laird approach [16]. Vaccine effectiveness estimates from the southern hemisphere, were grouped with those from the following northern hemisphere season. The Freeman Tukey double arcsine transformation was used to stabilize the variances [17]. We selected a random effects model, because we assumed that the effects are heterogeneous due to differences in the study settings, the parameters affecting influenza vaccination, and the vaccine effectiveness among different seasons.

For our secondary analyses, we stratified our data by influenza type (type A, type B), children age group (less than 5 years old, 6–17 years old) and vaccination status (partially vaccinated, fully vaccinated). A random effects meta-analysis was carried out in each group. If provided by study authors, influenza type A was further sub-grouped by strain (H1N1pdm09, H3N2), influenza type B by vaccine type used (trivalent, quadrivalent), and children less than 5 years old by specific age sub-groups (6mo–23mo, 24mo–59mo). Finally, if a study contained multiple estimates for the same sub-group (for example influenza VE in ages 6mo–11mo and 12mo–23mo), a combined random-effects estimate was calculated using the DerSimonian and Laird approach [16].

We assessed the heterogeneity among studies and subgroups using the I^2 statistic [18]. The Egger's test was used to explore publication bias and small study effects [19]. Stata v15 (Stata Corporation, College Station, TX) was used to perform the statistical analysis. The statistical significance threshold was set at 0.05.

3. Results

In our literature search, and after removing duplicate records, we accessed the titles and abstracts of 3202 studies. Among them, we identified potentially 87 eligible studies that we accessed for full text review. Ultimately, 28 studies fulfilled our inclusion criteria and were included in our analysis (Table S1). The detailed inclusion process is depicted in the selection flow diagram (Fig. S1).

Study characteristics are depicted on Table S1. All studies had a TND study design, and provided pediatric hospitalization data. The publication year of these studies ranged from 2012 to 2019, while the study years ranged from 2005 to 2019. Among the 28 included studies, 14 were from Asia [20–33], 6 from Australasia (3 from

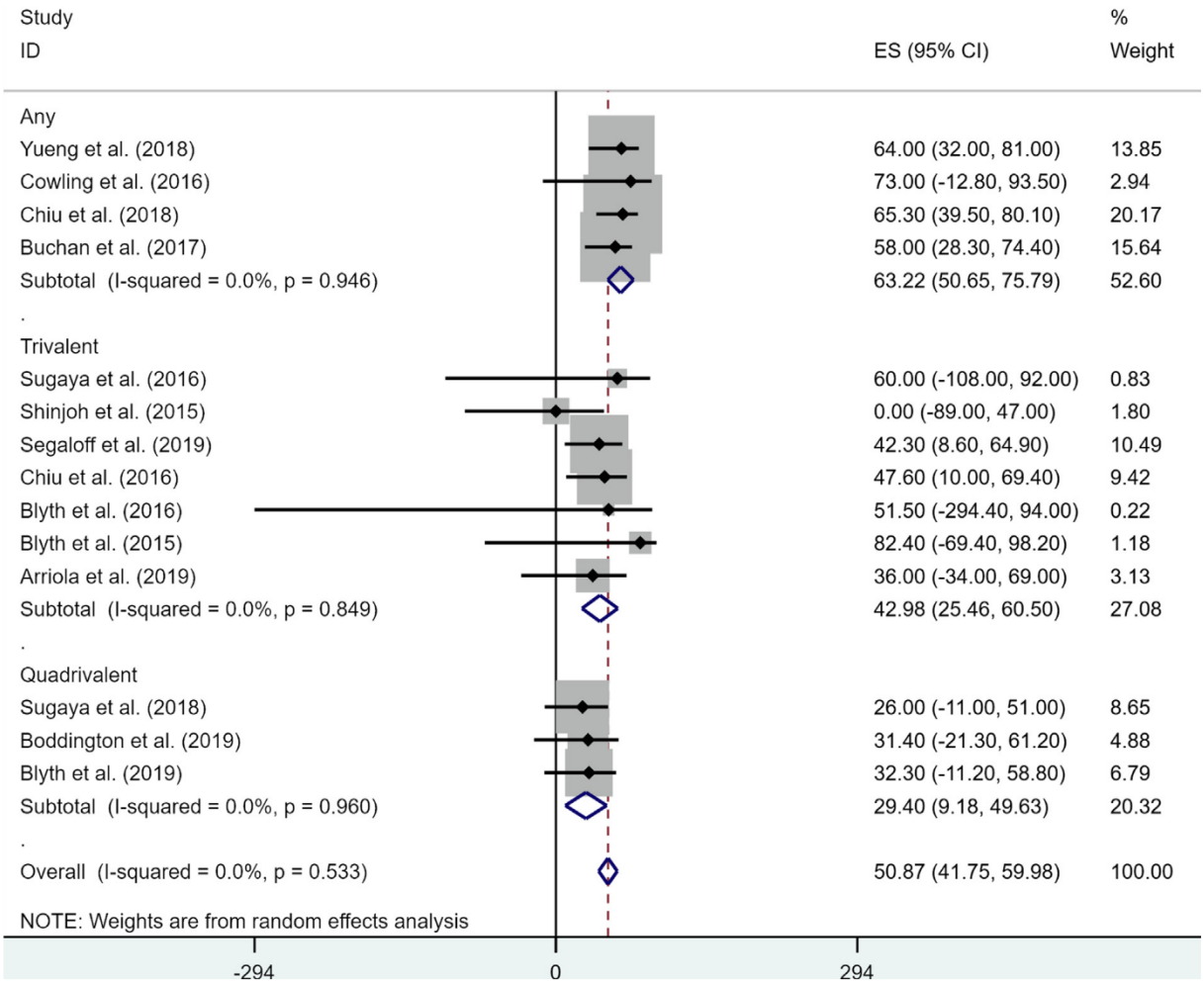

Fig. 3. Influenza vaccine effectiveness against type B influenza hospitalization.

Australia [34–36] and 3 from New Zealand [37–39]), 4 from Europe [40–43], 2 from North America [44,45], 1 from South America [46] and 1 was global (with data from 13 sites around the world) [47].

During the data extraction process, we came upon two problems which were resolved upon discussion between authors. First, we identified that studies from the same influenza surveillance networks provided reports with overlapping time periods. Thus, there was a possibility of extracting overlapping patient data. Our consensus was to first extract the non-overlapping unique data as provided by each study. Then, for studies with overlapping time periods we extracted data only from the study which provided the highest amount of information possible based on the number of patients. The second issue was the variable definition of "vaccinated" children among studies. Some authors calculated their VE estimates considering as vaccinated the children who received at least one vaccination dose for a given influenza season (and thus included both fully or partially vaccinated children), while other studies calculated VE estimates considering as vaccinated only the children who were in line with the recommended vaccination schedule (only fully vaccinated children). For those studies, our consensus was to use VE as provided by each study author. However, 4 studies [32,34,35,44] provided two separate influenza VE estimates based on different vaccination status (one estimate inclusive of only fully vaccinated children and another estimate inclusive of either fully or partially vaccinated children). For these studies our consensus was to utilize the estimates from children who were vaccinated appropriately for their age and influenza vaccination history (fully vaccinated).

3.1. Estimates of overall influenza vaccine effectiveness against hospitalization

Twenty-five studies provided influenza VE against any type of influenza associated hospitalization (Fig. 1). These studies provided seasonal estimates from 2005 to 2019. Among them, 4 studies [34,41,45,46] provided pooled estimates of IVE over multiple seasons. Over the years the overall IVE against pediatric hospitalization was 57.48% (95% CI 49.46–65.49), with moderate study heterogeneity (I^2 = 72.6% p less than 0.01). In a subgroup analysis per season, the lowest estimate was seen in the 2016–2017 season, with influenza VE being 43.72% (95% CI 25.32–62.12), while the highest estimate was for the season 2018–2019 with VE being 72.29% (95% CI 36.06–108.52). However, there were only 2 observations available for the 2018–2019 season and 1 of them was an interim report [21].

3.2. Estimates of influenza vaccine effectiveness per type and strain

Sixteen studies reported estimates of IVE against Influenza A hospitalization (Fig. 2). Of those, 6 did subclassify by influenza A strain (H1Npdm09 and H3N2) [21,25,35,42,44,46]. Overall, IVE

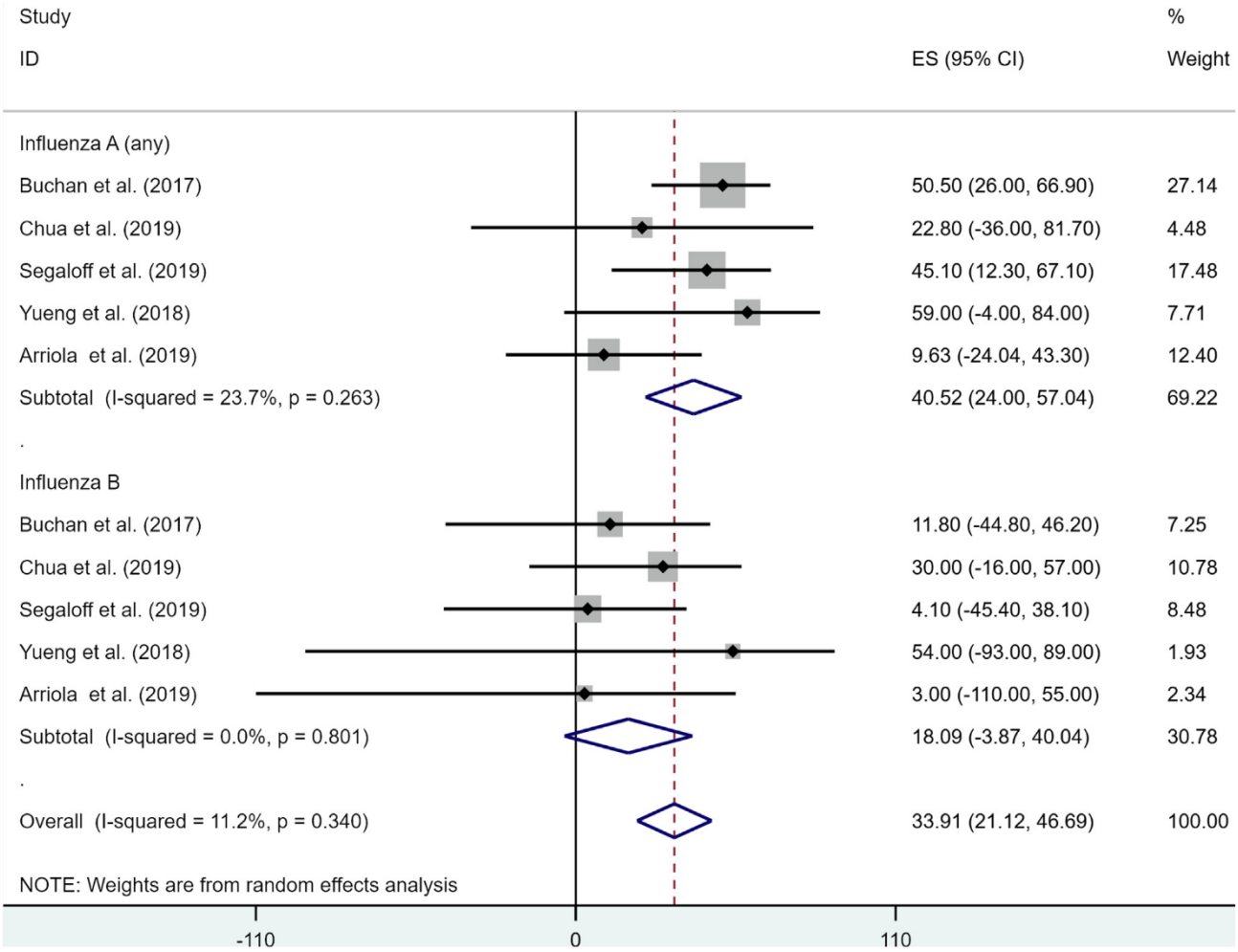

Fig. 4. Influenza vaccine effectiveness against influenza hospitalization in partially vaccinated children.

against influenza A hospitalization was 61.15% (95% CI: 51.28–71.02). In a subgroup analysis of studies providing specific IVE estimates per influenza A subtype, influenza VE against H1N1pmd09 and H3N2 were 74.07% (95% CI: 54.85–93.30) and 40.77% (95% CI: 25.65–55.89), respectively.

Thirteen studies reported estimates of IVE against influenza B hospitalization with the pooled VE estimate being 50.87% (95% CI: 41.75–59.98) (Fig. 3). In a subgroup analysis based on the different vaccine type, we did not find any significant VE difference between the quadrivalent 29.40% (95% CI: 9.18–49.63) and the trivalent vaccine 42.98% (95% CI: 25.46–60.50), despite the additional lineage coverage that quadrivalent vaccines provide. However, only 3 studies provided quadrivalent VE estimates [31,36,40].

3.3. The effect of partial versus full vaccination

Five studies compared the effectiveness of partial versus full vaccination in children [24,32,43,44,46]. Of note, not all of them used the same definition, since they were conducted during different time periods and guidelines were different. All studies categorized children who received 2 doses in the current season (at least 4 weeks apart and >14 days before admission) as fully vaccinated. Arriola et al. [46] utilized only the aforementioned definition, because only vaccine naïve children were assessed. Three studies [24,32,44] accepted additionally as fully vaccinated children who received 1 dose in the current season and at least 1 dose in any prior season, while Segaloff et al. [43] required 1 dose in the current season and at least 2 doses in the prior seasons as an alternative definition to full vaccination.

For partially vaccinated children, IVE against any influenza hospitalization was 33.91% (95% CI: 21.12–46.69) (Fig. 4), while in a subgroup analysis by influenza type, VE against influenza A hospitalization was 40.52% (95% CI: 24.00–57.04) and against influenza B 18.09% (95% CI: −3.87–40.04). Of note, when we compared partial vaccination estimates to those from fully vaccinated children, point estimates were higher and statistically significant difference in the "influenza B" and "overall" categories. More specifically, in fully vaccinated children IVE against any influenza type was 61.79% (95% CI: 54.45–69.13), against influenza A 63.21% (95% CI: 50.87–75.55), and against influenza B 62.36% (95% CI: 54.50–70.22) (Fig. 5).

3.4. Estimates of vaccine effectiveness by age

Eight studies [24,27,33,38,43–46] reported estimates of VE against influenza associated hospitalization in children 6 months to 5 years old and the pooled VE estimate was 61.71% (95% CI: 49.29–74.12). When we further sub-grouped by age, influenza VE against hospitalization was 54.40% (95% CI: 33.37–75.43) in children 6 months to 2 years old (Fig. 6), and 73.14% (95% CI: 67.53–78.76) in children 2–5 years old (Fig. 6). Also, based on 5 studies [22,25–27,38], influenza VE against hospitalization in children 6–17 years was 54.37% (95% CI: 35.14–73.60) (Fig. S2).

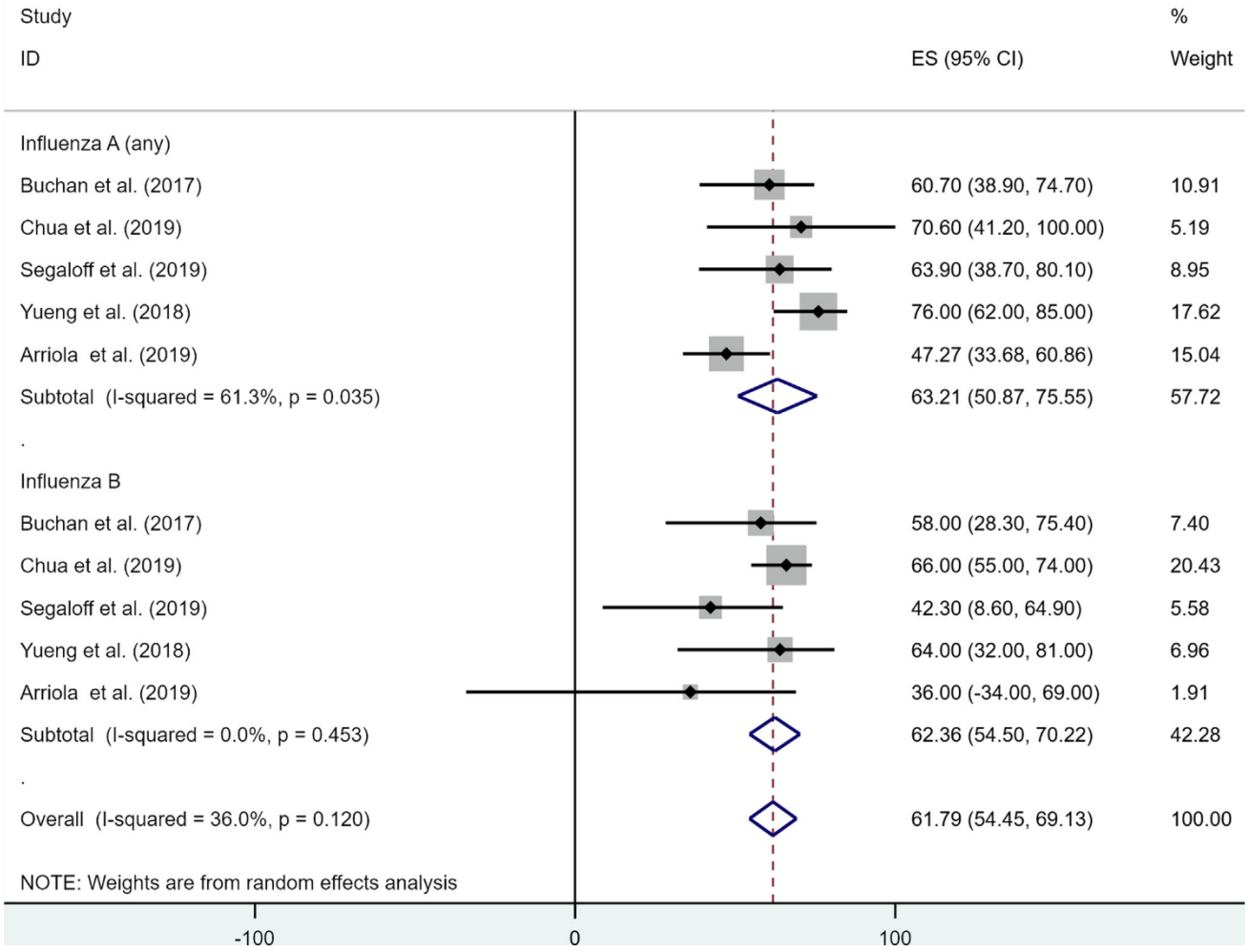

Fig. 5. Influenza vaccine effectiveness against influenza hospitalization in fully vaccinated children.

3.5. Quality assessment and bias

We utilized the Newcastle-Ottawa scale to assess included studies quality. All but one [41] of the included studies were deemed of high quality (8 or 9 stars). Due to quality concerns we ran the analysis with and without the study by Menniti-Ippolito et al. [41]. However, no significant differences were noted (Fig. S3). The most common reason for deducting a star was the vaccination ascertainment method, which was inadequate in 12 out of 28 studies. Cases and controls were comparable in all studies. Age, calendar week, region and the presence of other comorbidities were the most common adjustment/matching variables (Table S1). The detailed quality assessment of included studies can be found on Table S2. Also, Egger's test for publication bias did not detect any evidence of small study effects (bias = −0.15, p = 0.09).

4. Discussion

We report the first meta-analysis that provides pooled estimates of influenza VE against influenza-related hospitalizations in the pediatric population. Overall, we found significant protection against any influenza type (57.5%), while the protection per strain was higher for H1N1 and lower for H3N2 and influenza B. Of note, children who were fully vaccinated according to their immunization schedule, derived the highest benefit from influenza vaccination.

Belongnia et al. found that VE against medically attended influenza in children was 69% (49–81) for H1N1, 43% (28–55) for H3N2, and 56% (38–69) for influenza B [10]. Similarly, in our study influenza VE estimates were 74.1% (95% CI: 54.9–93.3) for H1N1, 40.8% (95% CI: 25.7–55.9) for H3N2 and 50.9% (95% CI: 41.8–60) for influenza B. Although it has been previously reported that influenza vaccination may modify influenza disease severity [48], we did not yield higher influenza VE estimates for the inpatient setting. Also, despite the additional data from recent influenza seasons in our meta-analysis, there was significant overlap of influenza seasons (2010–2015) between the studies included in our analysis and those included in the analysis by Belongnia et al. [10]. Thus, results concordance may support the view that inpatient and outpatient influenza VE estimates tend to produce similar estimates [49]. However, these findings need to be investigated further, ideally within the same population and during the same influenza seasons.

Compared to a similar design inpatient meta-analysis in adults [12], we found that influenza vaccine offered significantly higher protection against influenza-related hospitalization in the pediatric population. Rondy et al. [12] found that influenza VE against any influenza hospitalization in adults was 41% (95% CI: 34–48), while we found influenza VE to be 57.5% (95% CI: 49.4–65.4). However, when the authors reported their estimates separately for younger adults (less than 65 y.o), VE was 51% against any type influenza hospitalization, 55% against H1N1, 50% against H3N2, and 45% against influenza B. All of those estimates overlapped with

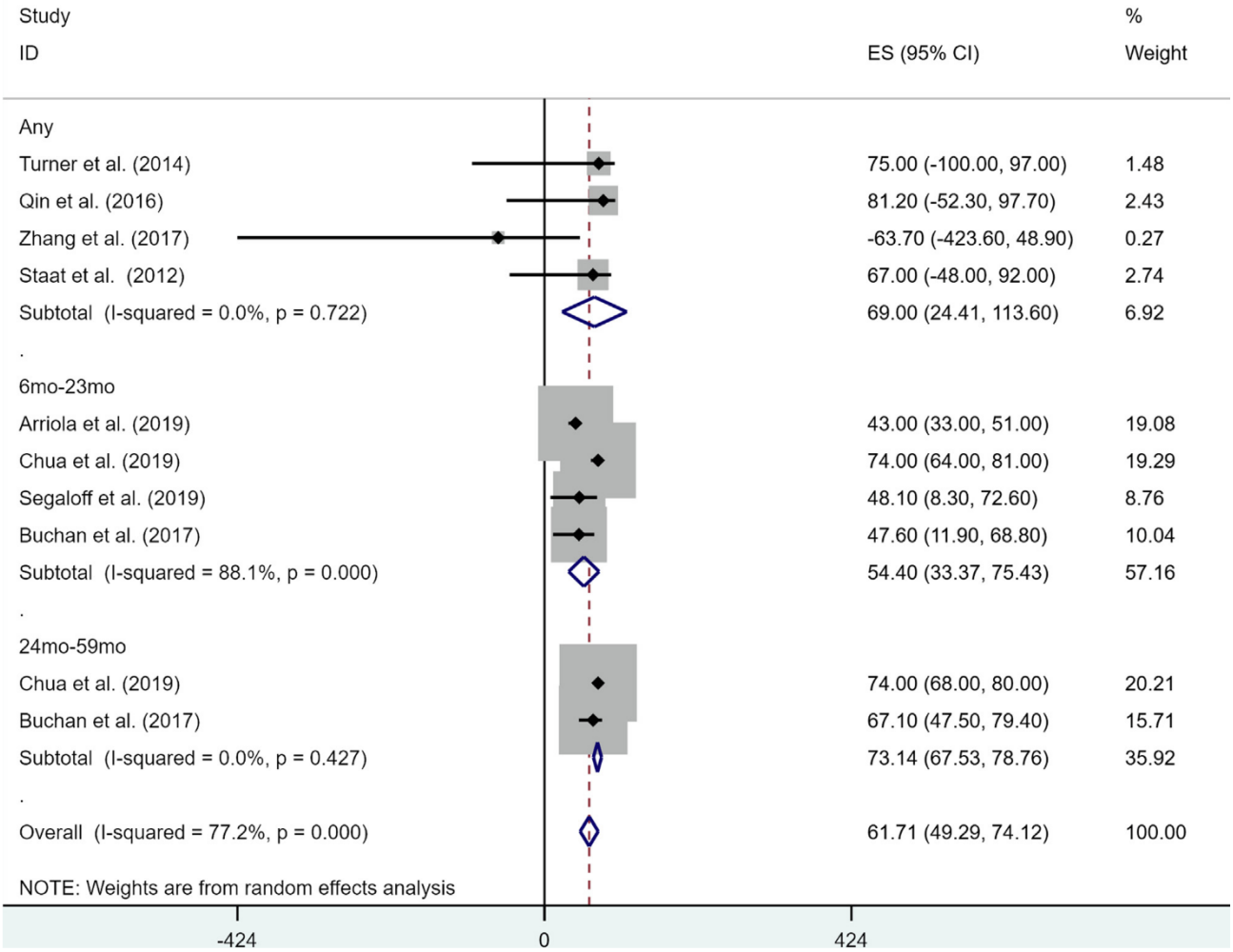

Fig. 6. Influenza vaccine effectiveness against any influenza hospitalization in children 6 months to 5 years old.

our pooled estimates, implying that influenza VE against influenza-related hospitalization may be comparable among children and younger adults (18–65 years old), but higher in children when compared to older adults (>65 years old).

Vaccine effectiveness estimates against influenza type A hospitalization, yielded significant overall protection (61.2%) with higher protection against H1N1 hospitalization (74.1%) and lower against H3N2 (40.8%). Our findings are in concordance with previous reports from the outpatient setting, which demonstrated high influenza VE against the pandemic H1N1 strain [10,50], with the exception of lower H1N1 VE estimates for live attenuated vaccines (LAIV) [50]. However, our estimates are more representative of the inactivated influenza vaccine (IIV) (5 out of 6 studies reporting VE against H1N1 used an IIV, and one study [42] used both IIV and LAIV). Additionally, although vaccination offered significant protection against H3N2 pediatric related hospitalizations, our findings confirm the view that in the post pandemic era, influenza VE against H3N2 is consistently lower compared to H1N1 and influenza B [51]. Factors such as viral antigenic drift [51,52], egg-induced mutations that may affect H3N2 vaccine strain during the manufacturing process [51–54], and greater intra-seasonal waning of influenza VE against H3N2 [52,55] have been identified as a possible reasons. In this regard, the role of non–egg-based vaccines remain to be determined, while the optimal influenza vaccination timing and dosing could also play a role [22].

In our analysis of influenza VE against influenza B hospitalization, vaccination offered significant protection (50.9%). Such findings are important because the burden of influenza B is significant [56–58] and influenza B infection can be associated with severe complications in the pediatric population [59,60]. For example, when Tran et al. studied children hospitalized with influenza, mortality was significantly higher in children with influenza B, compared to those with influenza A (adjusted OR 2.65) [61]. Notably, when we compared pooled quadrivalent and trivalent influenza VE estimates, we found no difference in terms of protection against influenza B hospitalization, despite the broader influenza B coverage provided by the quadrivalent vaccines. However, this finding should be further assessed in future studies, since it might be a result of the relatively small number of studies included in this sub-analysis. Of note, and in contrast with our findings, a recent phase 3 randomized study in children and adolescents, which compared quadrivalent and trivalent IIV, elicited a similar response for shared influenza stains but a superior response for quadrivalent IIV against alternate-linage B strains. [62].

The Advisory Committee on Immunization Practices (ACIP) recommends that children aged 6 months to 8 years may need up to 2 doses to be considered fully vaccinated, depending on the total doses of influenza vaccination received in previous influenza seasons [63]. Our results are in line with ACIP recommendations and show that full vaccination offers significantly higher protection (61.8%; 95% CI: 54.5–69.1) against any influenza hospitalization when compared to partial vaccination (33.9%; 95% CI: 21.1–46.7). In a sub-analysis based on influenza type, full vaccination offered higher VE point estimates compared to partial vaccination

regardless of the influenza type, albeit the difference was statistically significant only against influenza B. Also, our findings are in agreement with previous studies examining the potential benefit of full vaccination in the outpatient setting [45,64–66]. Despite the existing evidence, two-dose vaccine uptake remains suboptimal and efforts to increase compliance should be made [67,68].

Children younger than 5 years old are at higher risk of developing influenza complications, including hospitalization and death. Notably, our analysis yielded that influenza vaccine offered significant protection (61.7%) against any type influenza-associated hospitalization in this age group. Even in a sub-analysis of children <2 years old, which are at the greatest risk for influenza complications [5], vaccination offered significant protection against hospitalization (54.4%). Such results underline the significance of vaccinating this population, and the need for more effective vaccination strategies [69] and communication of correct information towards parents, who often remain unconvinced of influenza vaccination benefits [70].

Evaluating our study, a number of limitations should be considered. First, we could not assess the comparability of populations pooled in this meta-analysis, including their access to vaccination and healthcare. Second, additional limitations arise from the variability of vaccination ascertainment methods, the different clinical inclusion criteria and the inconsistent definitions for full and partial vaccination that were used among studies. Furthermore, we did not adjust for the effect of matching between influenza vaccine strain and the vaccines used at that season and we neither examined the effect of repeated vaccination. Finally there are limitations inherent to TND studies, including the inability of TND to completely eliminate selection bias, the potential lack of generalizability to the general population (since data are gathered only for patients with acute respiratory infection symptoms who seek healthcare), and the variability of assessed confounders across different studies which may complicate interpretation of pooled VE estimates [9,71,72]. However, by utilizing only TND studies and assessing for the same outcome (effectiveness against influenza hospitalization) we tried to reduce qualitative heterogeneity.

5. Conclusion

To the best of our knowledge, we report the first meta-analysis to systematically assess influenza VE against laboratory confirmed influenza hospitalization in children to date. Based on inpatient pediatric TND studies, our analysis yielded that influenza vaccination offered significant protection against any type influenza-related pediatric hospitalization. Influenza VE was higher against H1N1 and influenza B and moderate against H3N2. Our findings confirm the importance of full vaccination strategy in this pediatric population, while they also underline the significant protection that influenza vaccine offers to children younger than 5 years old, an age group at high risk for influenza related complications such as hospitalization.

CRediT authorship contribution statement

Markos Kalligeros: Conceptualization, Investigation, Methodology, Writing - original draft, Formal analysis, Writing - review & editing, Visualization. **Fadi Shehadeh:** Methodology, Writing - original draft, Software, Formal analysis, Validation. **Evangelia K. Mylona:** Investigation, Formal analysis, Validation. **Christine Dapaah-Afriyie:** Investigation, Writing - review & editing. **Robertus van Aalst:** Conceptualization, Writing - review & editing. **Ayman Chit:** Conceptualization, Writing - review & editing. **Eleftherios Mylonakis:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EM has received research funding from Sanofi-Pasteur. RVA and AC are employees of Sanofi Pasteur. MK, FS, EKM and CDA declare that they have no known competing interests. All authors attest they meet the ICMJE criteria for authorship.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.02.049.

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