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Review

Effectiveness of 2009 pandemic influenza A(H1N1) vaccines: A systematic review and meta-analysis

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ABSTRACT

Background: The clinical effectiveness of monovalent influenza A(H1N1)pdm09 vaccines has not been comprehensively summarised. We undertook a systematic review and meta-analysis to assess vaccine effectiveness (VE) for adjuvanted and unadjuvanted vaccines.

Methods: We searched healthcare databases and grey literature from 11 June 2009 to 12 November 2014. Two researchers independently assessed titles and abstracts to identify studies for full review. Random effects meta-analyses estimated the pooled effect size of vaccination compared to placebo or no vaccination for crude and adjusted odds ratios (OR) to prevent laboratory confirmed influenza illness (LCI) and related hospitalization. VE was calculated as (1-pooled OR) * 100. Narrative synthesis was undertaken where meta-analysis was not possible.

Results: We identified 9229 studies of which 38 at moderate risk of bias met protocol eligibility criteria; 23 were suitable for meta-analysis. Pooled adjusted VE against LCI with adjuvanted and unadjuvanted vaccines both reached statistical significance (adjuvanted: VE = 80%; 95% confidence interval [CI] 59–90%; unadjuvanted: VE = 66%; 95% CI 47–78%); in planned secondary analyses, VE in adults often failed to reach statistical significance and pooled point estimates were lower than observed in children. Overall pooled adjusted VE against hospitalization was 61% (95% CI 14–82%); in planned secondary analyses, adjusted VE attained statistical significance in adults aged 18–64 years and children for adjuvanted vaccines. Adjuvanted vaccines were significantly more effective in children compared to adults for both outcomes.

Conclusions: Adjuvanted and unadjuvanted monovalent influenza A(H1N1)pdm09 vaccines were both effective in preventing LCI. Overall, the vaccines were also effective against influenza-related hospitalization. For both outcomes adjuvanted vaccines were more effective in children than in adults.

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Contents

Abbreviations: CI, confidence interval; LCI, laboratory-confirmed influenza illness; OR, odds ratio; RT-PCR, reverse-transcriptase polymerase chain reaction.

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1. Background

The first ever global deployment of pandemic influenza vaccines was in response to the influenza A(H1N1) pandemic in 2009–10. Whilst many individual studies have supported the effectiveness of these vaccines in different populations and geographical areas, all have been observational designs and several were underpowered or calculated crude estimates of effectiveness without adjustment for confounding. Two previous systematic reviews and meta-analyses of 2009–10 vaccine against clinical endpoints exist, but were conducted too soon following the pandemic to capture all relevant information [1,2]. Furthermore, Yin et al. did not calculate adjusted pooled estimates and Osterholm et al. did not subject their findings to meta-analysis [1,2]. A third systematic review reported only on serological endpoints [3]. At this point in time it is unlikely that further novel data on the effectiveness of monovalent influenza A(H1N1) pdm09 vaccines will be published.

Comprehensive summaries of the available data are required to inform future public health policies for pandemic vaccine procurement and deployment, and the potential benefits of seasonal influenza vaccination in children. Here we report a systematic review and meta-analysis, which includes a substantial amount of data not included in prior meta-analyses, to assess the efficacy and effectiveness of inactivated monovalent influenza A(H1N1)pdm09 intramuscular vaccines versus placebo or no vaccination to prevent laboratory confirmed influenza illness (LCI), hospitalization and mortality due to infections with the vaccinated strain of influenza. We specified research questions *a priori* to separately estimate these outcomes for adjuvanted and unadjuvanted vaccines [4]. Given the reported potential association between narcolepsy and administration of AS03 adjuvanted monovalent influenza A (H1N1)pdm09 vaccine, our study may inform the discussion regarding risk-to-benefit of immunisation [5–8].

2. Methods

We followed guidance on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9]. The study protocol was registered with the National Institute for Health Research international prospective register of systematic reviews (PROSPERO) [4].

2.1. Definitions and outcomes

We defined the study population as people of all ages, from any setting and included both healthy individuals and those with pre-existing medical conditions. The interventions of interest were vaccination with inactivated adjuvanted or unadjuvanted monovalent intramuscular vaccines, which contained influenza A/California/7/2009 (H1N1)-like virus. We did not include data on live attenuated influenza vaccines (LAIV) or multi-valent preparations which included the pandemic strain. When studies reported using inactivated vaccine and LAIV in different subjects [10–12], we did not include the data on LAIV in meta-analyses. Comparator groups included people who received placebo or who were not vaccinated. Outcome measures were prevention of reverse transcriptase PCR (RT-PCR) or viral culture confirmed influenza A(H1N1)pdm09 illness, hospitalization and mortality. We excluded studies which only evaluated non-specific outcomes such as influenza-like illness or all-cause mortality. We assessed experimental and observational studies and systematic reviews +/− meta-analysis using the eligibility criteria defined in the study protocol [4].

2.2. Search strategy

Healthcare databases and sources of grey literature were searched in November 2014 and April 2016 (no new studies identified) using a pre-specified search strategy considering relevant papers published from June 2009 and pertaining to the influenza A(H1N1)pdm09 pandemic period (11 June 2009 to 10 August 2010) [4] (outlined in Supplementary Material). Two reviewers (LL and SS) independently screened studies for inclusion using a three-stage sifting approach and extracted data using a piloted template (see Supplementary Material), referring to CRB or JSN-V-T for resolution of any discordance.

2.3. Risk of bias assessment

We used the Cochrane Collaboration tool to assess risk of bias in prospective cohort studies, whilst the Newcastle-Ottawa scale was used to critique other eligible observational studies in the three domains of selection of study groups, comparability of the groups

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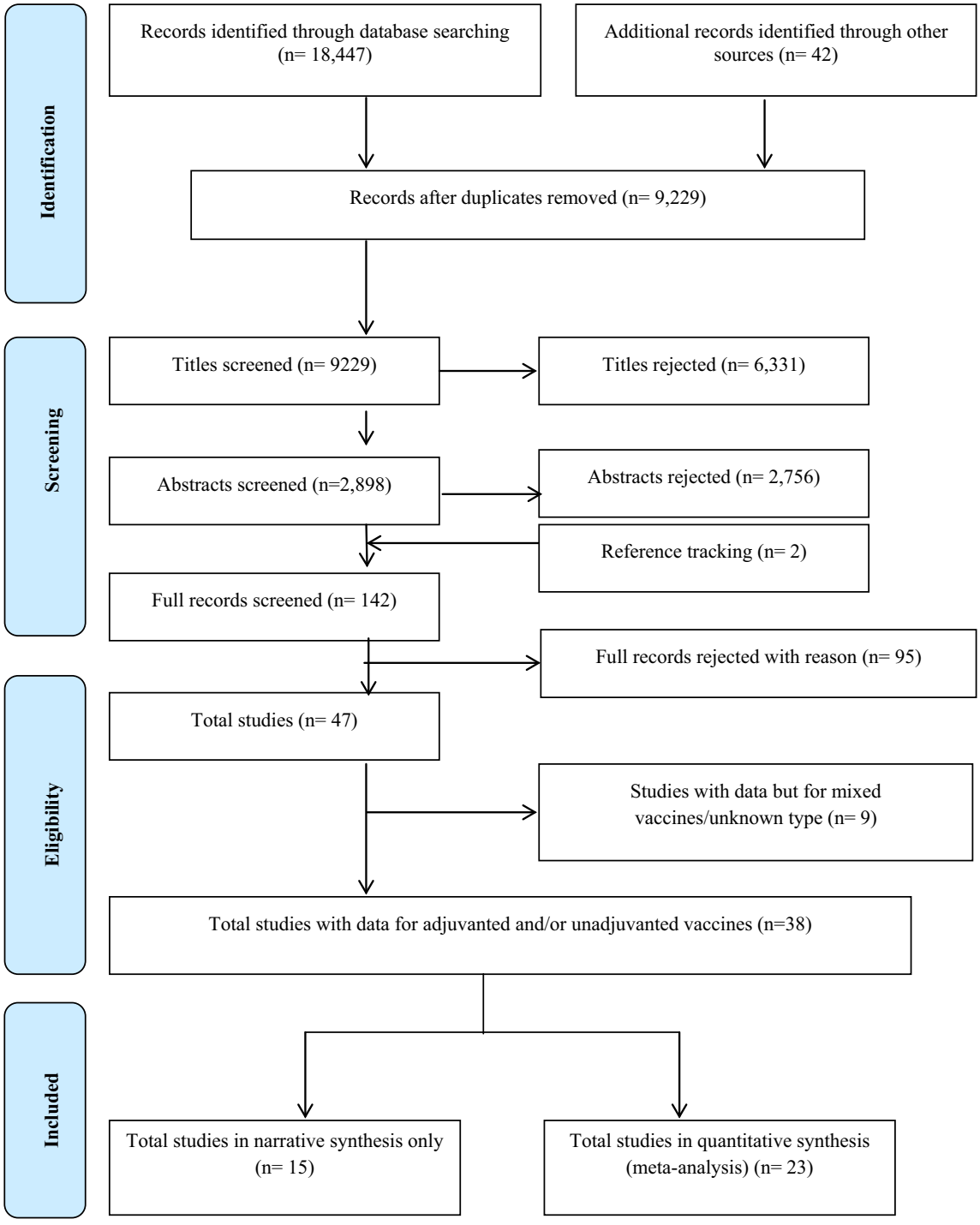

Fig. 1. PRISMA diagram. Details of the literature search and extraction for the systematic review.

and ascertainment of outcome [13,14]. Studies of test-negative design are less prone to bias from misclassification of influenza and health-seeking behaviour than traditional case-control studies, but are susceptible to confounding by calendar time [15], particularly during the pandemic when vaccine distribution occurred concurrently with the second epidemic wave in many countries. Therefore, we specifically sought evidence of adjustment by calendar time in studies of this design. Systematic reviews meeting the eligibility criteria were assessed for risk of bias using the US Agency Healthcare Research Quality domain and element-based evaluation instrument [16].

2.4. Data synthesis

We assessed adjuvanted and unadjuvanted vaccines separately before combining to give overall estimates of effect. We principally sought to analyse outcome measures recorded ≥14 days following immunisation, in order to allow adequate time for seroconversion. Secondary sub-group analyses were planned to study outcomes for clinical risk groups compared to other vaccinated groups, AS03 compared to MF59 adjuvantation, and by age bands (i.e., 0–4, 5–17, 18–64, and ≥65 years). Planned sensitivity analyses included studying outcomes for clinical risk groups, pregnant women,

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healthcare workers, and exploration of potential sources of statistical heterogeneity.

Where appropriate, we estimated the pooled effect size of vaccination by random effects model meta-analysis of crude and adjusted odds ratios (with 95% confidence intervals) for each outcome measure using the generic inverse variance method in Review Manager software version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed using I^2 and meta-analyses were abandoned where $I^2 > 85\%$. The Z test was used to assess if pooled estimates reached statistical significance at the 5% level. Pooled odds ratios were used to estimate vaccine effectiveness based on the formula:

$$VE\ (\%) = (1 - OR) * 100$$

Matched studies, which controlled for confounding variables by design, were pooled with unmatched studies reporting adjusted ORs. We pooled ORs which adjusted for the largest number of potential confounders and pooled unadjusted ORs in separate meta-analyses. We narratively synthesized extracted data not suitable for meta-analyses using a recognized framework [17]. Previous meta-analyses were described but their results were not entered into our *de novo* synthesis in order to avoid double-weighting primary papers included in earlier analyses. Publication bias of studies included in each meta-analysis was assessed through visual inspection of funnel plot symmetry (effect size vs sample size) and statistically using Egger's regression test or Harbord's modified regression test using Stata® software version 14 (StatCorp LP, Texas, USA).

3. Results

After screening 9229 papers (Fig. 1), 38 studies met the inclusion criteria. Characteristics of the included studies are provided in the on-line supplementary materials (Supplementary Table ST1). Data on 7,643,738 individuals from 13 test-negative design [10,18–29] and 10 traditional case control studies [11,12,30–37], four retrospective cohorts [38–41], seven prospective cohorts [42–48], and two screening method studies were included [49,50]. Two systematic reviews met the eligibility criteria [1,2].

No randomized controlled trials or studies which reported vaccine effectiveness against mortality met our eligibility criteria. Secondary analyses by specific risk groups were not possible due to inadequate data and varying definitions across studies.

We preferentially report pooled adjusted ORs where possible; pooled unadjusted ORs are shown in the online supplementary tables.

3.1. Risk of bias

One systematic review was at moderate or high risk of bias across most domains [2], whilst the second was at moderate or low risk (on-line supplementary figure (SF1) [1]. For the seven prospective cohort studies, most were at high or unclear risk of bias because of demographic differences between the vaccinated and unvaccinated cohorts and lack of information about non-participants (on-line supplementary figure SF2) [42–48]. Nine of 29 outcomes (31%) from 27 case-control and retrospective cohort studies were at moderate risk of selection bias [11,12,21,30,32,40,41,49,50]. Since baseline serological assessment was not undertaken in any of the studies, the inclusion of controls potentially previously infected with influenza A(H1N1)pdm09 is a possible source of bias. The inherent lack of randomization in observational studies increases the risk of selection bias. For 86% of outcomes, cases and non-cases were comparable on the basis of study design or analysis accounting for important potential confounding variables Three studies were at unclear risk of bias for comparability of participant groups [31,49,50], and seven were at high or very high risk of reporting bias (on-line supplementary figure SF3) [30–32,35–37,41]. Two studies were not assessed due to insufficient data [20,34]. Ten of the 13 test-negative design studies explicitly accounted for calendar time [10,18,21–28]. No evidence of publication bias was found.

3.2. Laboratory-confirmed influenza A(H1N1)pdm09 illness

Meta-analyses of VE from 14 days after vaccination compared with non-vaccinated subjects of all ages revealed a pooled point VE estimate of 80% for adjuvanted vaccines (95% CI 59–90%, $p < 0.00001$, $I^2 = 61\%$, studies = 4, n = 6361) [18,22,25,26] and 66% for unadjuvanted vaccines (95% CI 47–78%, $p < 0.00001$, $I^2 = 0\%$, studies = 3, n = 6876) [10,19,26]. These estimates were not statistically significantly different. After pooling adjuvanted and unadjuvanted vaccines we obtained an overall VE of 73% (95% CI 59–82%, $p < 0.00001$, $I^2 = 44\%$, studies = 7, n = 13,237; Fig. 2). Studies reporting adjusted VE seven days or more after vaccination showed that the vaccines were effective at preventing LCI (VE = 66%, 95% CI 57–74%, $p < 0.00001$, $I^2 = 0\%$, studies = 3, n = 11,980) [10,18,22]. The results of secondary analyses are summarised in Table 1.

Two earlier systematic reviews (not included in our meta-analyses) assessed the effect of vaccination on LCI. For adjuvanted vaccines only, Yin et al. reported crude vaccine effectiveness ranging from 79% (95% CI 22–94%, $I^2 = 49\%$) from meta-analysis of two cohort studies (n = 3149) to 90% (95% CI 25–99%, $I^2 = 84\%$) from meta-analysis of four case control studies (n = 2726) [1]. For unadjuvanted vaccines, the pooled crude VE estimate was 89% (95% CI 30–98%, $I^2 = 88\%$). Osterholm et al. reported a median adjusted VE of 69% (range 60–93%) from four studies (n = 11,592) [2].

Effect estimates from six studies were not suitable for inclusion in the meta-analyses and are summarised in on-line supplementary table ST2 [23,29,38,39,49,50].

3.2.1. Adults ≥18 years

Neither adjuvanted nor unadjuvanted vaccines showed significant effectiveness in adults aged 18 years and over when considered separately. When both vaccine types were considered together, vaccine was moderately protective (VE = 49%, 95% CI 13–71%, $p = 0.01$, $I^2 = 23\%$, studies = 5, n = 3979) (Table 1). However, when two studies at high risk of bias were excluded on sensitivity analysis [19,37], the overall pooled VE point estimate reduced and became non-significant (VE = 31%, 95% CI −22–61%, $p = 0.2$, $I^2 = 0\%$, studies = 3, n = 3445) (on-line supplementary table ST3). Pooled point estimates of unadjusted ORs in adults were higher than point estimates of adjusted ORs for both adjuvanted and unadjuvanted vaccines, and reached statistical significance in all cases (on-line supplementary table ST4). There were no statistically significant differences between adjuvanted and unadjuvanted vaccines in adults ≥18 years.

3.2.2. Adults ≥50 years

Three studies offered data on VE in adults ≥50 years [10,18,22]. For studies reporting adjusted outcomes using adjuvanted vaccines [18,22], the pooled estimated VE was 46% (95% CI −17–75%, $p = 0.22$, $I^2 = 0\%$, studies = 2, n = 1149). Only one study reported VE for unadjuvanted vaccine [10]. There was no significant difference between adjuvanted and unadjuvanted vaccines ($p = 0.34$).

3.2.3. Children <18 years

Overall pooled adjusted VE in children under 18 years was 76% (95% CI 48–89%, $p = 0.0003$, $I^2 = 50\%$, studies = 7, n = 3994)

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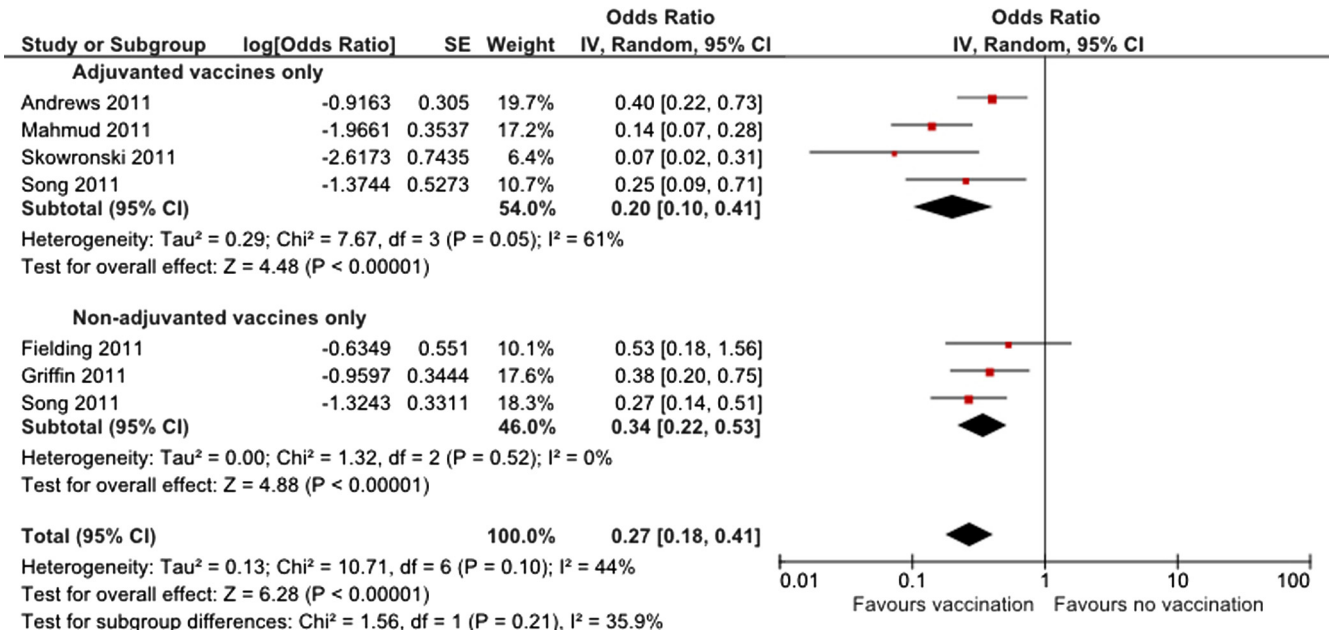

Fig. 2. Forest plot of studies of laboratory-confirmed influenza A(H1N1) pdm09 illness, adjusted ORs, vaccinated versus non-vaccinated persons of all ages, vaccine assumed to be effective 14 days or more after receipt.

[10,12,18,19,22,27,28]. Pooled VE was 88% for adjuvanted vaccines (95% CI 69–95%, p < 0.0001, I^2 = 34%, studies = 4, n = 932) [18,22,27,28], and 45% for unadjuvanted vaccines (95% CI −13–73%, p = 0.83, I^2 = 0%, studies = 3, n = 3062;Fig. 3) [10,12,19]. The difference between these estimates was statistically significant (χ^2 = 6.34, p = 0.01). Restricting the analysis to those studies in which vaccine effectiveness was assumed from 14 days after vaccination did not affect the overall results with pooled point VE of 73% (95% CI 35–88%, p = 0.003, I^2 = 47%, studies = 5, n = 2272; on-line supplementary table ST3).

Pooled estimates from unadjusted data [10,12,22,25,28,38,41] are shown in the on-line supplementary table ST4.

3.2.4. VE in adults ≥18 years vs. children

Subgroup analysis of VE for adults compared with children was not statistically significant (χ^2 = 2.39, p = 0.12; Fig. 4). However, when considering adjusted outcome data for adjuvanted and unadjuvanted vaccines separately, subgroup analysis showed adjuvanted vaccines were significantly more effective in children than adults (χ^2 = 7.48, p = 0.0006). For unadjuvanted vaccines, the difference in VE was not statistically significant.

3.3. Hospitalization due to laboratory-confirmed influenza A(H1N1) pdm09 illness

Pooling adjusted outcome data on hospitalization 14 days after vaccination revealed a VE of 61% (95% CI 14–82%, p = 0.02, I^2 = 56%, studies = 3, n = 12,683; Fig. 5) [18,34,36]. For adjuvanted vaccines the pooled VE was not statistically significant (VE = 82%, 95% CI −110–98%, p = 0.17, I^2 = 77%, studies = 2, n = 12,053) [18,34]. Only one study assessed VE of unadjuvanted vaccine [36].

3.3.1. Adults

For all adults 18 years and above, pooled adjusted VE of adjuvanted vaccines was 48% (95% CI −35–80%, p = 0.18, I^2 = 45%, studies = 3, n = 1479) [18,21,30].

No significant difference in VE was seen on subgroup analysis of adjusted data [21,30] for adjuvanted vaccines by adult age groups (χ^2 = 0.29, p = 0.59); VE was 78% in adults aged ≥65 years (95% CI 1–95%, p = 0.05, I^2 = not applicable, studies = 1, n = 120), and 64% in adults aged <65 years (95% CI 9–86%, p = 0.03, I^2 = 0%, studies = 2, n = 684) respectively.

3.3.2. Children

Pooled adjusted VE of adjuvanted vaccines in children was 86% (95% CI 67–94%, p < 0.00001, I^2 = 0%, studies = 2, n = 1126) [23,33]. There were no studies of unadjuvanted vaccines with suitable adjusted data for meta-analysis. Unadjusted data for both vaccine types are shown in supplementary table ST4.

3.3.3. VE in adults vs. children

Subgroup analysis of adjusted outcome data for studies of adjuvanted vaccines indicated that these were statistically significantly more effective at preventing hospitalization in children than adults (χ^2 = 4.08, p = 0.04; Fig. 6). There were insufficient adjusted outcome data to compare age groups for unadjuvanted vaccines.

4. Discussion

Overall we found that inactivated monovalent pandemic influenza vaccines were effective in preventing laboratory-confirmed illness and hospitalization due to A(H1N1)pdm09. Adjuvanted vaccines tended to yield higher point estimates of effectiveness, although superiority was only apparent in children. These findings are broadly consistent with previous meta-analyses [1,2]. However, our estimates are generally more conservative, perhaps reflecting the larger number of studies included and, where possible, the calculation of pooled adjusted point estimates. We noted that crude outcome measures tended to produce pooled estimates of effectiveness that were a magnitude higher than for adjusted outcome measures. We suggest that data from adjusted outcome measures are likely to offer more accurate pooled estimates of effectiveness.

Although monovalent LAIVs were also deployed during the 2009 pandemic (mainly in India, Russia, Thailand and USA) overall they accounted for <5% of global vaccine production and were not available in most countries. We therefore have focused on

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Table 1
Secondary analyses for pooled vaccine effectiveness against laboratory-confirmed influenza illness (adjusted data).

Subjects	Vaccine type	Number of participants (number of datasets) [citation]	VE (%)*	95% CI (p-value)*	I^2 (%)	Sensitivity analyses/comments
Laboratory-confirmed influenza illness						
Adults (≥18 years)	Adjuvanted	1676(3) [18,22]	40	−15 to 68 (p = 0.80)	0	
	Unadjuvanted	2303(3) [10,19,37]	59	−36 to 88 (p = 0.26)	64	
	All types	3979(6) [10,18,19,22,37]	**49**	**13 to 71 (p = 0.01)**	23	No significant difference between adjuvanted and unadjuvanted vaccines (X^2 = 0.30, p=0.58). After exclusion of two studies at high risk of bias: VE = 31% (95% CI −22–61%), p = 0.20, I^2 = 0%
Adults (≥50 years)	Adjuvanted	1149(2) [18,22]	46	−17 to 75 (p = 0.12)	0	
	Unadjuvanted	1859(1) [10]	–	–	–	Single study, non-significant result; pooled analysis not possible: VE = −6% (95% CI −231–66%, p = 0.92)
	All types	3008(3) [10,18,22]	33	−27 to 65 (p = 0.22)	0	No significant difference between adjuvanted and unadjuvanted vaccines (X^2 = 0.92, p = 0.34)
Children (<18 years)	Adjuvanted	>932(4) [18,22,27,28]	**88**	**69 to 95 (p < 0.0001)**	34	All AS03 adjuvanted.
	Unadjuvanted	3062 (3) [10,12,19]	45	−13 to 73 (p = 0.10)	0	
	All types	>3994(7) [10,12,18,19,22,27,28,]	**76**	**48 to 89 (p = 0.0003)**	50	Significant difference in VE between adjuvanted and unadjuvanted vaccines: X^2 = 6.34, p = 0.01. Two included studies reported VE at >10 days and >7 days respectively. Restricting to those studies in which vaccine effectiveness was assumed from 14 days after vaccination: **VE = 73% (95% CI 35–88%, p = 0.003, I^2 = 47%)** After exclusion of two studies at high risk of bias: **VE = 83% (95% CI 51–94%), p = 0.003, I^2 = 63%**
Hospitalization due to laboratory-confirmed influenza						
Adults (≥18 years)	Adjuvanted	1479(3) [18,21,30]	48	−35 to 80 (p = 0.18)	45	
	Unadjuvanted	–	–	–	–	No studies
	All types	n/a	n/a	n/a	n/a	All studies reporting adjusted outcomes used adjuvanted vaccines
Adults ≥ 65 years	Adjuvanted	120(1) [30]	–	–	–	Single study; pooled analysis not possible: **VE = 78% (95% CI 1–95%), p = 0.05**
	Unadjuvanted	–	–	–	–	No studies
	All types	n/a	n/a	n/a	n/a	Single study reporting adjusted outcomes used adjuvanted vaccine
Adults 18–64 years	Adjuvanted	684(2) [21,30]	**64**	**9 to 86 (p = 0.03)**	0	
	Unadjuvanted	–	–	–	–	No studies
	All types	n/a	n/a	n/a	n/a	All studies reporting adjusted outcomes used adjuvanted vaccines
Children (<18 years)	Adjuvanted	1136(2) [23,33]	**86**	**67 to 94 (p < 0.00001)**	0	Both AS03 adjuvanted.
	Unadjuvanted	–	–	–	–	No studies
	All types	n/a	n/a	n/a	n/a	All studies reporting adjusted outcomes used adjuvanted vaccines

Table footnotes: Statistically significant results highlighted in bold type.
VE vaccine effectiveness; CI confidence interval.

inactivated monovalent vaccines which were widely available [51,52]. We did not consider it appropriate in this meta-analysis to compare the effectiveness of vaccines administered by different routes, nor multivalent formulations; data pertaining to these vaccine types were explicitly excluded per protocol. The available studies on intranasal monovalent A(H1N1)pdm09 LAIV have reported clinical effectiveness against LCI, albeit constrained by lack of statistical power, broadly in line with our current findings [10–12,53,54]. It is nonetheless difficult to make a direct comparison due to numerous sources of clinical heterogeneity such as vaccine formulation characteristics, antigen components, comorbidities or sociodemographic differences and prior vaccination or natural exposure to seasonal influenza A(H1N1)pdm09 conferring cross-protection in populations since the 2009 pandemic among other factors [55]. In the post-pandemic period, trivalent or quadrivalent LAIVs incorporating A(H1N1)pdm09 antigens have been given mainly to children; but their effectiveness against A (H1N1)pdm09 has been inconsistent, and recently subject to considerable uncertainty [56].

The current study offers important new granularity on the effectiveness of inactivated 2009 pandemic vaccines by age group and vaccine type. These vaccines were more effective in children than adults and effectiveness was lowest (and non-significant) in recipients aged >50 years. This trend was observed for laboratory confirmed influenza illness and hospitalization. Van Kerkhove and colleagues have previously described how the prevalence of pre-existing antibody to A(H1N1)pdm09 was sharply aged related, with a substantially higher level of immunity in people over 50 years of age [57], (presumably due to previous historical exposure to a similar virus), and that the incidence of A(H1N1)pdm09 infection correspondingly declined at this age. Therefore we surmise that comparisons of vaccinated individuals with non-vaccinated individuals age >50 years may have been made against a background of generally high background immunity, biasing our findings in this age group towards the null and statistical under-powering.

We further explained the overall inverse gradient between effectiveness and age by comparing adjuvanted versus unadjuvanted vaccines in each age band. Our results show that adjuvanted vaccines were significantly more effective in children than unadjuvanted vaccines in preventing laboratory confirmed influenza illness by almost a twofold difference in effectiveness. A similar pattern was also seen for hospitalization. However, in

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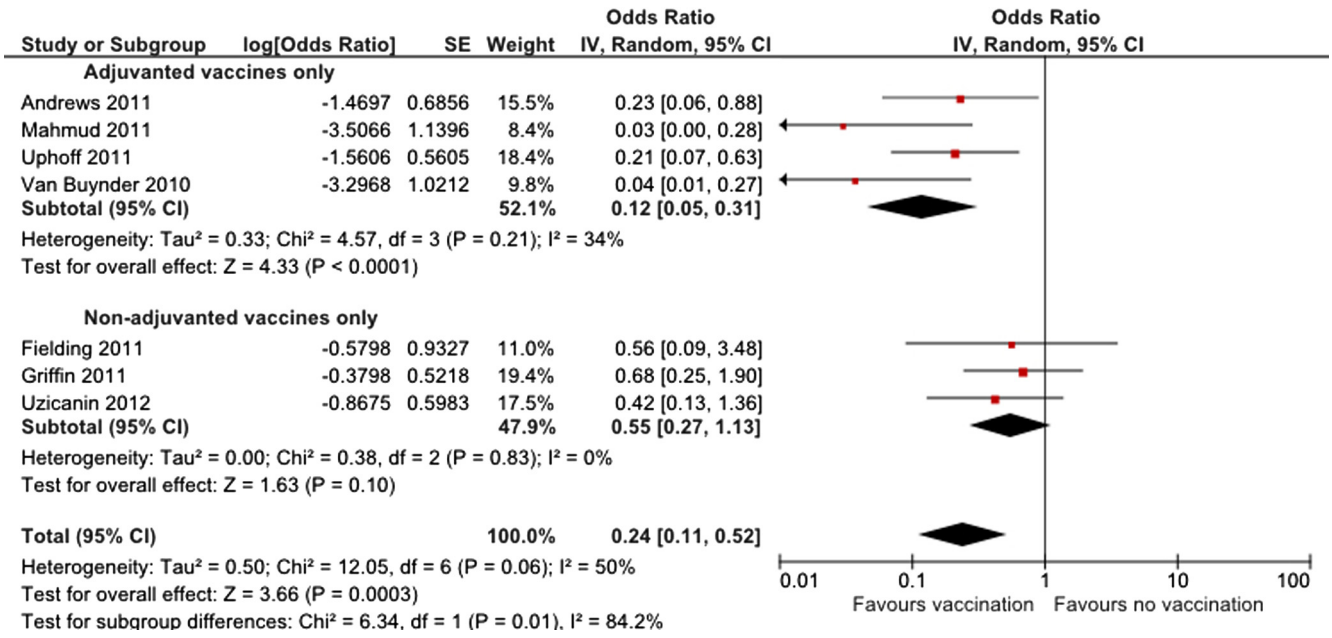

Fig. 3. Forest plot of studies of laboratory-confirmed influenza A(H1N1) pdm09 illness, adjusted ORs, vaccinated versus non-vaccinated persons in children under 18 years.

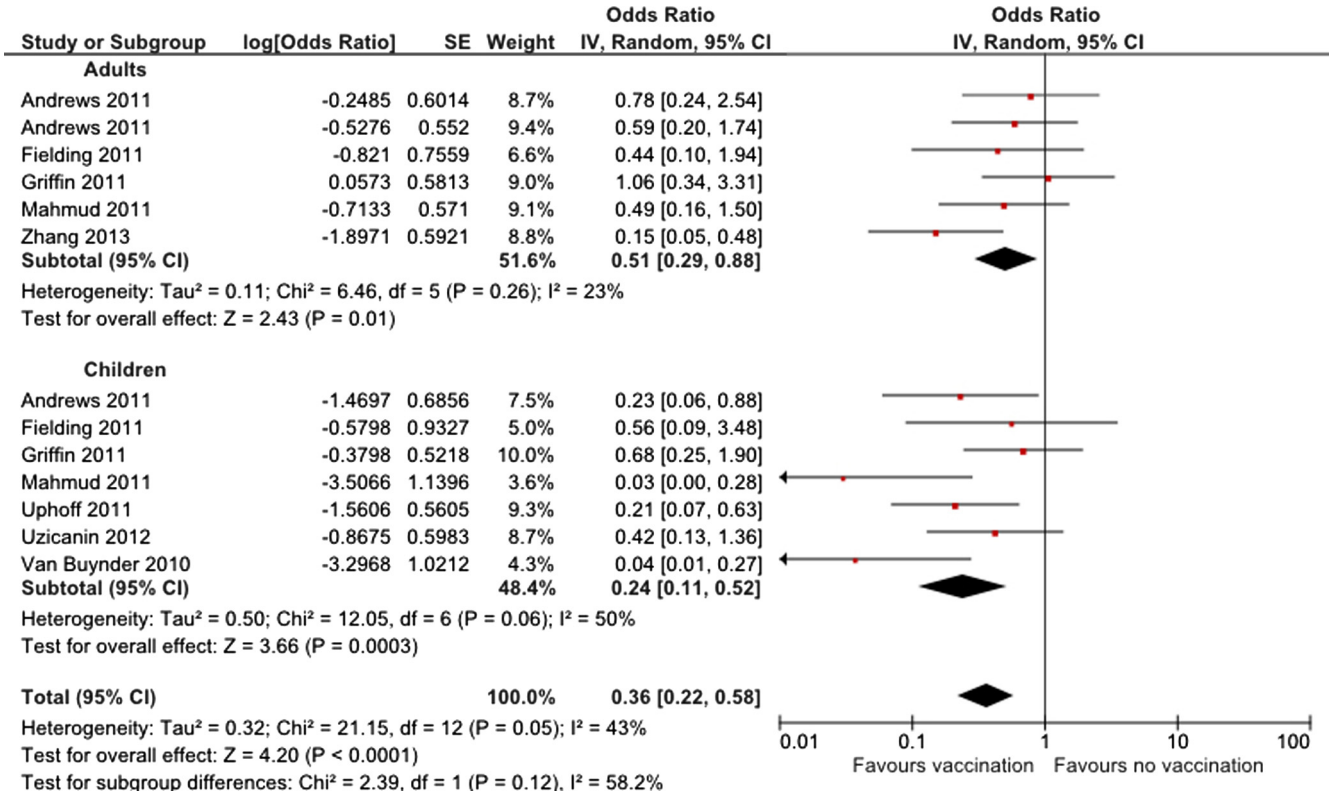

Fig. 4. Forest plot of studies of laboratory-confirmed influenza A(H1N1) pdm09 illness, adjusted ORs, adults versus children, adjuvanted and unadjuvanted vaccines.

adults there were fewer apparent differences between the performance of adjuvanted and unadjuvanted vaccines for both outcomes. The higher effectiveness in children of adjuvanted vaccines compared to unadjuvanted vaccines noted here has also been seen in efficacy studies of seasonal trivalent influenza vaccines (TIV) in young children up to 72 months of age, in whom efficacy against PCR-confirmed influenza was 92% for adjuvanted vaccines versus 45% for unadjuvanted vaccines [58].

4.1. Limitations

Although, where possible, we report pooled estimates of adjusted data to reduce the impact of known confounders on our pooled point estimates, the included eligible studies were nevertheless non-randomized observational studies, many of which were judged to have some risk of bias or unclear risk of bias across most domains. Indeed, exclusion of two studies at high risk of bias

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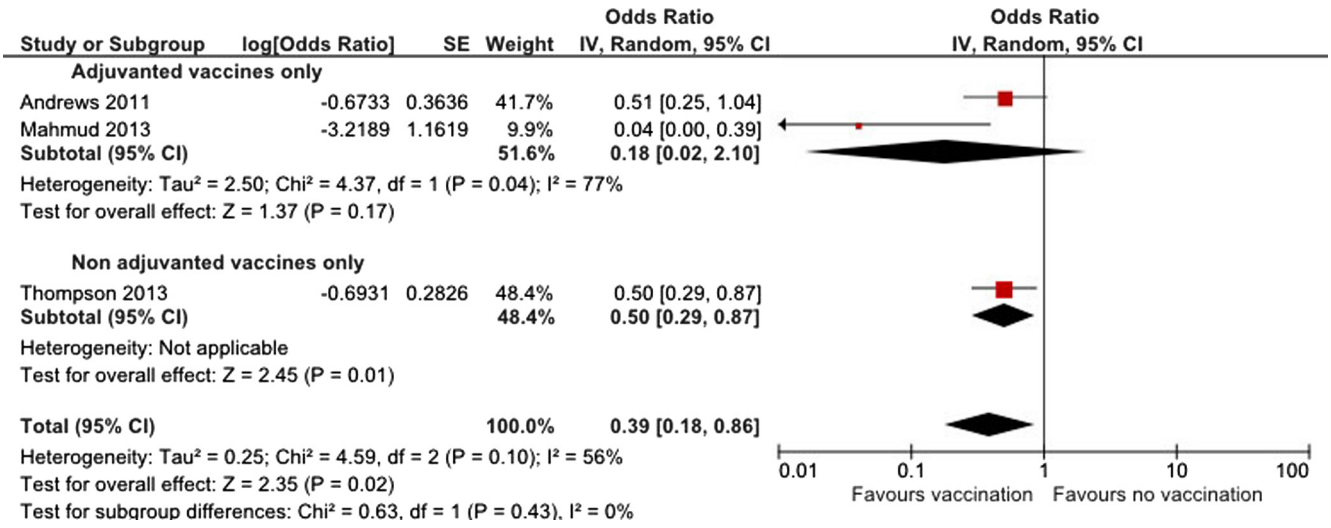

Fig. 5. Forest plot of studies of hospitalization due to laboratory-confirmed A(H1N1)pdm09 illness, adjusted ORs, vaccinated versus unvaccinated persons of all ages, vaccine assumed to be effective 14 days or more after vaccination.

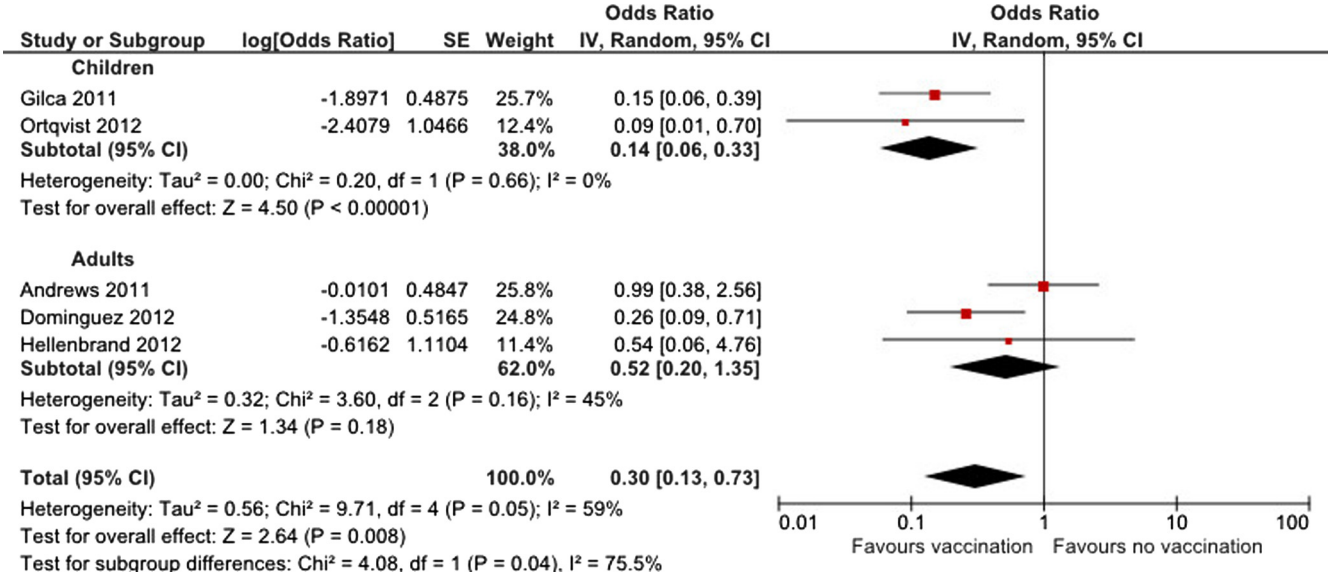

Fig. 6. Forest plot of studies of hospitalization due to laboratory-confirmed influenza A(H1N1) pdm09 illness, adjusted ORs, adults versus children, all adjuvanted vaccine studies.

across two domains changed a significantly protective VE to non-significant during sensitivity analysis [19,37]. Without randomization it is not possible to exclude selection bias. We were unable to account for prior immunity due to a previous historical exposure to a closely related virus, asymptomatic infection or mild infection.

Moderate levels of statistical heterogeneity were present in some meta-analyses, reaching significance in the comparisons of adjuvanted vaccines in adults and children. Potential confounders related to prior exposure to influenza viruses, vaccination or participant characteristics may be partly responsible. In addition to study design issues, heterogeneity may also occur due to real difference in VE in different populations. Although it was our intention evaluate vaccine effectiveness in different clinical risk groups lack of data precluded this. No randomized controlled trials were identified. Although not an unexpected finding in this scenario, it meant that we were unable to evaluate the efficacy of the vaccines.

Lack of data limited or prevented some planned analyses. Although we intended to explore potential differences between influenza A(H1N1)pdm09 vaccines with AS03 and MF-59 proprietary adjuvants, we encountered insufficient data to do so, since almost all studies included used the AS03 adjuvant. Notwithstanding we have pooled these adjuvanted studies for our analysis and believe this is rational based on the fact that both are 'same-class' squalene-based, oil-in-water, adjuvants. Analysis of the effect of giving a scheduled second dose of vaccine was precluded due to the low number of people who received more than one dose in the relevant studies.

4.2. Implications for public health policy

Our results establish that influenza A(H1N1)pdm09 vaccines produced globally in response to the 2009–10 pandemic were broadly effective in reducing influenza illness and hospitalization. For the time being, the potential impact on mortality remains an assumption or derivation in future pandemic planning, as this potential benefit is currently unsupported by existing scientific evidence.

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The findings need to be placed in the context that the A(H1N1) pdm09 virus emerged in March–April 2009 but vaccine was not available for widespread distribution until October 2009, during the second pandemic wave, owing to the lead times in production. Although highly successful in averting cases of influenza, vaccines would have achieved a far greater public health impact if their arrival had been a few months sooner [59,60]. There remains a joint scientific, regulatory, and public health imperative to streamline the process of triggering pandemic vaccine production and decrease production lead times, whilst simultaneously pursuing opportunities to develop a 'universal' influenza vaccine, as endorsed in the WHO Pandemic Influenza Preparedness Framework [61].

Since pandemic planning gathered momentum in 2003 until 2009, health authorities focused mainly on the potential pandemic threat posed by avian influenza A(H5N1). It is widely recognized that human vaccines targeted against this subtype are relatively poorly immunogenic, and that in general two doses are required for adequate seroconversion [62]. This was generally not the case with A(H1N1)pdm09 vaccines [63]. The data we have generated may constitute important knowledge if a future pandemic virus necessitates two doses to confer clinical protection and antigen sparing strategies involving the use of adjuvants are required to achieve rapid population coverage.

Evidence from modeling studies suggests that children are a credible target group for pandemic vaccination, along with patients who have high-risk conditions [64–66]. This assertion is now supported for seasonal influenza by data from the UK childhood influenza vaccination programme [67]. Since there is evidence from our meta-analyses that adjuvanted vaccines were more effective in children than unadjuvanted vaccines and given that antigen sparing strategies may be critically important during a future pandemic [68], this draws the current narcolepsy signal associated with AS03-containing influenza vaccines into sharp relief in the context of a potentially altered risk-benefit profile during a more severe pandemic [69]. Efforts to study expansion of adjuvanted vaccines in paediatric populations for seasonal use are warranted, both to improve prevention of seasonal influenza, and potentially to expedite potential use of adjuvanted vaccines during a future pandemic.

5. Conclusion

Through a comprehensive global systematic review and meta-analysis, we have identified that inactivated monovalent A (H1N1)pdm09 vaccines were effective in preventing laboratory-confirmed influenza illness and related hospitalization. In children, adjuvanted vaccines were more effective than unadjuvanted vaccines.

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Potential conflicts of interest

JSN-V-T declares funding for a 3-year PhD research fellowship from GlaxoSmithKline Biologicals SA which ended in 2014. In 2000–2001 he was an employee of SmithKline Beecham plc (now a part of the GlaxoSmithKline) and from 2002 to 2004 an employee of Aventis Pasteur MSD (now Sanofi Pasteur MSD), but has held no shares, share options or accrued pension rights in either company since 2005. He has given lectures (without fees or honoraria) at two scientific meetings of the European Scientific Working Group on Influenza (ESWI) in 2014 and 2015 for which travel expenses and accommodation were reimbursed). JSN-V-T's brother was an employee of GlaxoSmithKline in an unrelated area until mid-2015.

WB declares grants outside the submitted work from Abbott (pharmaceutical firm) for conference attendance and from Mylan (pharmaceutical firm) for an expert report.

CRB commenced this work at the University of Nottingham but has subsequently transferred employment to Public Health England. Funding costed against CRB's involvement has been transferred to Public Health England.

All other authors declare no competing interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.02.059.

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