

## **Supplementary Material**

Supplement to:

**Lin et al. Oil-in-water emulsion adjuvants for pediatric influenza vaccines:  
a systematic review and meta-analysis**

## **Supplementary Notes**

Supplementary Note 1. MEDLINE (PubMed) search strategy

Supplementary Note 2. CENTRAL (Search Manger) search strategy

Supplementary Note 3. Embase (Elsevier) strategy

Supplementary Note 4. CINAHL/Web of Science/Scopus search strategy

Supplementary Note 5. Google Scholar strategy

Supplementary Note 6. WHO ICTRP (Search for clinical trials in children), Grey Literature Report, Open Grey, RePORT, HSRProj, AHRQ Grants On-Line Database, HSRR search strategy

Supplementary Note 7. Clinical Trials.gov search strategy

Supplementary Note 8. List of excluded studies and the reasons for exclusion

## Supplementary Tables

Supplementary Table 1. Randomized controlled trials that reported efficacy data

Supplementary Table 2. Randomized controlled trials that reported seroprotection data

Supplementary Table 3. Randomized controlled trials that reported serious adverse events  
(SAEs)

Supplementary Table 4. Randomized controlled trials that reported neurological events

Supplementary Table 5. Randomized controlled trials that reported reactogenicity data

Supplementary Table 6. Summary of findings: certainty of evidence for effect outcomes

Supplementary Table 7. Summary of findings: certainty of evidence for harm outcomes

## Supplementary Figures

- Supplementary Figure 1. Forest plot showing the ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 2. Meta-regression showing a linear relationship (slope = 0.98, P <0.001) between the ratios of seroprotection rates against H1N1 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 95.47%
- Supplementary Figure 3. Forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 4. Meta-regression showing a linear relationship (slope = 0.91, P <0.001) between the ratios of seroprotection rates against H3N2 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 88.92%
- Supplementary Figure 5. Forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 6. Forest plot showing the risk ratios of pain/tenderness at the injection site during the 7 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 7. Forest plot showing the risk ratios of fever during the 7 days

after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

- Supplementary Figure 8. Forest plot showing the risk ratios of pain/tenderness at the injection site during the 7 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 9. Forest plot showing the risk ratios of fever during the 7 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 10. Funnel plot with pseudo 95% confidence limits.
- Supplementary Figure 11. Risk of bias summary.
- Supplementary Figure 12. Risk of bias graph.
- Supplementary Figure 13. Sensitivity analysis by excluding Langley (2012): forest plot showing the ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 14. Sensitivity analysis by excluding Langley (2012): meta-regression showing a linear relationship (slope = 0.79, P <0.001) between the ratios of seroprotection rates against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 99.81%.
- Supplementary Figure 15. Sensitivity analysis by excluding Zedda (2015): forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received

adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

- Supplementary Figure 16. Sensitivity analysis by excluding Zedda (2015): meta-regression showing a linear relationship (slope = 0.91, P <0.001) between the ratios of seroprotection rates against H3N2 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 88.54%.
- Supplementary Figure 17. Sensitivity analysis by excluding Zedda (2015): forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a ≥1:40 haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 18. Sensitivity analysis by excluding Zedda (2015): meta-regression showing a linear relationship (slope = 0.88, P <0.001) between the ratios of seroprotection rates against influenza B after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 99.63%.
- Supplementary Figure 19. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of RT-PCR-confirmed influenza among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 20. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the

ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

- Supplementary Figure 21. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship (slope = 0.90,  $P < 0.001$ ) between the ratios of the seroprotection rate against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 99.56%.
- Supplementary Figure 22. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 23. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship (slope = 0.95,  $P < 0.001$ ) between the ratios of the seroprotection rate against H3N2 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with

an  $R^2$  of 100%.

- Supplementary Figure 24. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 25. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship ( $\text{slope}=0.83$ ,  $p<0.001$ ) between the ratios of the seroprotection rate against influenza B after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 99.84%.
- Supplementary Figure 26. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of serious adverse events during the follow-up time after the vaccinations among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).
- Supplementary Figure 27. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using

adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of neurological events during the follow-up time after the vaccinations among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

- Supplementary Figure 28. Sensitivity analysis by excluding 2 data points (both reported in Diallo 2018) with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression still showed a linear relationship (slope = 0.90,  $P < 0.001$ ) between the ratios of seroprotection rates against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 98.67%.
- Supplementary Figure 29. Sensitivity analysis by excluding 2 data points (Vesikari 2011 and Della Cioppa 2011) with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression results became imprecise (slope = 0.47,  $P=0.075$ ) between the ratios of seroprotection rates against H3N2 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 42.98%, after the sample size decreased to only seven.
- Supplementary Figure 30. Sensitivity analysis by excluding 2 data points (Vesikari 2011 and Della Cioppa 2011), with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression still showed a linear relationship (slope = 0.86,  $P < 0.001$ ) between the ratios of seroprotection rates against influenza B after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 96.21%.

## **Supplementary Note 1. MEDLINE (PubMed) search strategy**

No.	Query
#1	((influenza vaccin* [Text Word]) OR ((influenza [Text Word] OR flu [Text Word]) and (vaccin* [Text Word] OR immuni* [Text Word] or inocula* [Text Word] OR efficacy [Text Word] OR effectiveness [Text Word])))
#2	"influenza vaccines" [MeSH] OR ("influenza, human/immunology" [MeSH] OR "influenza, human/prevention and control" [MeSH])
#3	#2 AND #3
#4	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])
#5	("cross over" OR "crossover" OR "follow Up" OR ("cross-over studies [MeSH] OR "follow-up studies" [MeSH] OR ""prospective studies" [MeSH])) OR ("time series" OR "interrupted time series" OR (placebo* OR random* OR "double blind" OR "single blind" OR clinical trial* OR trial design) OR ("case-control studies" [MeSH] OR (cases [Title/Abstract] AND controls [Title/Abstract])) OR ("cohort studies" [MeSH] OR cohort*) OR ("comparative study" [Publication Type]) OR ("before after" [Title/Abstract] OR "before-after" [Title/Abstract] OR "before/after" [Title/Abstract] OR "before and after" [Title/Abstract]) OR (volunteer* [Title/Abstract]) OR (control* [Text Word] AND evaluation [Text Word]) OR (longitudinal [Text Word]) OR (retrospective* [Text Word]))
#6	#5 OR #6
#7	#4 AND #7
#8	child* OR preschool* OR school* OR young OR adolescent* OR infant* OR toddler* OR pediatric* OR paediatric* OR infant*
#9	#8 AND #9
#10	(adjuvant [All Fields] OR adjuvanted [All Fields] OR adjuvants [All Fields]) OR ("MF59 oil emulsion" [All Fields] OR MF59 [Text Word]) OR AS03 [All Fields])
#11	#10 AND #11

## **Supplementary Note 2. CENTRAL (Search Manger) search strategy**

No.	Query
#1	adjuvant* OR MF59 OR AS03
#2	(influenza vaccin*) OR ((influenza or flu*) AND (vaccin* OR immun* OR inocul*))
#3	child* OR infant* OR toddler*
#4	#1 AND #3 AND #4

### **Supplementary Note 3. Embase (Elsevier) strategy**

No.	Query
#1	influenza AND vaccin* AND (influenza OR flu*) AND (vaccin* OR immun* OR inocul*)
#2	randomized controlled trial/exp OR single blind procedure/exp OR double blind procedure/exp OR crossover procedure/exp
#3	random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR cross-over:ab,ti OR cross over:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR ((singl*:ab,ti OR doubl*:ab,ti) AND (blind*:ab,ti OR mask*:ab,ti))
#4	#2 OR #3
#5	#1 AND #4
#6	child*:de,ab,ti OR preschool*:de,ab,ti OR school*:de,ab,ti OR young:de,ab,ti OR adolescent*:de,ab,ti OR toddler*:de,ab,ti OR pediatric*:de,ab,ti OR paediatric*:de,ab,ti OR infant*:de,ab,ti
#7	#5 AND #6
#8	adjuvant* OR MF59 OR AS03
#9	#7 AND #8

**Supplementary Note 4. CINAHL/ Web of Science/ Scopus search strategy**

(adjuvant\* OR MF59 OR AS03) AND (influenza vaccin\*) AND (influenza or flu\*) AND (vaccin\* OR immun\* OR inocul\*) AND (child\* OR infant\* OR toddler\* OR pediatric\* OR paediatric\*)

### **Supplementary Note 5. Google Scholar strategy**

(adjuvant\* OR MF59 OR AS03) AND (influenza vaccin\*) AND (influenza or flu\*) AND (vaccin\* OR immun\* OR inocul\*) AND (child\* OR infant\* OR toddler\* OR pediatric\* OR paediatric\*) -avian -adult -elderly -animal -cell

**Supplementary Note 6. WHO ICTRP (Search for clinical trials in children), Grey Literature Report, Open Grey, RePORT, HSRProj, AHRQ Grants On-Line Database, HSRR search strategy**

(Vaccine\* AND influenza) AND (adjuvant\* OR MF59 OR AS03)

(immuni\* AND influenza) AND (adjuvant\* OR MF59 OR AS03)

(inocul\* AND influenza) AND (adjuvant\* OR MF59 OR AS03)

(vaccine\* AND flu) AND (adjuvant\* OR MF59 OR AS03)

(immuni\* AND flu) AND (adjuvant\* OR MF59 OR AS03)

(inocul\* AND flu) AND (adjuvant\* OR MF59 OR AS03)

### **Supplementary Note 7. Clinical Trials.gov search strategy**

(adjuvant OR MF59 OR AS03) AND (influenza vaccine) AND (vaccination OR immunization  
OR inoculation) AND (child OR infant OR toddler OR pediatric OR paediatric)

#### **Supplementary Note 8. List of excluded studies and the reasons for exclusion**

<b>Trial</b>	<b>Reason for exclusion</b>
Höschler 2018	Not under 9 years of age
Canelle 2016	Not under 9 years of age
Knuf 2015	Duplicated data
Örtqvist 2015	Not under 9 years of age
Sicilia 2015	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Thebault 2015	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Vesikari 2015	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Hoschler 2014	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Knuf 2014	Duplicated data
Martinez 2014	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Poder 2014	Not under 9 years of age
Winstone 2014	Not under 9 years of age
Buynder 2013	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Launay 2013	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Baselli 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Fukase 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Kulkarni 2012	Not under 9 years of age
Langley 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines

<b>Trial</b>	<b>Reason for exclusion</b>
Nassim 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Nohynek 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Örtqvist 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Saitoh 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Walker 2012	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Andrews 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Banzhoff 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Bardage 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Black 2011	Duplicated data
Cristiani 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Esposito 2011	Not under 9 years of age
Esposito 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Gilca 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Griffin 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Kries 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Ortqvist 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Parretta 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Scheifele 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Sicilia 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines

<b>Trial</b>	<b>Reason for exclusion</b>
Skowronski 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Uphoff 2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Whalley2011	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Buynder 2010	Not under 9 years of age
Carmona 2010	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Gagnon 2010	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Waddington 2010	Duplicated data
Yasuda 2010	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Liang 2009	Not under 9 years of age
Zhu 2009	Not under 9 years of age
Vesikari 2008	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Marchetti 2007	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Woodhour 1969	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Stokes 1969	Not under 9 years of age
Davenport 1968	Not trials that compared adjuvanted vs. non-adjuvanted vaccines
Quilligan 1966	Not under 9 years of age

Supplementary Table 1. Randomized controlled trials that reported efficacy data against RT-PCR confirmed influenza

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/ HA content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Follow-up time (day)	Funding source
Vesikari 2011	Phase 3, Observer-blind, Randomized	Study centers in Germany and Finland	H1N1, H3N2, B	6-35 months  36-71 months	MF59- adjuvanted /Novartis/30 µg (n=1,103)  MF59- adjuvanted /Novartis/30 µg (n=834)	Subunit and split trivalent inactivated /Novartis/30 µg (n=995)  Subunit and split trivalent inactivated /Novartis/30 µg (n=777)	6-12 months after each vaccination	Novartis
Nolan 2014*	Phase 3, Observer-blind, Randomized	17 centers in Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, Thailand	H1N1	6-35 months	AS03- adjuvanted /GSK/7.5 µg (n=569)	Non-adjuvanted /GSK/30 µg (n=561)	385 days after randomization	GlaxoSmithKline

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/ HA content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Follow-up time (day)	Funding source
Vesikari 2018†	Phase 3 Observer-blind, Randomized	146 sites including hospitals, clinics and clinician offices in Finland, USA, Canada, Italy, Poland, Spain, Philippines, Thailand, Taiwan	H1N1, H3N2, B	6-23 months  2-5 years	MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=1,299)  MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=3,979)	Non-adjuvanted inactivated /Sanofi Pasteur/30 µg (n=1,339)  Non-adjuvanted inactivated /Sanofi Pasteur/30 µg (n=3,854)	180 days after last vaccination	Seqirus UK Ltd.

\*This trial compared adjuvanted and non-adjuvanted vaccine formulations with unequal hemagglutinin antigen dose. The hemagglutinin antigen dose was reduced in the adjuvanted arm (antigen-sparing design).

†This trial compared adjuvanted influenza vaccines and non-adjuvanted influenza vaccines from different manufacturers.

Supplementary Table 2. Randomized controlled trials that reported seroprotection data

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/HA content per ml (n)	Follow-up time (day)	Funding source
Vesikari 2009 † (PIDJ)	Observer-blind Randomized	Finland	H1N1, H3N2, B	6-35 months	MF59-adjuvanted subunit /Novartis/7.5 µg (n=104)	Non-adjuvanted split /Sanofi Pasteur/7.5 µg (n=118)	21 d after 2nd dose	Novartis
Vesikari 2009† (Vaccine)	Observer-blind Randomized	Finland	H1N1, H3N2, B	16-47 months	MF59-adjuvanted subunit /Novartis/30 µg (n=41)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=40)	21 d after 1st dose	Novartis
Arguedas 2011*†	Phase 3 Open-label Randomized	Costa Rica	H1N1	3-8 years	MF59-adjuvanted /Novartis/15 µg (n=46)	Non-adjuvanted /Novartis/30 µg (n=75)	21 d after 1st and 2nd doses	Novartis
Della Cioppa 2011†	Observer-blind Randomized	15 study centers in Finland and Belgium	H1N1, H3N2, B	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=37)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=43)	21 d after 1st and 2nd doses	Novartis
Vesikari 2011	Phase 3 Observer-blind Randomized	Germany, Finland	H1N1, H3N2, B	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=1103)	Non-adjuvanted subunit /Novartis/30 µg (n=995)	28 d after 1st and 2nd doses	Novartis
				36-71 months	MF59-adjuvanted /Novartis/30 µg (n=834)	Non-adjuvanted subunit /Novartis/30 µg (n=777)	28 d after 1st and 2nd doses	

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time (day)</b>	<b>Funding source</b>
Block 2012	Phase 2	29 sites in USA and Mexico	H1N1	6-35 months	MF59-adjuvanted monovalent subunit /Novartis/30 µg (n=127)	Non-adjuvanted monovalent subunit /Novartis/30 µg (n=124)	21 d after 1st and 2nd doses	Novartis, Federal funds
	Phase 3 Double-blind Randomized							
Langley 2012*	Double-blind Randomized	12 centers in Canada	H1N1	6-11 months	AS03-adjuvanted monovalent /GSK/15 µg (n=5)	Non-adjuvanted monovalent /GSK/30 µg (n=4)	21 d after 1st and 2nd doses	GlaxoSmithKline, US Department of Health and Human Service
Nassim 2012	Phase 2 phase 3 Single-blind Randomized	34 centers in USA	H1N1	12-35 months	AS03-adjuvanted monovalent /GSK/15 µg (n=15)	Non-adjuvanted monovalent /GSK/30 µg (n=16)	21 d after 1st and 2nd doses	US CDC
				3-8 years	AS03-adjuvanted monovalent /GSK/15 µg (n=39)	Non-adjuvanted monovalent /GSK/30 µg (n=37)	21 d after 1st and 2nd doses	
				3-8 years (antigen 7.5µg)	MF59-adjuvanted monovalent /Novartis/30 µg (n=156)	Non-adjuvanted monovalent /Novartis/30 µg (n=156)	21 d after 1st and 2nd doses	

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/HA content per ml (n)	Follow-up time (day)	Funding source
				3-8 years (antigen 15 µg)	MF59-adjuvanted monovalent /Novartis/30 µg (n=156)	Non-adjuvanted monovalent /Novartis/30 µg (n=155)	21 d after 1st and 2nd doses	
Nolan 2014†	Phase 3 Observer-blind Randomized	32 sites in Argentina, Australia, Chile, Philippines, South Africa	H1N1, H3N2, B	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=266)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=389)	21 d after 2nd dose	Novartis
Nolan 2014*	Phase 3 Observer-blind Randomized	17 centers in Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, Thailand	H1N1	6-35 months	AS03-adjuvanted monovalent /GSK/7.5 µg (n=233)	Non-adjuvanted monovalent /GSK/30 µg (n=223)	21 d after 2nd dose	GlaxoSmithKline
Solares 2014†	phase 2 Observer-blind Randomized	5 sites in Guatemala	H1N1, H3N2, B	6-35 months	MF59-adjuvanted TIV /Novartis/30 µg (n=97)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=102)	21 d after 1st and 2nd doses	Novartis

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time (day)</b>	<b>Funding source</b>
Knuf 2015*	Single-blind Randomized	13 centers in Germany, Belgium, Dominican Republic, Netherlands	H1N1	36-59 months	MF59-adjuvanted TIV /Novartis/30 µg (n=23)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=20)	21 d after 1st and 2nd doses	Novartis
				12-35 months	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=53)	Non-adjuvanted monovalent /Novartis/15 µg (n=25)	21 d after 1st and 2nd doses	
				3-8 years	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=60)	Non-adjuvanted monovalent /Novartis/15 µg (n=31)	21 d after 1st and 2nd doses	
Vesikari 2015	Phase 3b Observer-blind Randomized	15 sites across Finland Finland	H1N1, H3N2, B	6-71 months (ATIV primed)	MF59-adjuvanted TIV /Novartis/30 µg (n=17)	Non-adjuvanted TIV /Novartis/30 µg (n=12)	22 d after 1st dose	Novartis
				6-71 months (TIV primed)	MF59-adjuvanted TIV /Novartis/30 µg (n=23)	Non-adjuvanted TIV /Novartis/30 µg (n=24)	22 d after 1st dose	

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time (day)</b>	<b>Funding source</b>
Zedda 2015	Randomized	Belgium	H1N1, H3N2, B	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=25)	Non-adjuvanted /Novartis/30 µg (n=30)	21 d after 2nd dose	Novartis
Vesikari 2018†	Phase 3 Observer-blind, Randomized	146 sites including hospitals, clinics and clinician offices in Finland, USA, Canada, Italy, Poland, Spain, Philippines, Thailand, Taiwan	H1N1, H3N2, B	6-60 months	MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=922)	Non-adjuvanted inactivated /Sanofi Pasteur/30 µg (n=866)	28 d after 1st and 2nd doses	Seqirus UK Ltd.
Cruz-Valdez 2018	Phase 3 Observer-blind randomized	Mexico	H1N1, H3N2, B	6-71 months	MF59-adjuvanted TIV /Novartis/30 µg (n=114)	Non-adjuvanted TIV /Novartis/30 µg (n=112)	21 d after 2nd dose	Novartis
Diallo 2018†	Observer-blind randomized	Senegal	H1N1, H3N2, B	6-11 months 12-35 months	MF59-adjuvanted TIV /Novartis/30 µg (n=30) MF59-adjuvanted TIV /Novartis/30 µg (n=31)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=26) Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=34)	28 d after 1st and 2nd doses 28 d after 1st and 2nd doses	US CDC

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time (day)</b>	<b>Funding source</b>
				36-71 months	MF59-adjuvanted TIV /Novartis/30 µg (n=38)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=33)	28 d after 1st and 2nd doses	

\*This trial compared adjuvanted and non-adjuvanted vaccine formulations with unequal hemagglutinin antigen dose. The hemagglutinin antigen dose was reduced in the adjuvanted arm (antigen-sparing design).

†This trial compared adjuvanted influenza vaccines and non-adjuvanted influenza vaccines from different manufacturers.

Supplementary Table 3. Randomized controlled trials that reported serious adverse events (SAEs)

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Vesikari 2009 † (PIDJ)	6-35 months	MF59-adjuvanted subunit /Novartis/30 µg (n=130)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=139)	Up to 3 weeks	2 subjects in adjuvanted arm, 6 subjects in non-adjuvanted arm.
Vesikari 2009† (Vaccine)	16-47 months	MF59-adjuvanted subunit /Novartis/30 µg (n=43)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=46)	Up to 6 months	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Waddington 2010*†	Waddington 2010	AS03-adjuvanted split virion /GSK/1.875 µg (n=270)	Non-adjuvanted whole virion /Baxter/3.75 µg (n=279)	Did not report follow-up time for SAE	Did not report SAE data
Arguedas 2011*	3-8 years	MF59-adjuvanted /Novartis/15 µg (n=56)	Non-adjuvanted /Novartis/30 µg (n=54)	Up to 43 days	0 subjects in adjuvanted arm, 1 subjects in non-adjuvanted arm.
Della Cioppa 2011†	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=37)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=43)	Up to 50 days	4 subjects in adjuvanted arm, 3subjects in non-adjuvanted arm.
Vesikari 2011	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=2,012)	Non-adjuvanted subunit /Novartis/30 µg (n=1,846)	Up to 12 months	2 subjects in adjuvanted arm, 2 subjects in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Block 2012	6-35 months	MF59-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	Non-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	Up to 12 months	6 subjects in adjuvanted arm, 16 subjects in non-adjuvanted arm.
Langley 2012*	6 months-8 years	AS03-adjuvanted monovalent /GSK/15 µg (n=59)	Non-adjuvanted monovalent /GSK/30 µg (n=57)	Up to 385 days	4 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Nassim 2012	3-8 years	MF59-adjuvanted monovalent /Novartis/30 µg (n=334)	Non-adjuvanted monovalent /Novartis/30 µg (n=334)	Up to 387 days	6 subjects in adjuvanted arm, 6 subjects in non-adjuvanted arm.
Nolan 2014†	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=3,123)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=1,474)	Up to 394 days	123 subjects in adjuvanted arm, 58 subjects in non-adjuvanted arm.
Nolan 2014*	6-35 months	AS03-adjuvanted monovalent /GSK/7.5 µg (n=2,048)	Non-adjuvanted monovalent /GSK/30 µg (n=2,049)	Up to 385 days	76 subjects in adjuvanted arm, 68 subjects in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Solares 2014†	6-59 months	MF59-adjuvanted TIV /Novartis/30 µg (n=180)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=180)	Up to 211 days	0 subjects in adjuvanted arm, 2 subjects in non-adjuvanted arm.
Knuf 2015*	12 months-8 years	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=145)	Non-adjuvanted monovalent /Novartis /15 µg (n=72)	Up to 18 months	14 subjects were reported, similarly distributed between adjuvanted and non-adjuvanted arms (the exact number of events in each arm was not specified).
Vesikari 2015	6-71 months (ATIV primed)	MF59-adjuvanted TIV /Novartis/30 µg (n=33)	Non-adjuvanted TIV /Novartis/30 µg (n=24)	Up to 6 months	1 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Zedda 2015	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=43)	Non-adjuvanted /Novartis/30 µg (n=39)	Did not report follow-up time for SAE	Did not report SAE data
Vesikari 2018†	6-60 months	MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=5,243)	Non-adjuvanted inactivated /Sanofi Pasteur/30 µg (n=5,161)	Up to 366 to 390 days	229 subjects in adjuvanted arm, 225 subjects in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Cruz-Valdez 2018	6-71 months	MF59-adjuvanted TIV /Novartis/30 µg (n=140)	Non-adjuvanted TIV /Novartis/30 µg (n=137)	Up to 50 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Diallo 2018†	6-71 months	MF59-adjuvanted TIV /Novartis/30µg (n=118)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=119)	Up to 112 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.

\*This trial compared adjuvanted and non-adjuvanted vaccine formulations with unequal hemagglutinin antigen dose. The hemagglutinin antigen dose was reduced in the adjuvanted arm (antigen-sparing design).

†This trial compared adjuvanted influenza vaccines and non-adjuvanted influenza vaccines from different manufacturers.

Supplementary Table 4. Randomized controlled trials that reported neurological events

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Vesikari 2009 † (PIDJ)	6-35 months	MF59-adjuvanted subunit /Novartis/30 µg (n=130)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=139)	Up to 3 weeks	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Vesikari 2009† (Vaccine)	16-47 months	MF59-adjuvanted subunit /Novartis/30 µg (n=43)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=46)	Up to 6 months	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Waddington 2010*†	Waddington 2010	AS03-adjuvanted split virion /GSK/1.875 µg (n=270)	Non-adjuvanted whole virion /Baxter/3.75 µg (n=279)	Did not report follow-up time for SAE	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Arguedas 2011*	3-8 years	MF59-adjuvanted /Novartis/15 µg (n=56)	Non-adjuvanted /Novartis/30 µg (n=54)	Up to 43 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Della Cioppa 2011†	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=37)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=43)	Up to 50 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Vesikari 2011	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=2,012)	Non-adjuvanted subunit /Novartis/30 µg (n=1,846)	Up to 12 months	1 subjects (convulsion) in adjuvanted arm, 0 subjects in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Block 2012	6-35 months	MF59-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	Non-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	Up to 12 months	Did not report neurological event data.
Langley 2012*	6 months- 8 years	AS03-adjuvanted monovalent /GSK/15 µg (n=59)	Non-adjuvanted monovalent /GSK/30 µg (n=57)	Up to 385 days	2 subjects (convulsion) in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Nassim 2012	3-8 years	MF59-adjuvanted monovalent /Novartis/30 µg (n=334)	Non-adjuvanted monovalent /Novartis/30 µg (n=334)	Up to 387 days	Did not report neurological event data.
Nolan 2014†	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=3,123)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=1,474)	Up to 394 days	27 subjects were reported (the exact number of events in each arm was not specified).
Nolan 2014*	6-35 months	AS03-adjuvanted monovalent /GSK/7.5 µg (n=2,048)	Non-adjuvanted monovalent /GSK/30 µg (n=2,049)	Up to 385 days	1 subjects (febrile convulsion) in adjuvanted arm, 2 subjects (febrile convulsion) in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Solares 2014†	6-59 months	MF59-adjuvanted TIV /Novartis/30 µg (n=180)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=180)	Up to 211 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Knuf 2015*	12 months-8 years	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=145)	Non-adjuvanted monovalent /Novartis /15 µg (n=72)	Up to 18 months	5 subjects (3 multiple seizure, 2 febrile convulsion) in adjuvanted arm, 2 subjects (febrile convulsion) in non-adjuvanted group.
Vesikari 2015	6-71 months (ATIV primed)	MF59-adjuvanted TIV /Novartis/30 µg (n=33)	Non-adjuvanted TIV /Novartis/30 µg (n=24)	Up to 6 months	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Zedda 2015	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=43)	Non-adjuvanted /Novartis/30 µg (n=39)	Did not report follow-up time for SAE	Did not report neurological event data.
Vesikari 2018†	6-60 months	MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=5,243)	Non-adjuvanted inactivated /Sanofi Pasteur/30 µg (n=5,161)	Up to 366 to 390 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.

<b>Study</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/HA content per ml (n)</b>	<b>Comparator /manufacturer/HA content per ml (n)</b>	<b>Follow-up time</b>	<b>Results</b>
Cruz-Valdez 2018	6-71 months	MF59-adjuvanted TIV /Novartis/30 µg (n=140)	Non-adjuvanted TIV /Novartis/30 µg (n=137)	Up to 50 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.
Diallo 2018†	6-71 months	MF59-adjuvanted TIV /Novartis/30µg (n=118)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=119)	Up to 112 days	0 subjects in adjuvanted arm, 0 subjects in non-adjuvanted arm.

\*This trial compared adjuvanted and non-adjuvanted vaccine formulations with unequal hemagglutinin antigen dose. The hemagglutinin antigen dose was reduced in the adjuvanted arm (antigen-sparing design).

†This trial compared adjuvanted influenza vaccines and non-adjuvanted influenza vaccines from different manufacturers.

Supplementary Table 5. Randomized controlled trials that reported reactogenicity data

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/ HA content per ml (n)</b>	<b>Time point</b>	<b>Symptoms</b>
Vesikari 2009† (PIDJ)	Observer-blind Randomized	Finland	H1N1, H3N2, B	6-35 months	MF59-adjuvanted subunit /Novartis/30 µg (n=130)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=139)	after 1st and 2nd doses	Pain Fever
Vesikari 2009† (Vaccine)	Observer-blind Randomized	Finland	H1N1, H3N2, B	16-47 months	MF59-adjuvanted subunit /Novartis/30 µg (n=43)	Non-adjuvanted split /Sanofi Pasteur/30 µg (n=46)	after 1st dose	Fever
Waddington 2010*† (Funded by UK NIHR)	Phase 2 Open-label Randomized	5 sites in UK	H1N1	6-59 months	AS03-adjuvanted split virion /GSK/1.875 µg (n=270)	Non-adjuvanted whole virion /Baxter/3.75 µg (n=279)	after 1st and 2nd doses	Pain Fever
Arguedas 2011*	Phase 3 Open-label Randomized	Costa Rica	H1N1	3-8 years	MF59-adjuvanted /Novartis/15 µg (n=56)	Non-adjuvanted /Novartis/30 µg (n=54)	after 1st and 2nd doses	Pain

<b>Study</b>	<b>Study design</b>	<b>Setting</b>	<b>Vaccine strain</b>	<b>Age of participants</b>	<b>Intervention /manufacturer/H A content per ml (n)</b>	<b>Comparator /manufacturer/ HA content per ml (n)</b>	<b>Time point</b>	<b>Symptoms</b>
Della Cioppa 2011†	Observer-blind Randomized	15 study centers in Finland and Belgium	H1N1, H3N2, B	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=37)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=43)	after 1st and 2nd doses	Reported pool solicited data by local and systemic reactions
Vesikari 2011	Phase 3 Observer-blind Randomized	Germany, Finland	H1N1, H3N2, B	6-35 months 36-71 months	MF59-adjuvanted /Novartis/30 µg (n=1100) MF59-adjuvanted /Novartis/30 µg (n=833)	Non-adjuvanted subunit /Novartis/30 µg (n=992) Non-adjuvanted subunit /Novartis/30 µg (n=777)	after 1st and 2nd doses after 1st and 2nd doses	Fever Pain Fever
Block 2012	Phase 2 Phase 3 Double-blind Randomized	29 sites in USA and Mexico	H1N1	6-35 months	MF59-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	Non-adjuvanted monovalent subunit /Novartis/30 µg (n=161)	after 1st and 2nd doses	Pain Fever

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Time point	Symptoms
Langley 2012*	Double-blind Randomized	12 centers in Canada	H1N1	6 months-8 years	AS03-adjuvanted monovalent /GSK /15 µg (n=59)	Non-adjuvanted monovalent /GSK/30 µg (n=57)	7 d after 1st and 2nd doses	Pain Fever (did not report case number or percentage for adjuvanted and non-adjuvanted groups respectively )
Nassim 2012	Phase 2 phase 3 Single-blind Randomized	34 centers in USA	H1N1	3-8 years (antigen 7.5µg)	MF59-adjuvanted monovalent /Novartis/30 µg (n=168)	Non-adjuvanted monovalent /Novartis/30 µg (n=167)	after 1st and 2nd doses	Pain Fever
Nolan 2014†	Phase 3 Observer-blind Randomized	32 sites in Argentina, Australia, Chile, Philippines, South Africa	H1N1, H3N2, B	6-71 months	MF59-adjuvanted /Novartis/30 µg (n=3,074)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=1,443)	after 1st and 2nd doses	Pain Fever

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Time point	Symptoms
Nolan 2014*	Phase 3 Observer-blind Randomized	17 centers in Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, Thailand	H1N1	6-35 months	AS03-adjuvanted monovalent /GSK/7.5 µg (n=2,048)	Non-adjuvanted monovalent /GSK/30 µg (n=2,049)	after 1st and 2nd doses	Pain Fever
Solares 2014†	phase 2 Observer-blind Randomized	5 sites in Guatemala	H1N1, H3N2, B	6-35 months	MF59-adjuvanted TIV /Novartis/30 µg (n=130)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=130)	after 1st and 2nd doses	Pain Fever
				36-59 months	MF59-adjuvanted TIV /Novartis/30 µg (n=50)	Non-adjuvanted TIV /Sanofi Pasteur/30 µg (n=50)	after 1st and 2nd doses	Pain Fever
Knuf 2015*	Single-blind Randomized	13 centers in Germany, Belgium, Dominican Republic, Netherlands	H1N1	12-35 months	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=73)	Non-adjuvanted monovalent /Novartis/15 µg (n=33)	after 1st and 2nd doses	Pain Fever

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Time point	Symptoms
Vesikari 2015	Observer-blind Randomized	15 sites in Finland	H1N1, H3N2, B	3-8 years	MF59-adjuvanted monovalent /Novartis/7.5 µg (n=72)	Non-adjuvanted monovalent /Novartis/15 µg (n=39)	after 1st and 2nd doses	Pain Fever
					MF59-adjuvanted TIV /Novartis/30 µg (n=12)	Non-adjuvanted TIV /Novartis/30 µg (n=10)		
				6-71 months (TIV primed)	MF59-adjuvanted TIV /Novartis/30 µg (n=21)	Non-adjuvanted TIV /Novartis/30 µg (n=14)	after 1st dose	Pain Fever
					MF59-adjuvanted TIV /Novartis/30 µg (n=43)	Non-adjuvanted TIV /Novartis/30 µg (n=39)		
Zedda 2015	Randomized	Belgium	H1N1, H3N2, B	6-35 months	MF59-adjuvanted /Novartis/30 µg (n=43)	Non-adjuvanted /Novartis/30 µg (n=39)	after 1st and 2nd doses	Pain Fever
Vesikari 2018†	Phase 3 Observer-blind, Randomized	146 sites including hospitals, clinics and clinician offices in Finland, USA, Canada, Italy, Poland, Spain, Philippines, Thailand, Taiwan	H1N1, H3N2, B	6-60 months	MF59-adjuvanted, subunit quadrivalent, inactivated /Seqirus/30 µg (n=5,138)	Non-adjuvanted, split virion, inactivated /Sanofi Pasteur/30 µg (n=5,056)	Pooled data of after 1st and 2nd doses	Pain Fever

Study	Study design	Setting	Vaccine strain	Age of participants	Intervention /manufacturer/H A content per ml (n)	Comparator /manufacturer/ HA content per ml (n)	Time point	Symptoms
Diallo 2018†	Observer-blind randomized	Senegal	H1N1, H3N2, B	6-35 months	MF59-adjuvanted TIV /Novartis/30 µg (n=78)	Non-adjuvanted /Sanofi Pasteur/30 µg TIV (n=79)	after 1st and 2nd doses	Pain Fever
					MF59-adjuvanted TIV /Novartis/30 µg (n=40)	Non-adjuvanted /Sanofi Pasteur/30 µg (n=40)		
Cruz-Valdez 2018	Phase 3 Observer-blind randomized	Mexico	H1N1, H3N2, B	36-71 months	MF59-adjuvanted TIV /Novartis/30 µg (n=140)	Non-adjuvanted TIV /Novartis/30 µg (n=137)	after 1st and 2nd doses	Reported pool solicited data by local and systemic reactions
					MF59-adjuvanted TIV /Novartis/30 µg (n=140)	Non-adjuvanted TIV /Novartis/30 µg (n=137)		

\*This trial compared adjuvanted and non-adjuvanted vaccine formulations with unequal hemagglutinin antigen dose. The hemagglutinin antigen dose was reduced in the adjuvanted arm (antigen-sparing design).

†This trial compared adjuvanted influenza vaccines and non-adjuvanted influenza vaccines from different manufacturers.

Supplementary Table 6. Summary of findings: certainty of evidence for effect outcomes

**Summary of findings:**

**Oil-in-water emulsion adjuvanted influenza vaccine compared to non adjuvanted influenza vaccine in children**

Patient or population: children

Setting: Poor response ( a <25% seroprotection after a single dose of nonadjuvanted influenza vaccine)

Intervention: oil-in-water emulsion adjuvanted influenza vaccine

Comparison: non adjuvanted influenza vaccine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non adjuvanted influenza vaccine	Risk with oil-in- water emulsion adjuvanted influenza vaccine				
vaccine efficacy assessed with RT-PCR test	22 per 1,000	<b>6 per 1,000</b> (3 to 10)	<b>RR 0.26</b> (0.14 to 0.47)	4839 (3 RCTs)	⊕⊕⊕⊕ HIGH <sup>a,b</sup>	
seroprotection assessed with: HI titer for H1N1 influenza virus after the first dose follow up: range 21 days to 28 days	195 per 1,000	<b>897 per 1,000</b> (800 to 1,015)	<b>Rate ratio 4.6</b> (4.1 to 5.2)	2308 (4 RCTs)	⊕⊕⊕○ MODERATE <sup>c,d,e,f</sup>	
seroprotection assessed with: HI titer for H3N2 influenza virus after the first dose follow up: range 21 days to 28 days	119 per 1,000	<b>944 per 1,000</b> (800 to 1,123)	<b>Rate ratio 7.9</b> (6.7 to 9.4)	2178 (2 RCTs)	⊕⊕⊕○ MODERATE <sup>d,e,g</sup>	
seroprotection assessed with: HI titer for influenza B after the first dose follow up: range 21 days to 28 days	120 per 1,000	<b>168 per 1,000</b> (96 to 276)	<b>Rate ratio 1.4</b> (0.8 to 2.3)	2377 (3 RCTs)	⊕○○○ VERY LOW <sup>e,g,h,i,j</sup>	
seroprotection assessed with: HI titer for influenza B after the second dose follow up: range 21 days to 28 days	187 per 1,000	<b>1010 per 1,000</b> (711 to 1,403)	<b>Rate ratio 5.4</b> (3.8 to 7.5)	2176 (2 RCTs)	⊕⊕⊕○ MODERATE <sup>d,e,f,k</sup>	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

- a. Only 3 of the 18 included trials reported efficacy data.
- b. RR<0.5
- c. Only 21 of the 26 included comparisons reported seroprotection rate data after the first-dose vaccination.
- d. The rate ratio was for poor response group. Meta-regression shows that between-trials heterogeneity in rate ratio was nearly all explained by serological response rates in the non-adjuvanted arm (see text for details).
- e. Measurement of immunogenicity was used as a surrogate for real-life protection against infection, disease and death
- f. RR>2.0
- g. Only 12 of the 26 included comparisons reported seroprotection rate data after the first-dose vaccination.
- h. Test for heterogeneity p=0.05, I-square 67%
- i. The rate ratio was for poor response group
- j. Wide confidence interval
- k. Only 13 of the 26 included comparisons reported seroprotection rate data after the second-dose vaccination.

Supplementary Table 7. Summary of findings: certainty of evidence for harm outcomes

**Summary of findings:**

**Oil-in-water emulsion adjuvanted influenza vaccine compared to non adjuvanted influenza vaccine in children**

Patient or population: children

Setting:

Intervention: oil-in-water emulsion adjuvanted influenza vaccine

Comparison: non adjuvanted influenza vaccine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non adjuvanted influenza vaccine	Risk with oil-in- water emulsion adjuvanted influenza vaccine				
Severe adverse events 47 per 1,000	<b>42 per 1,000</b> (33 to 52)	<b>RR 0.9</b> (0.7 to 1.1)	25541 (15 RCTs)	⊕○○○	VERY LOW <sup>a,b,c</sup>	
Neurological events 0 per 1,000	<b>1 per 1,000</b> (0 to 2)	<b>RR 1.4</b> (0.4 to 4.3)	20802 (15 RCTs)	⊕⊕○○	LOW <sup>d,e</sup>	
pain at the injection site after the first dose assessed with: yes or no 326 per 1,000	<b>424 per 1,000</b> (391 to 489)	<b>RR 1.3</b> (1.2 to 1.5)	23184 (14 RCTs)	⊕⊕○○	LOW <sup>f,g</sup>	
pain at the injection site after the second dose assessed with: yes or no 199 per 1,000	<b>299 per 1,000</b> (239 to 359)	<b>RR 1.5</b> (1.2 to 1.8)	12791 (13 RCTs)	⊕⊕○○	LOW <sup>h,i</sup>	
fever after the first dose assessed with: body temperature higher than 38 Celsius degree 93 per 1,000	<b>149 per 1,000</b> (130 to 167)	<b>RR 1.6</b> (1.4 to 1.8)	25359 (14 RCTs)	⊕⊕○○	LOW <sup>j,k</sup>	
fever after the second dose assessed with: body temperature higher than 38 celsius degree 89 per 1,000	<b>134 per 1,000</b> (107 to 169)	<b>RR 1.5</b> (1.2 to 1.9)	14719 (12 RCTs)	⊕⊕○○	LOW <sup>l,m</sup>	

\*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

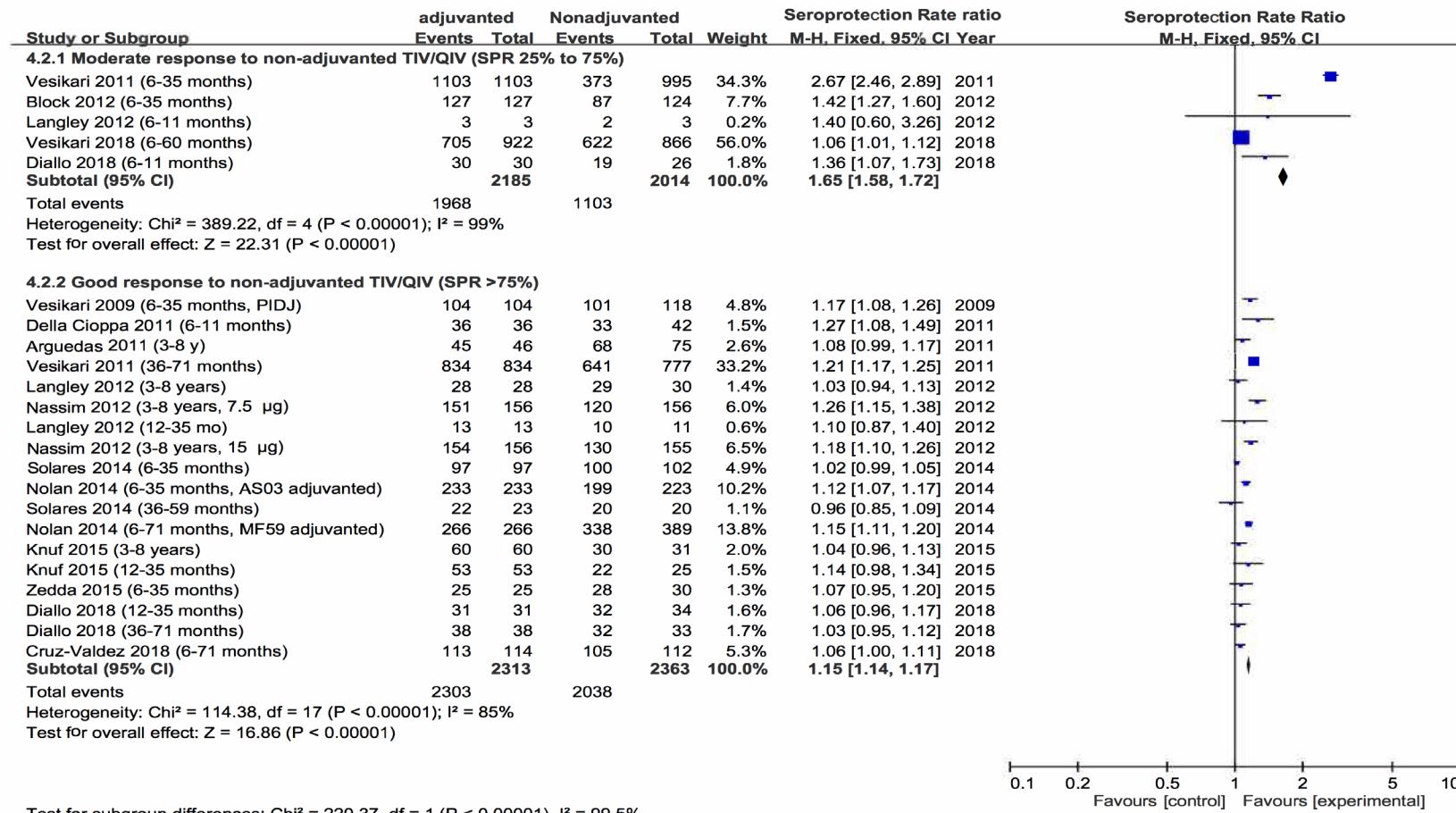
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

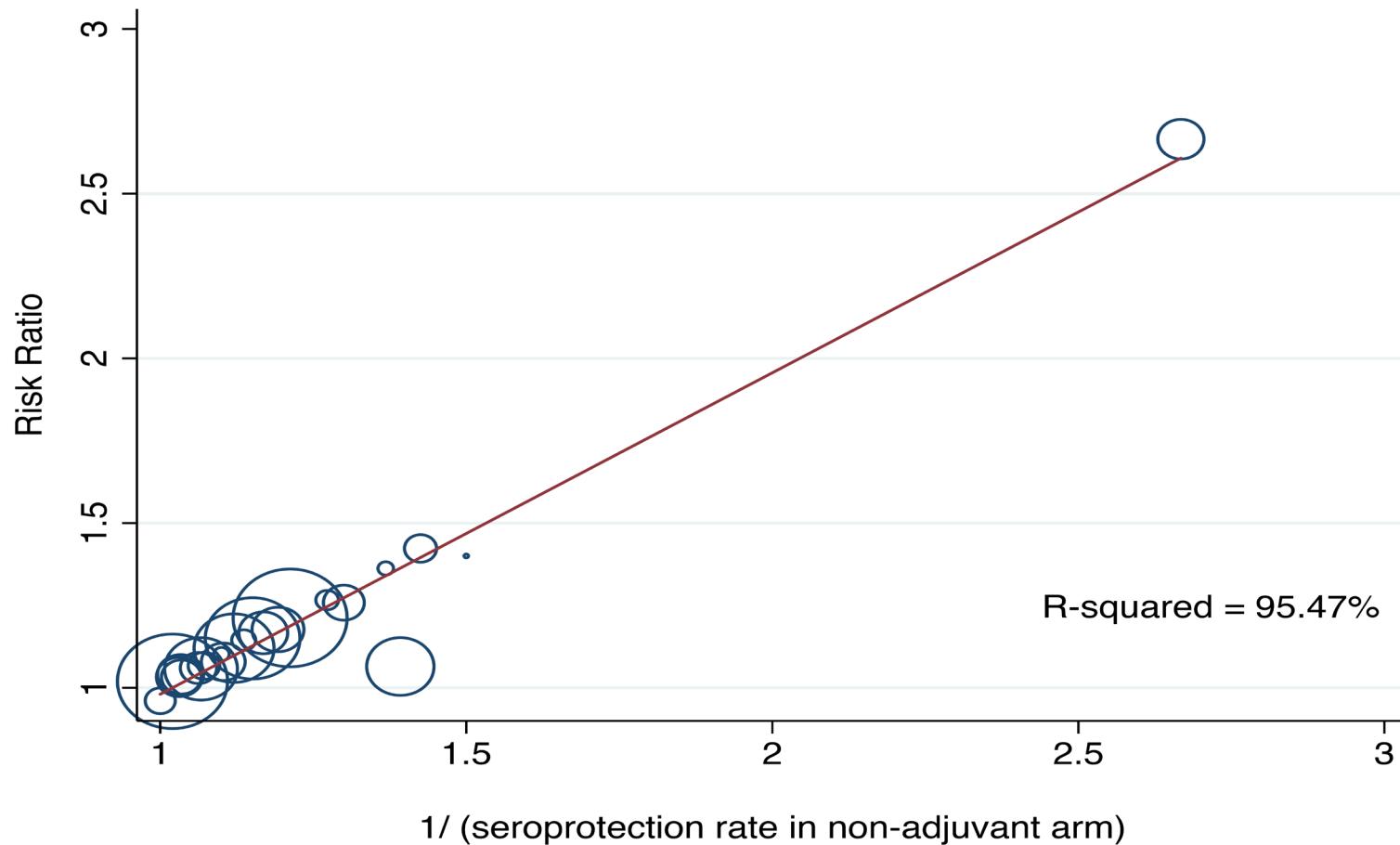
## Explanations

- a. Only 15 of the 18 included trials reported rate data of SAEs during the follow-up period
- b. Test for heterogeneity P=0.02, I-square 50%
- c. Confidence interval 0.69-1.12
- d. Only 15 of the 18 included trials reported rate data of neurological events during the follow-up period
- e. Wide confidence interval
- f. Only 19 of the 21 included comparisons reported rate data of pain after the first-dose vaccination
- g. Test for heterogeneity P<0.01, I-square 76%
- h. Only 17 of the 21 included comparisons reported rate data of pain after the second-dose vaccination
- i. Test for heterogeneity P<0.01, I-square 81%
- j. Only 20 of the 21 included comparisons reported rate data of fever after the first-dose vaccination
- k. Test for heterogeneity P=0.01, I-square 46%
- l. Only 17 of the 21 included comparisons reported rate data of fever after the second-dose vaccination
- m. Test for heterogeneity P<0.01, I-square 65%

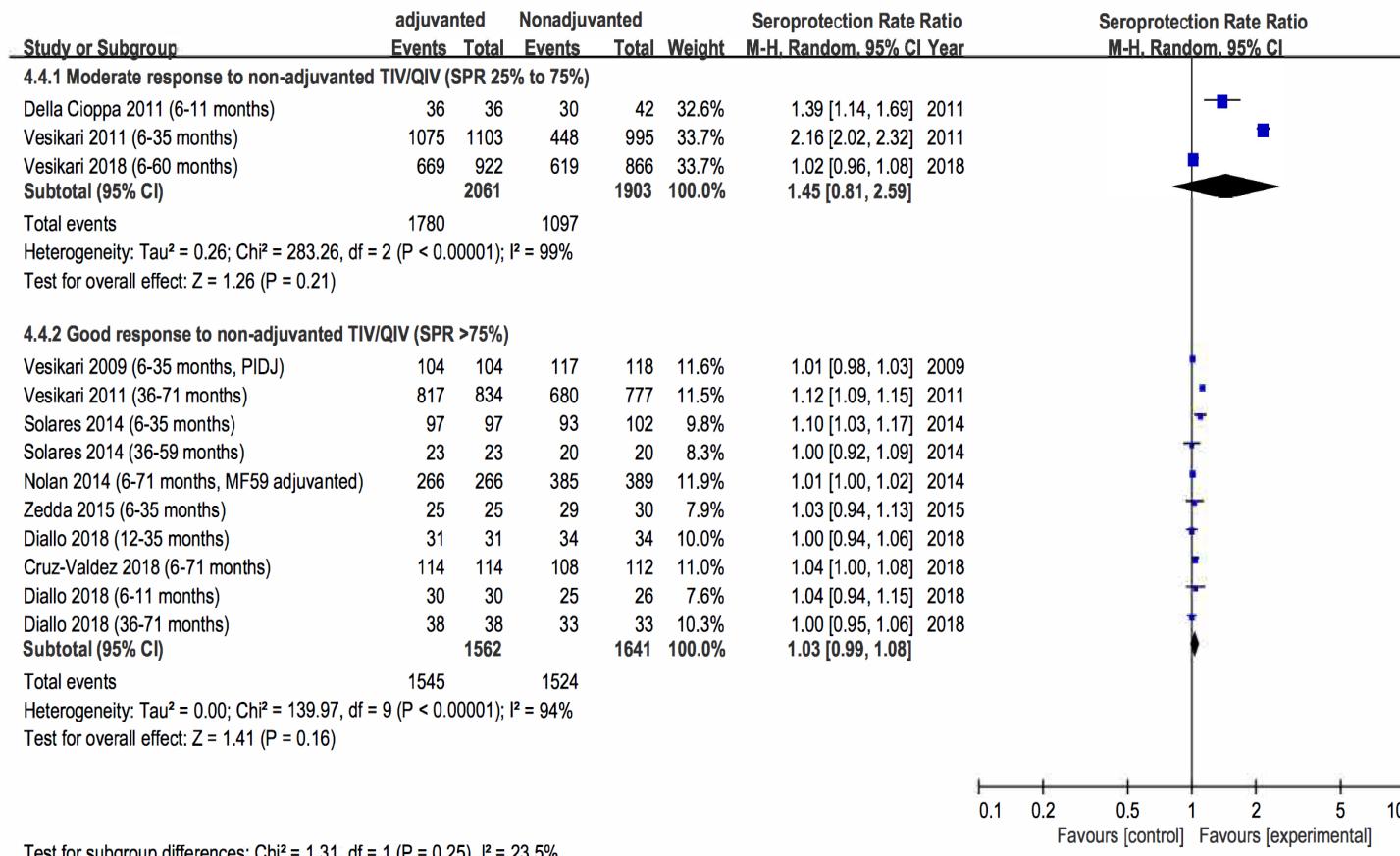
Supplementary Figure 1. Forest plot showing the ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



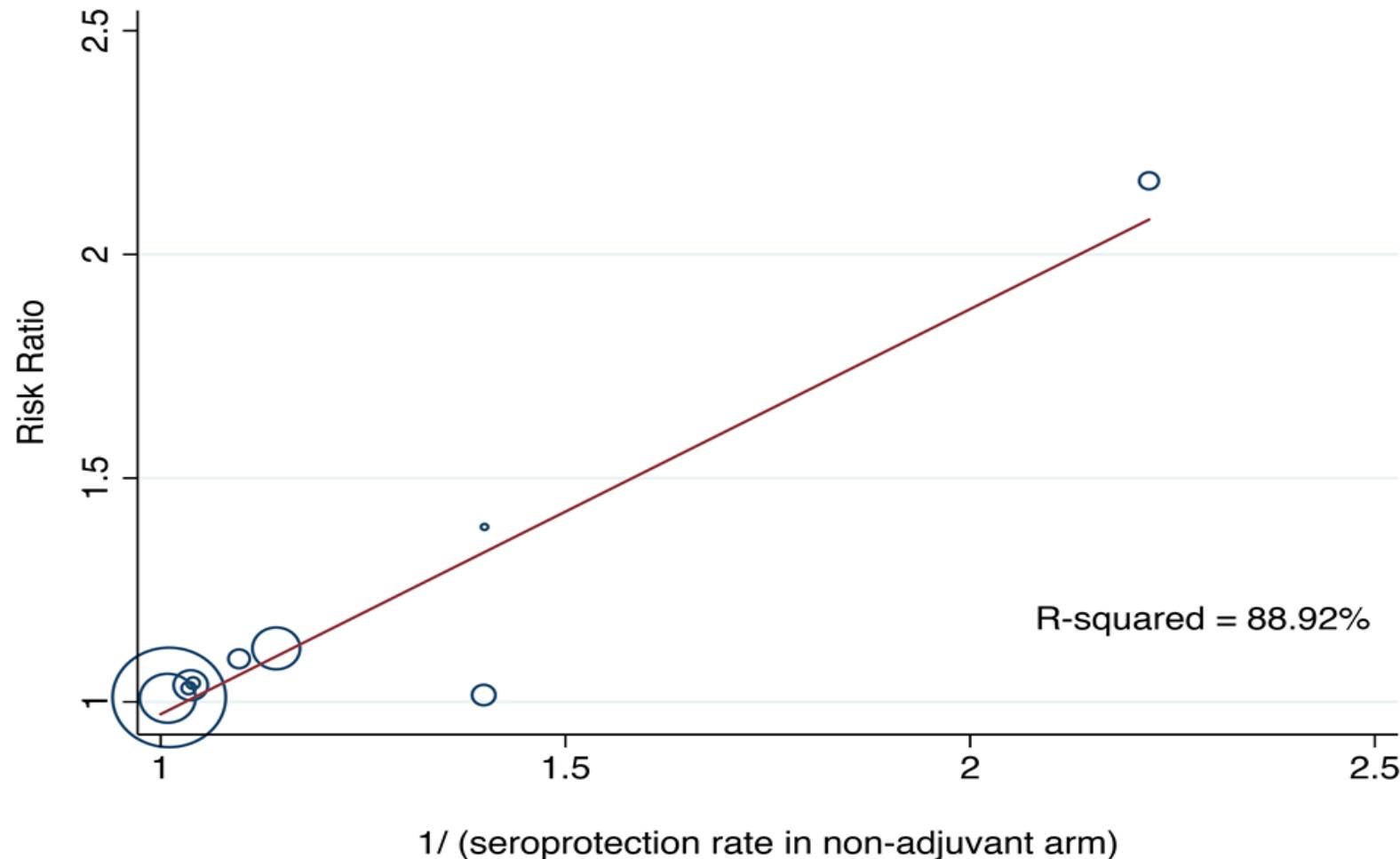
Supplementary Figure 2. Meta-regression showing a linear relationship (slope = 0.98,  $P < 0.001$ ) between the ratios of the seroprotection rate against H1N1 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 95.47%



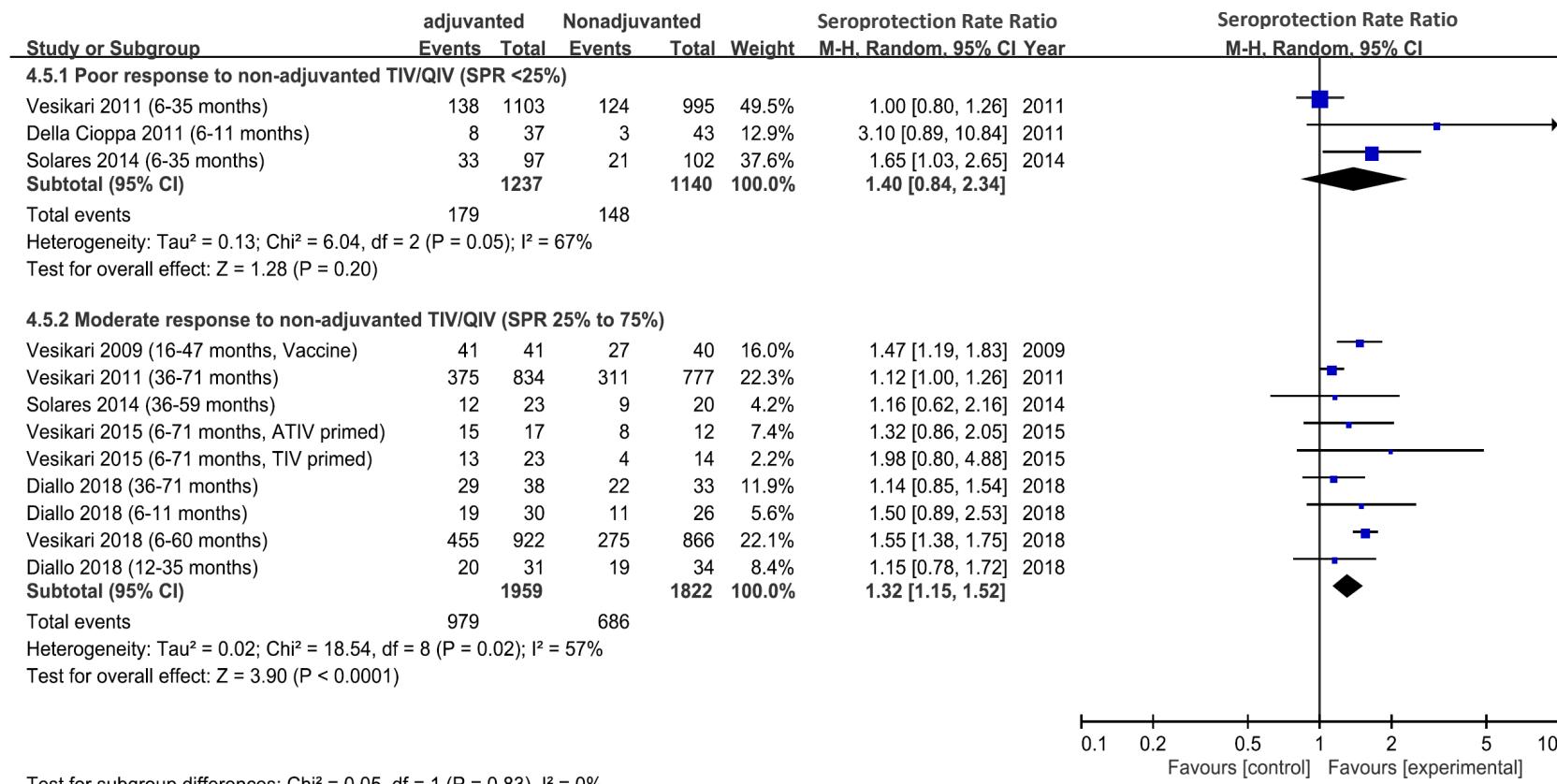
Supplementary Figure 3. Forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



Supplementary Figure 4. Meta-regression showing a linear relationship (slope = 0.91, P <0.001) between the ratios of seroprotection rates against H3N2 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 88.92%

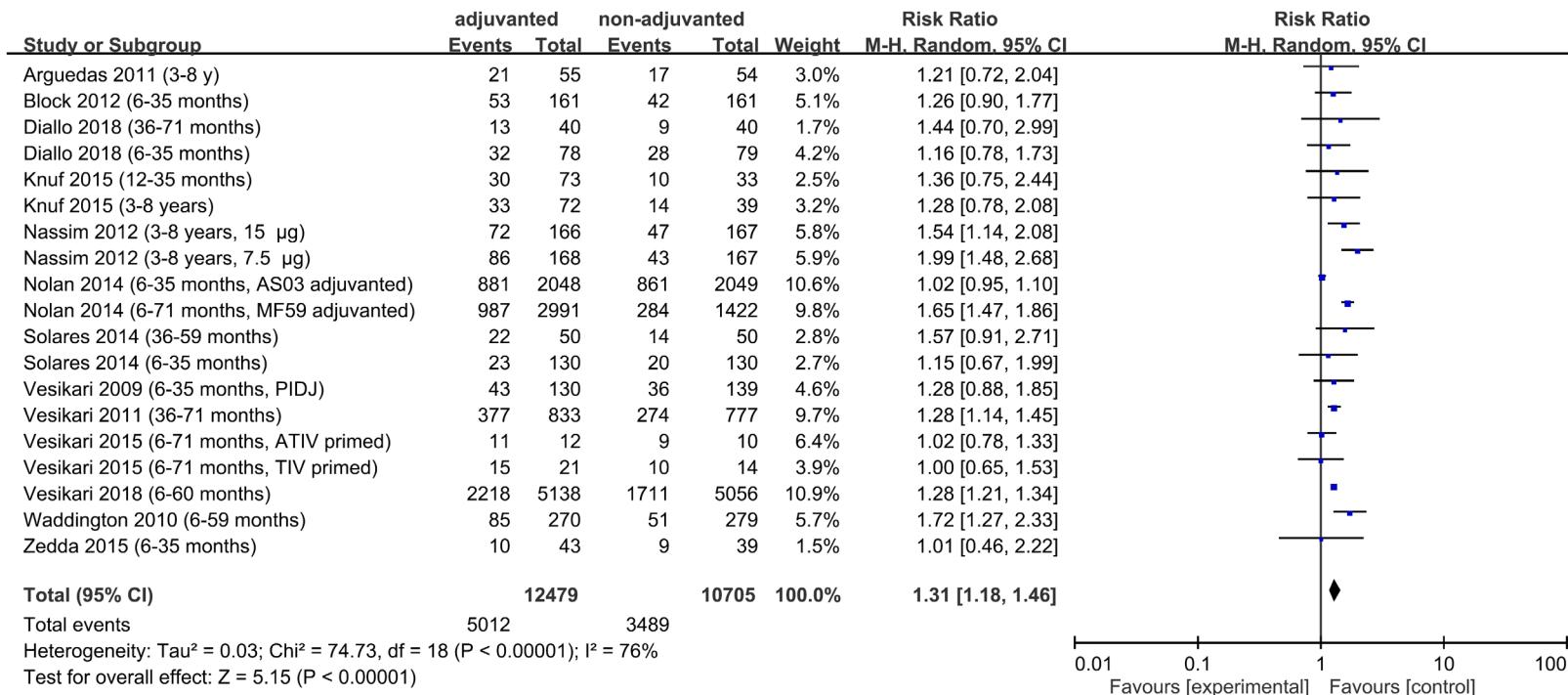


Supplementary Figure 5. Forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a  $\geq 1:40$  haemagglutinin-inhibition HI titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

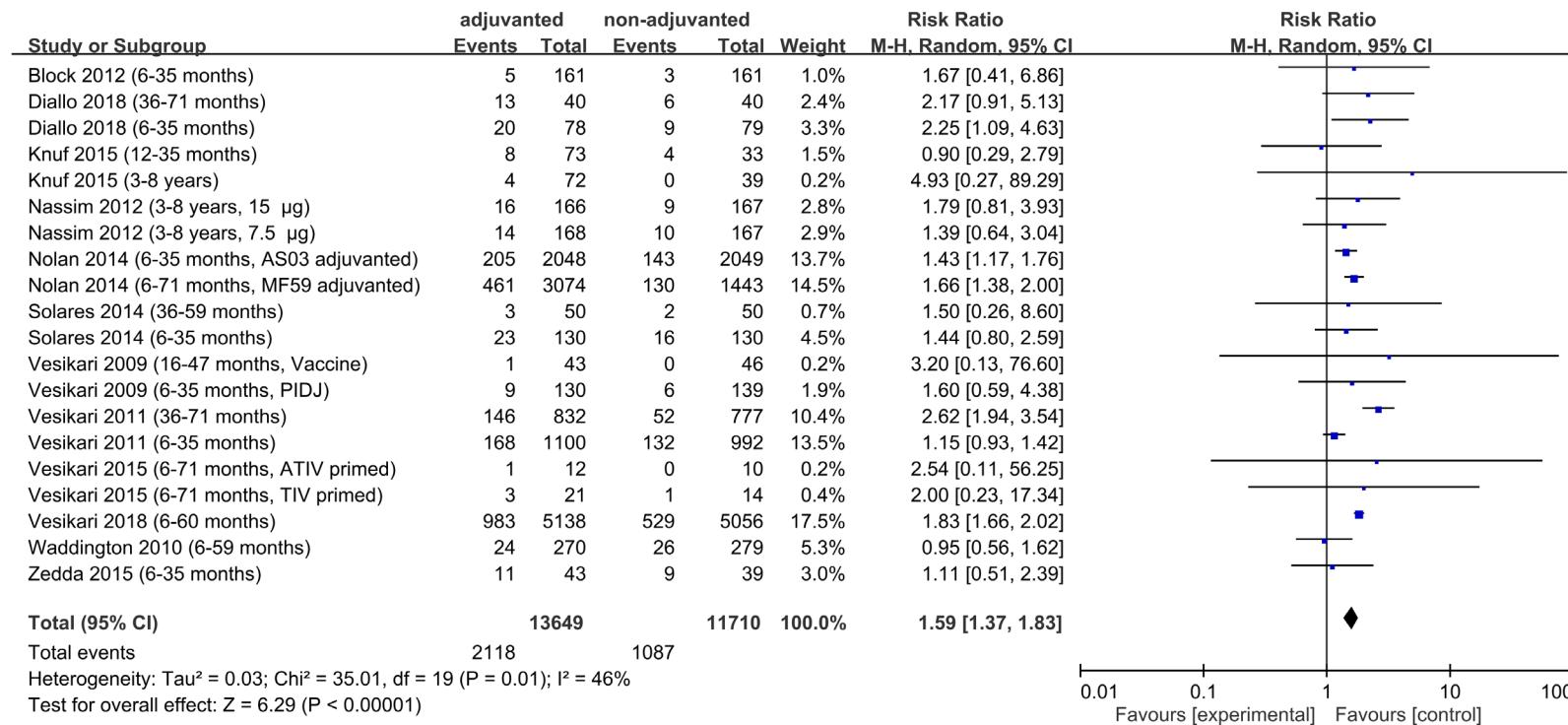


Supplementary Figure 6.

Forest plot showing the risk ratios of pain/tenderness at the injection site during the 7 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

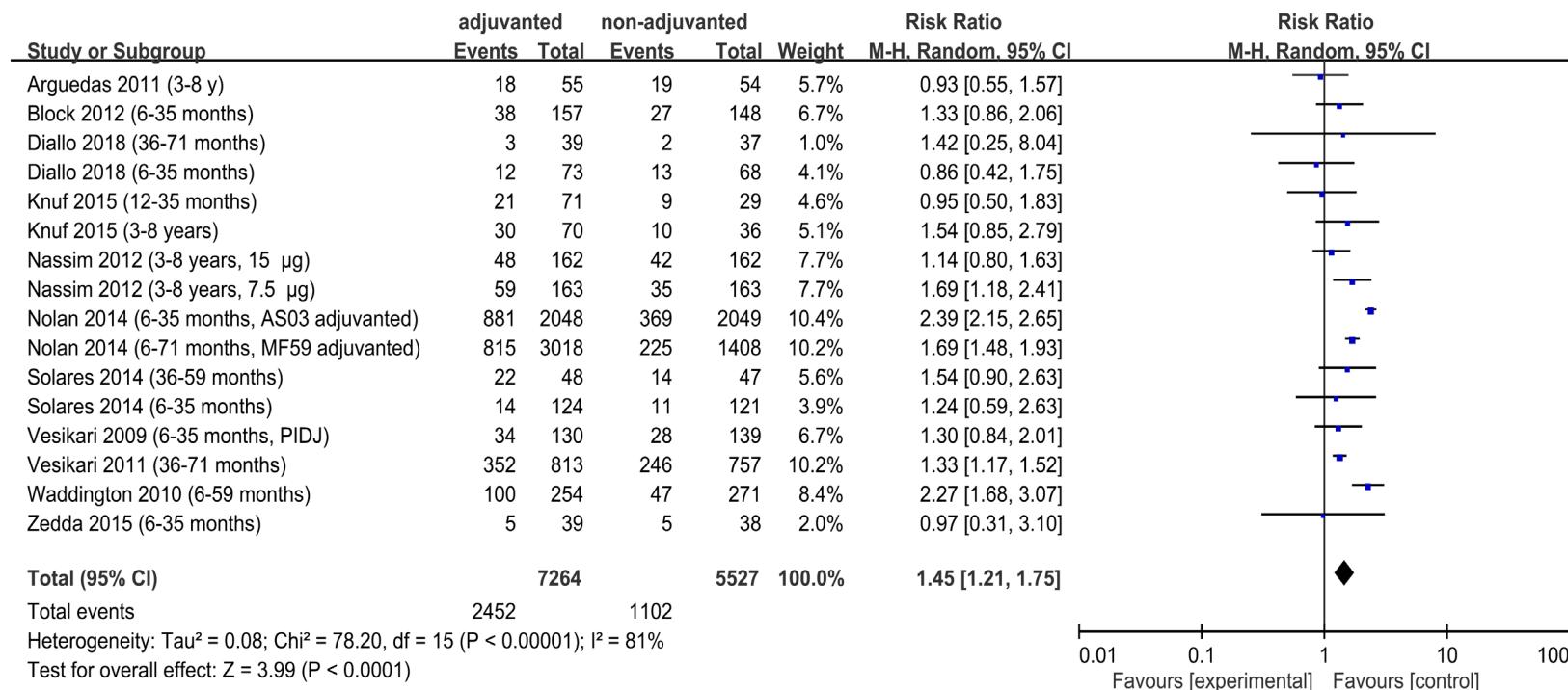


Supplementary Figure 7. Forest plot showing the risk ratios of fever during the 7 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

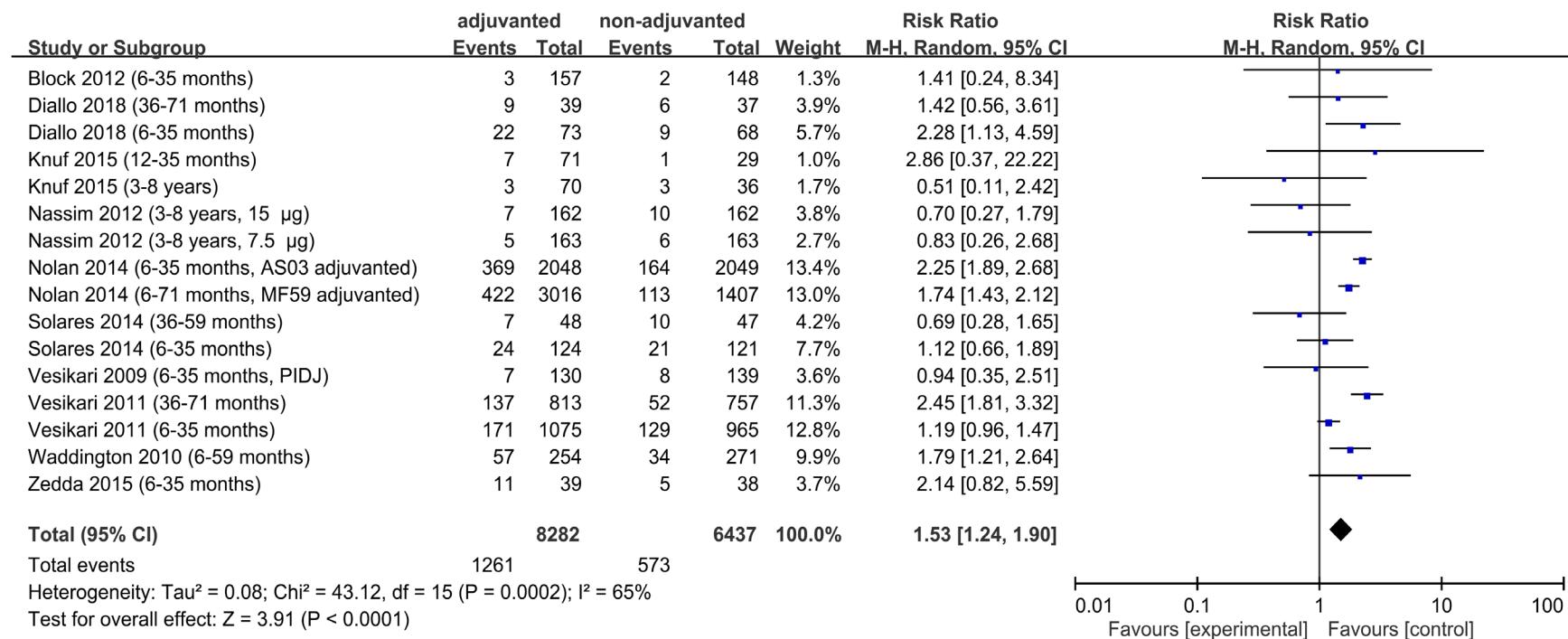


Supplementary Figure 8.

Forest plot showing the risk ratios of pain/tenderness at the injection site during the 7 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

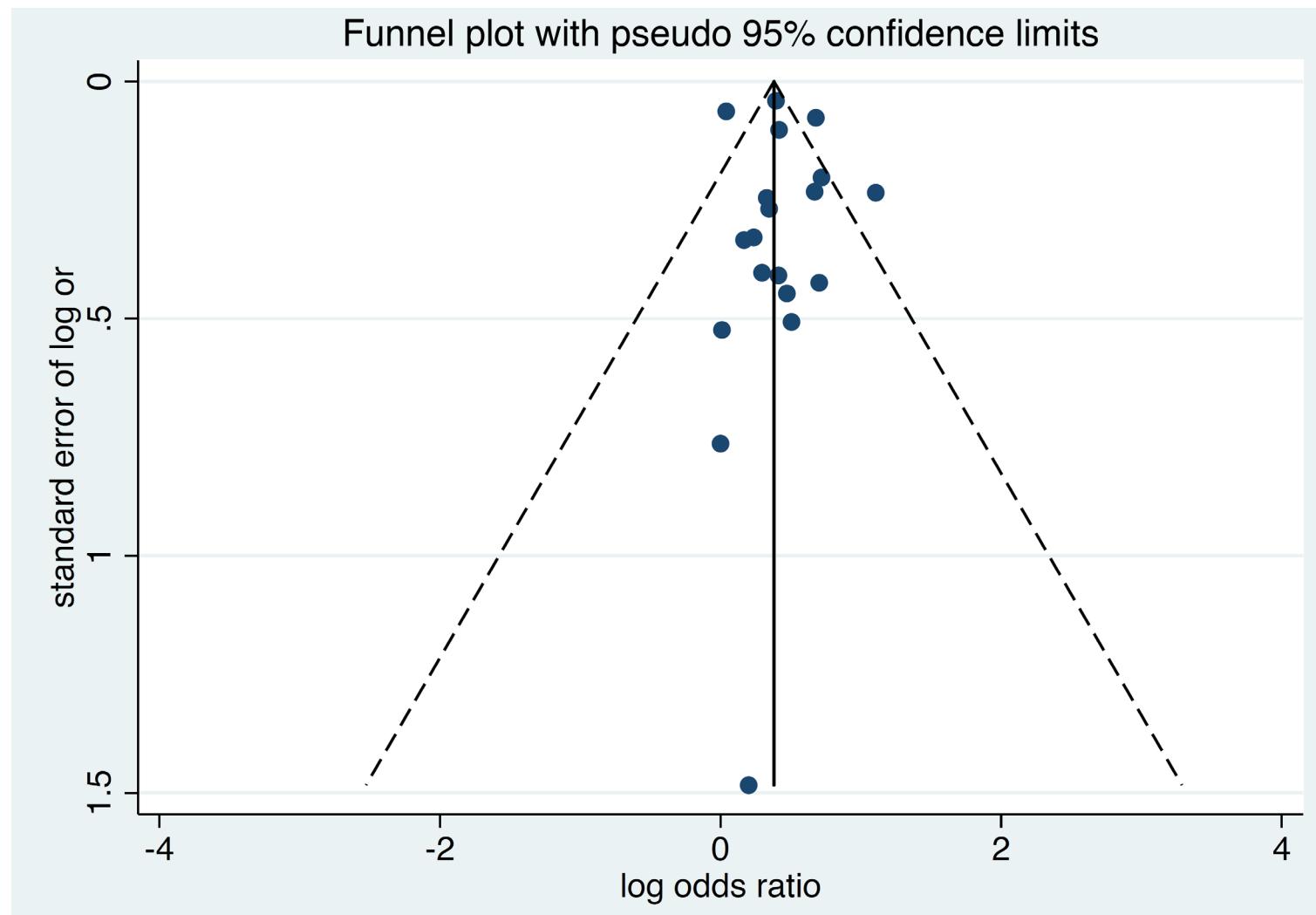


Supplementary Figure 9. Forest plot showing the risk ratios of fever during the 7 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).

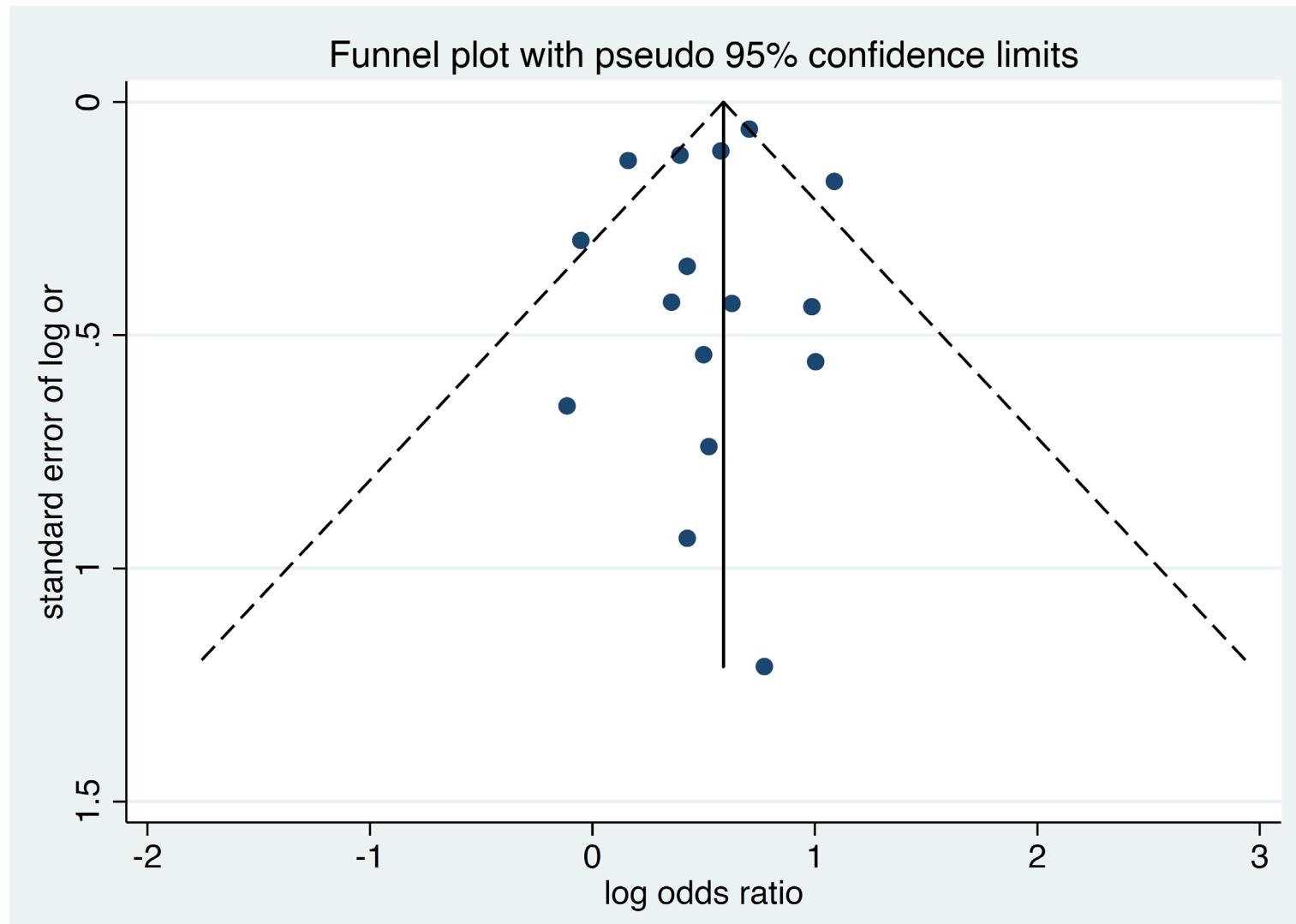


Supplementary Figure 10. Funnel plot with pseudo 95% confidence limits.

(A) Risk ratios of pain/tenderness at the injection site, during the 7 days after the first dose of influenza vaccines.



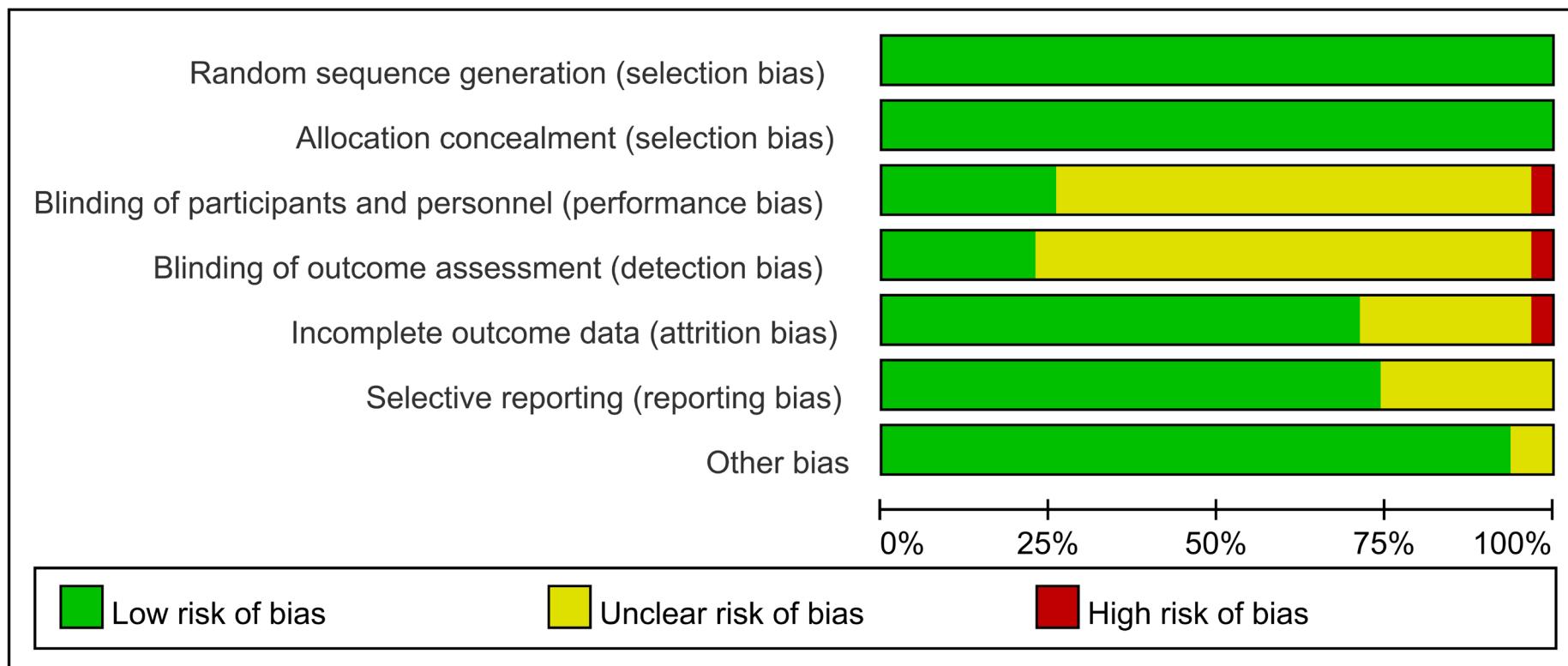
(B) Risk ratios of fever, during the 7 days after the first dose of influenza vaccines.



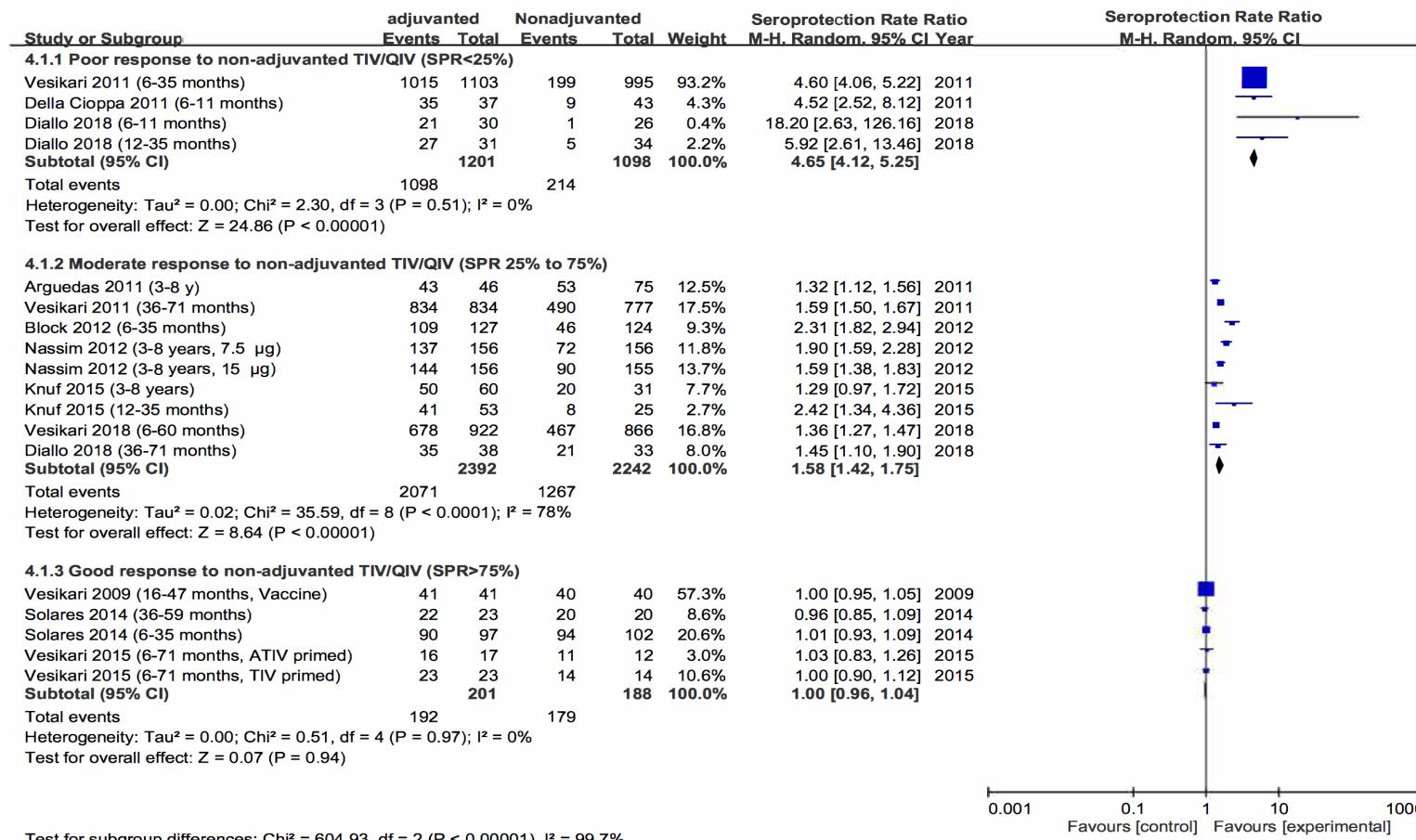
Supplementary Figure 11. Risk of bias summary.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arguedas 2011 (3-8 y)	+	+	?	?	+	+	+
Block 2012 (6-35 months)	+	+	?	?	+	+	+
Cruz-Valdez 2018 (6-71 months)	+	+	+	+	?	?	+
Della Cioppa 2011 (6-11 months)	+	+	?	?	+	+	+
Diallo 2018 (12-35 months)	+	+	+	+	+	+	+
Diallo 2018 (36-71 months)	+	+	+	+	+	+	+
Diallo 2018 (6-11 months)	+	+	+	+	+	+	+
Diallo 2018 (6-35 months)	+	+	+	+	+	+	+
Knuf 2015 (12-35 months)	+	+	?	?	+	+	+
Knuf 2015 (3-8 years)	+	+	?	?	+	+	+
Langley 2012 (12-35 mo)	+	+	?	?	+	+	?
Langley 2012 (3-8 years)	+	+	?	?	+	+	+
Langley 2012 (6-11 months)	+	+	?	?	—	+	+
Nassim 2012 (3-8 years, 15 µg)	+	+	?	?	+	+	+
Nassim 2012 (3-8 years, 7.5 µg)	+	+	?	?	+	+	+
NCT00972816, 2010 (3-8 years, 15 µg)	+	+	+	+	+	+	+
NCT00972816, 2010 (3-8 years, 7.5 µg)	+	+	+	?	+	+	+
NCT00996307 2010 (6-35 months)	+	+	+	+	+	+	+
Nolan 2014 (6-35 months, AS03 adjuvanted)	+	+	?	?	?	?	+
Nolan 2014 (6-71 months, MF59 adjuvanted)	+	+	?	?	?	?	+
Solares 2014 (36-59 months)	+	+	?	?	+	+	+
Solares 2014 (6-35 months)	+	+	?	?	+	+	+
Vesikari 2009 (16-47 months, Vaccine)	+	+	?	?	?	?	+
Vesikari 2009 (6-35 months, P1D.J)	+	+	?	?	?	?	+
Vesikari 2011 (36-71 months)	+	+	?	?	+	+	+
Vesikari 2011 (6-35 months)	+	+	?	?	+	+	+
Vesikari 2015 (6-71 months, ATIV primed)	+	+	?	?	?	?	+
Vesikari 2015 (6-71 months, TIV primed)	+	+	?	?	?	?	+
Vesikari 2018 (6-60 months)	+	+	?	?	+	+	+
Waddington 2010 (6-59 months)	+	+	?	?	+	+	+
Zedda 2015 (6-35 months)	+	+	—	—	?	?	?

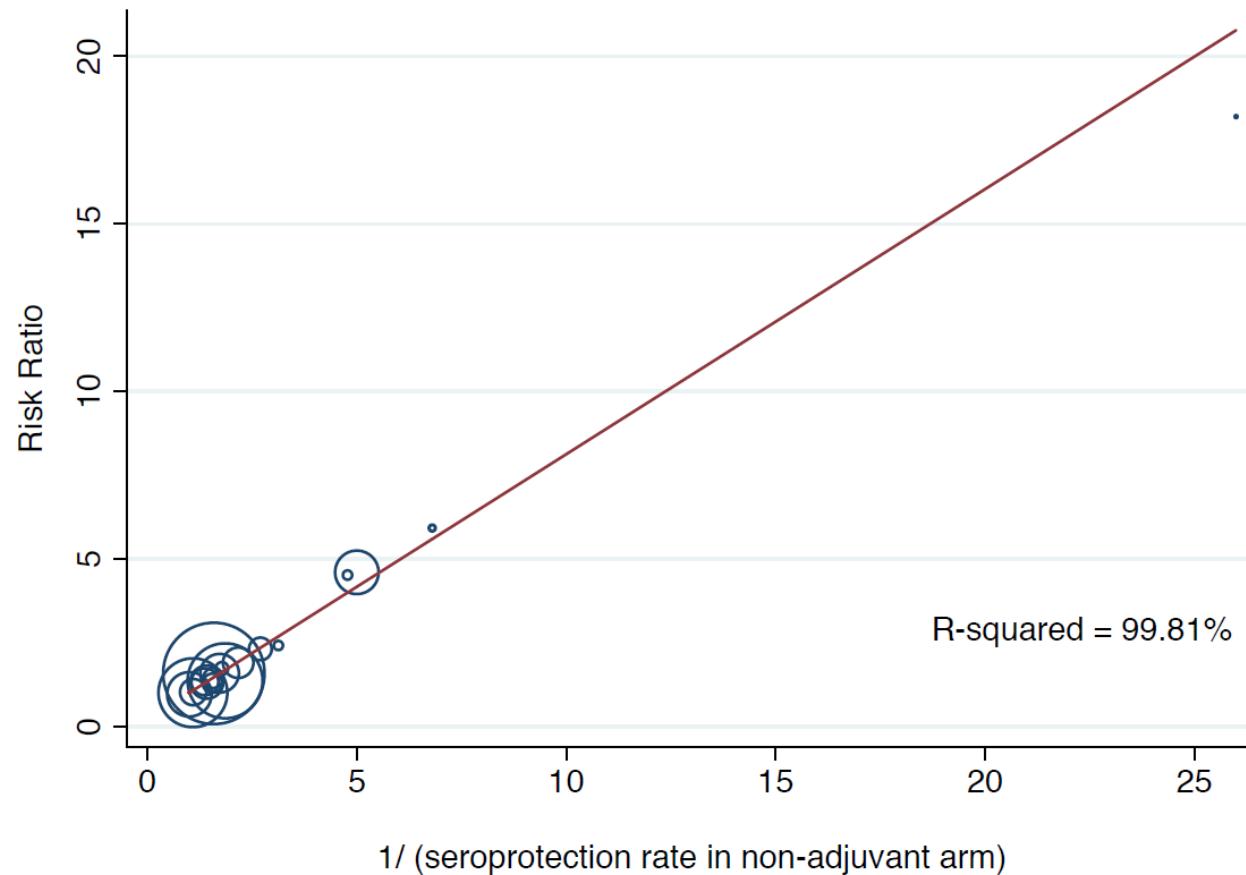
Supplementary Figure 12. Risk of bias graph.



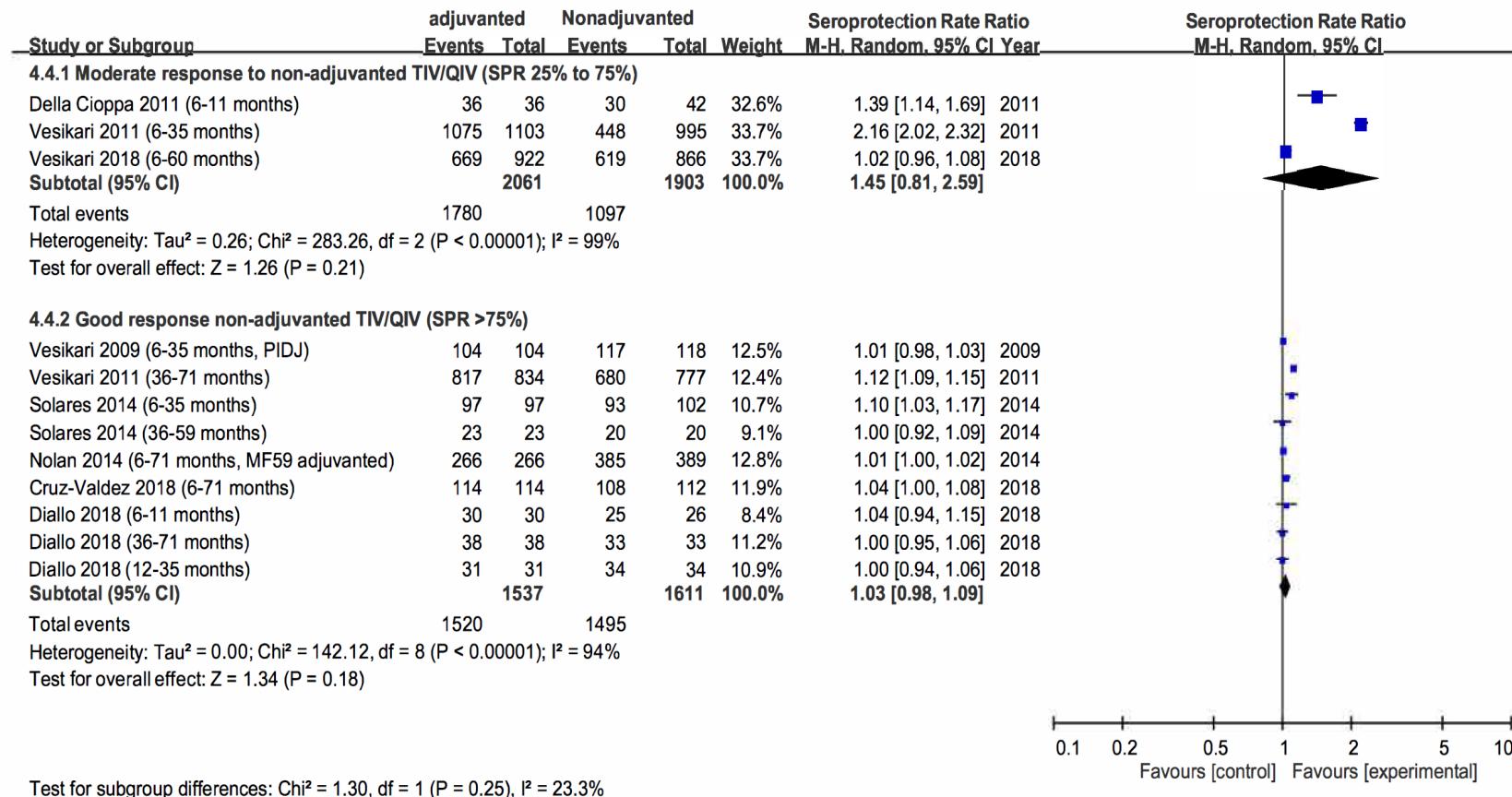
Supplementary Figure 13. Sensitivity analysis by excluding Langley (2012): forest plot showing the ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



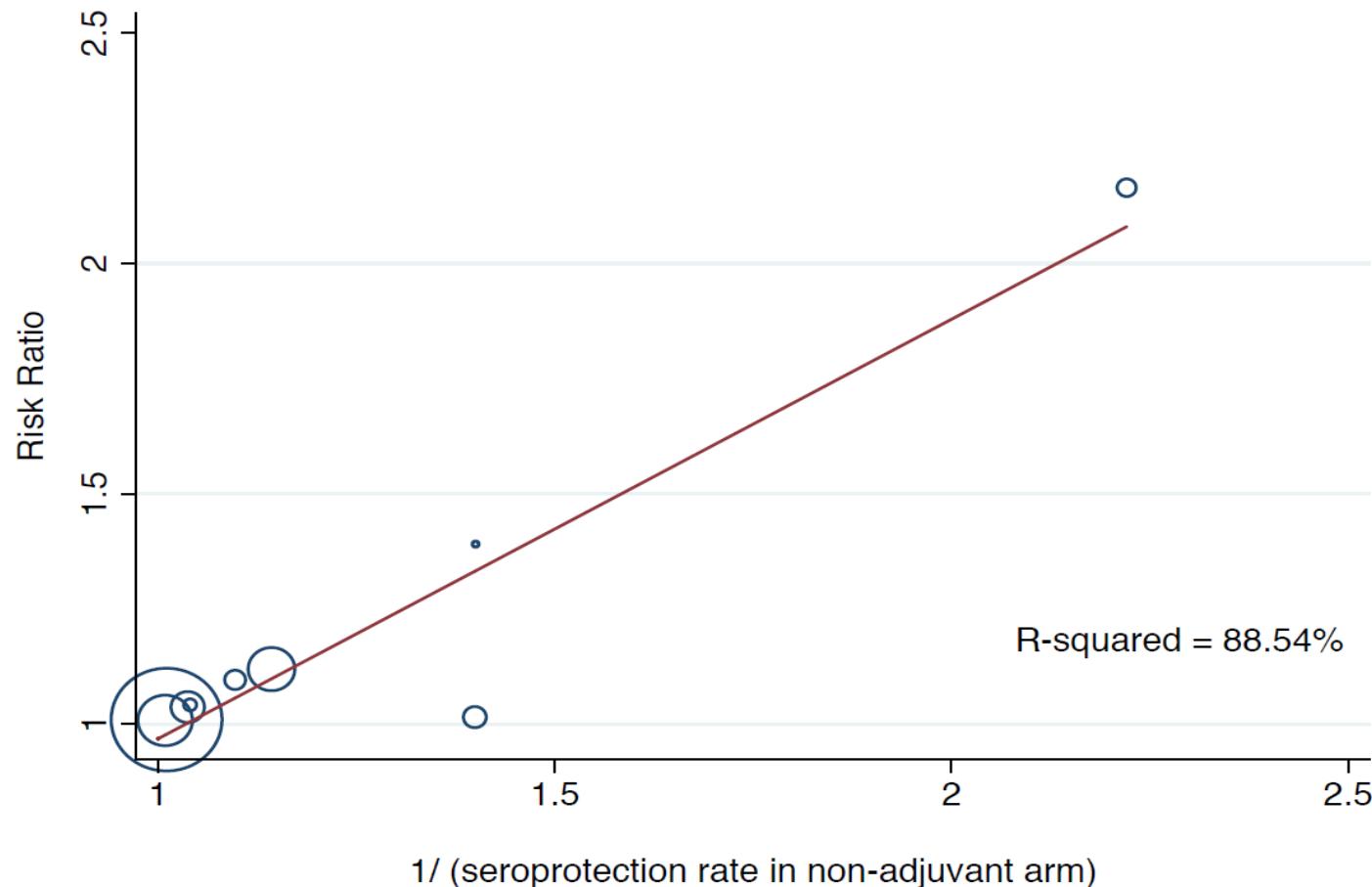
Supplementary Figure 14. Sensitivity analysis by excluding Langley (2012): meta-regression showing a linear relationship (slope = 0.79, P <0.001) between the ratios of seroprotection rates against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 99.81%.



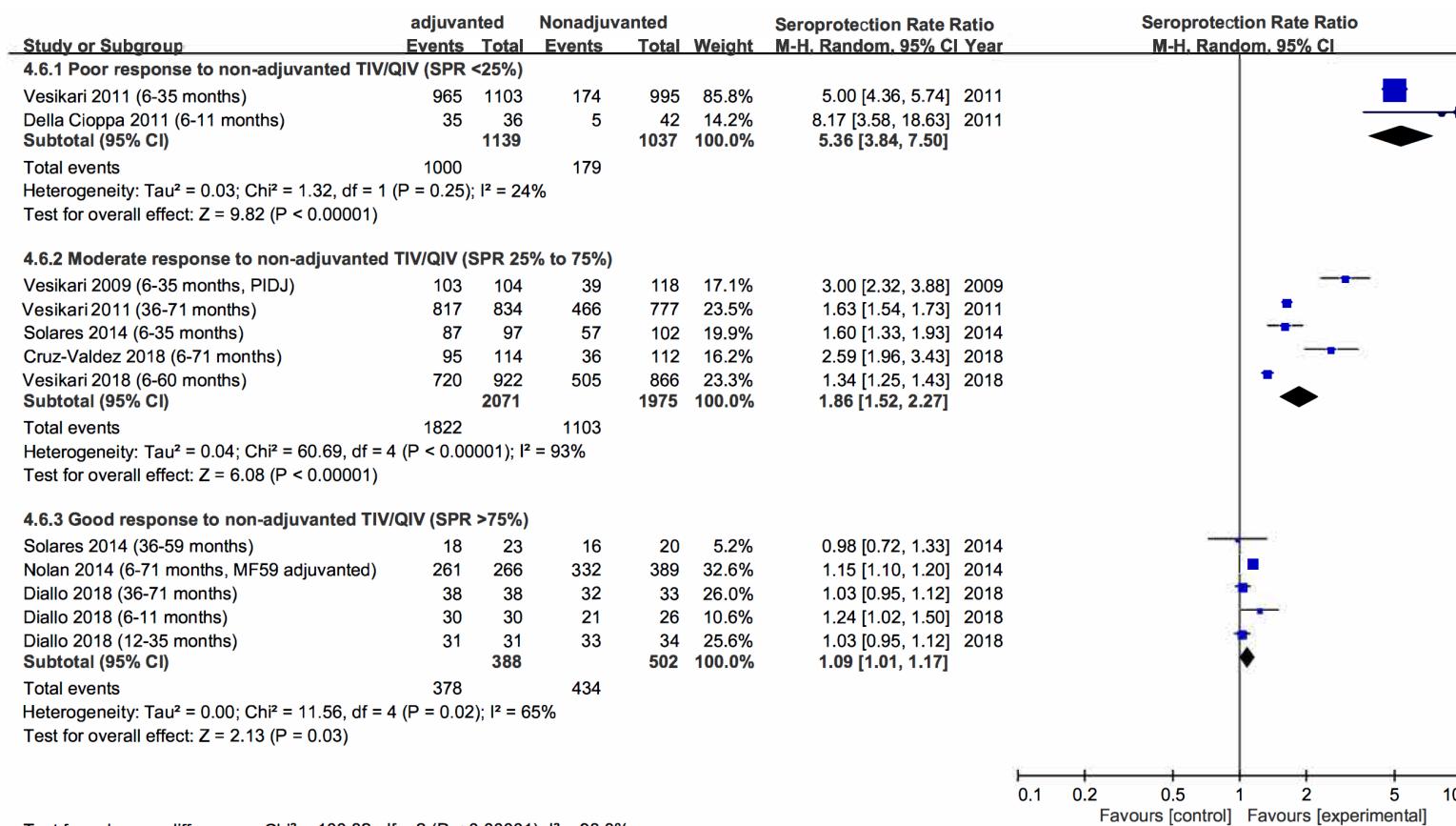
Supplementary Figure 15. Sensitivity analysis by excluding Zedda (2015): forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



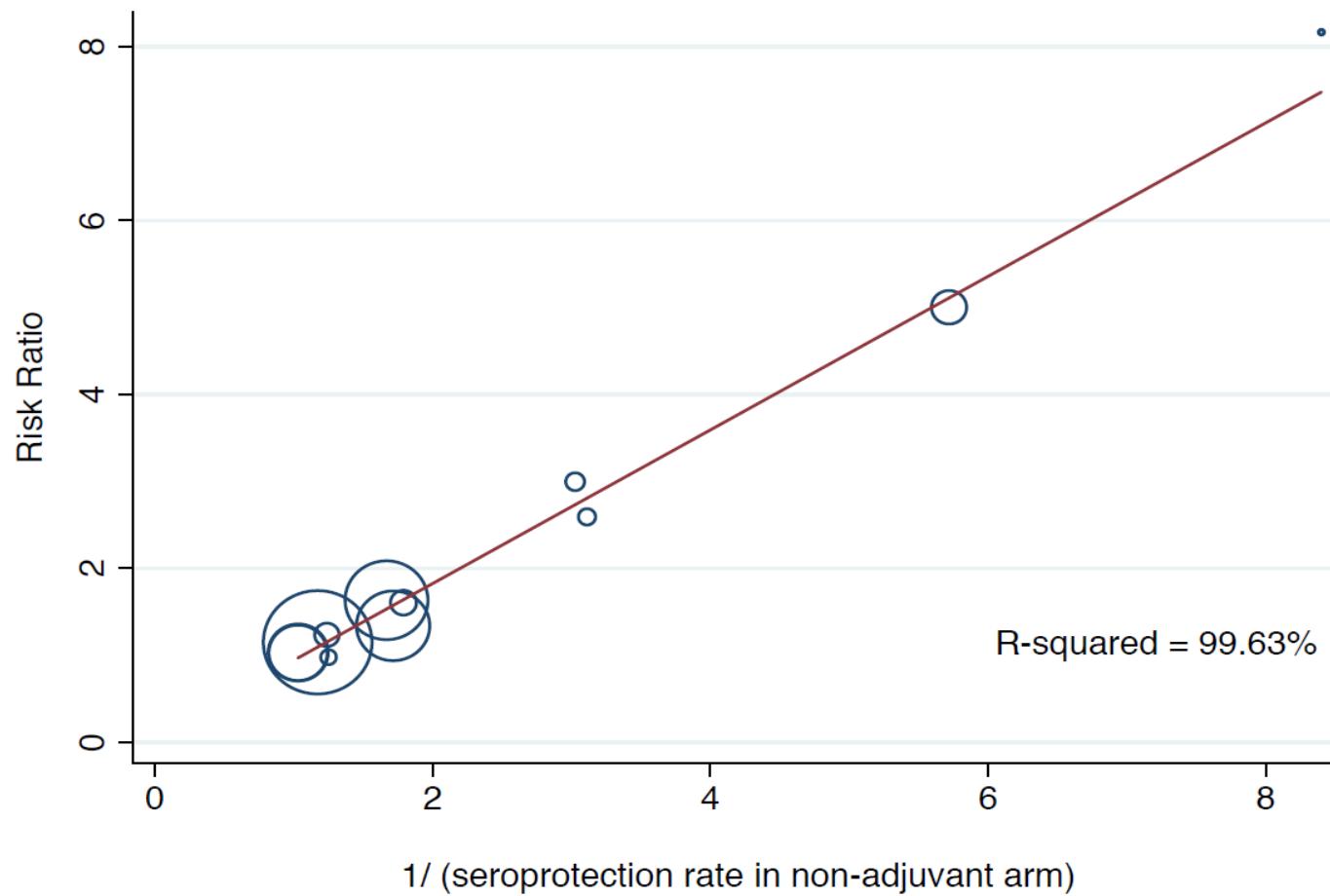
Supplementary Figure 16. Sensitivity analysis by excluding Zedda (2015): meta-regression showing a linear relationship (slope = 0.91, P <0.001) between the ratios of seroprotection rates against H3N2 after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 88.54%.



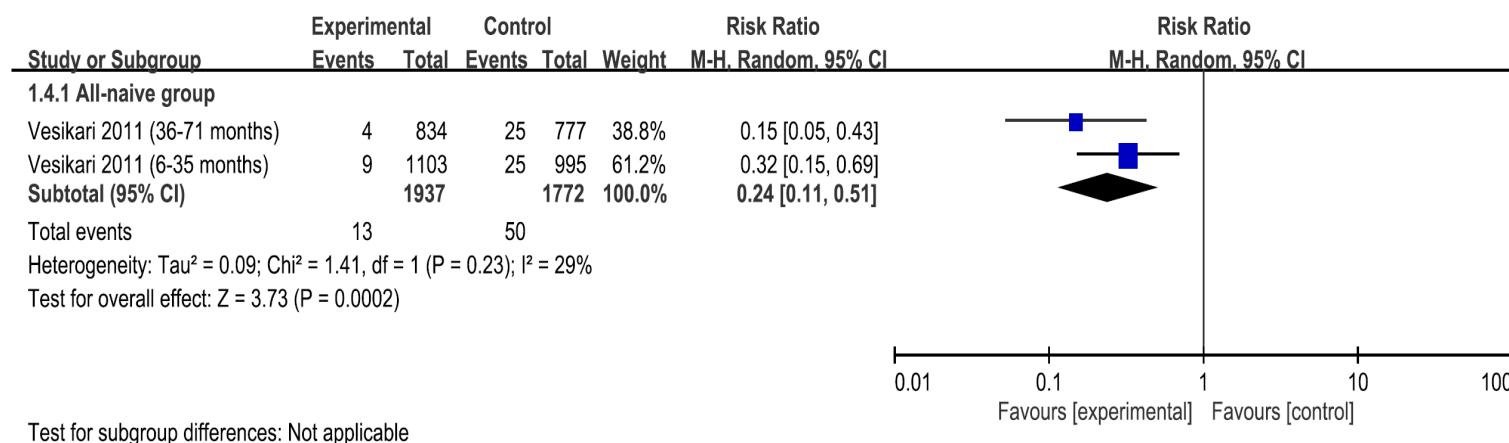
Supplementary Figure 17. Sensitivity analysis by excluding Zedda (2015): forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



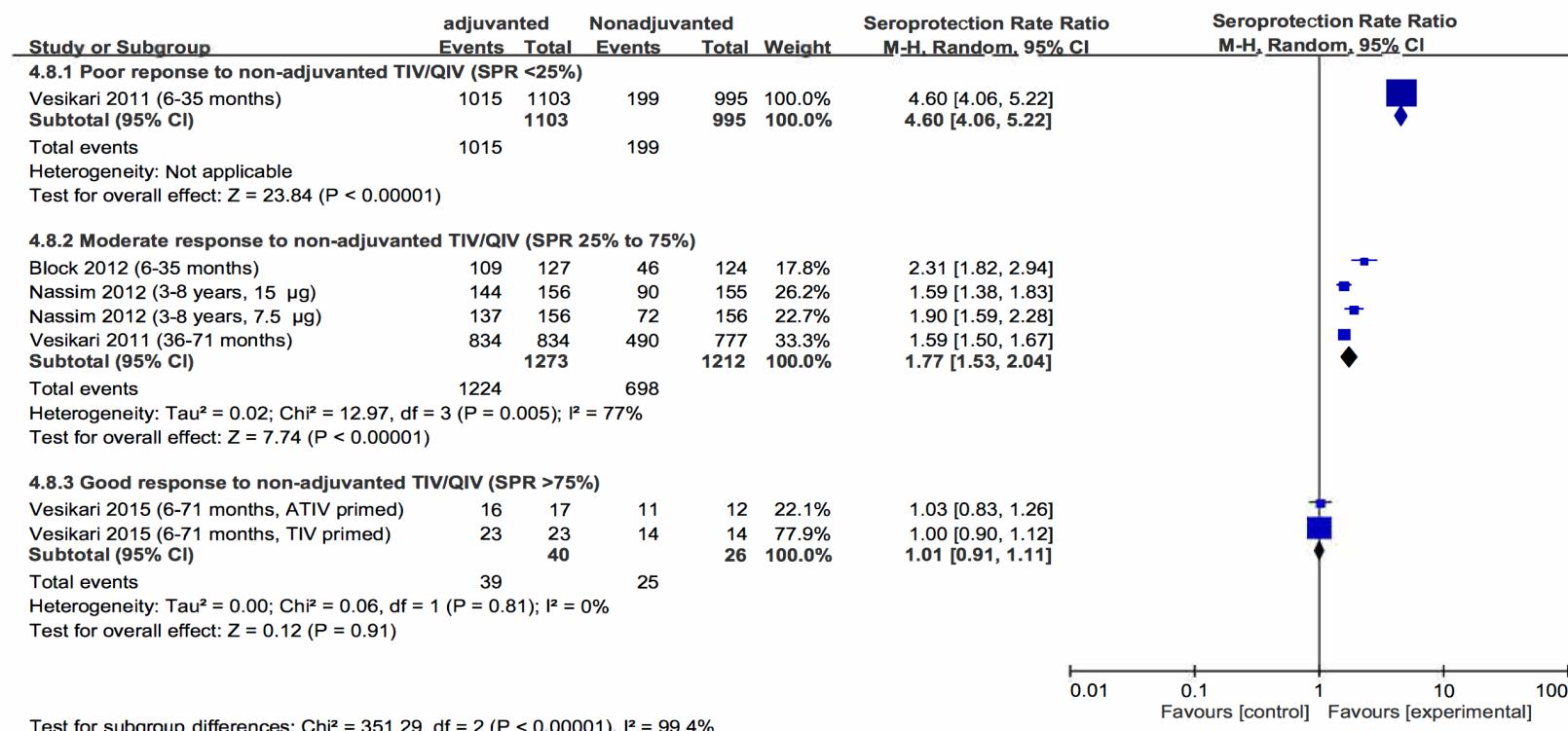
Supplementary Figure 18. Sensitivity analysis by excluding Zedda (2015): meta-regression showing a linear relationship (slope = 0.88, P <0.001) between the ratios of seroprotection rates against influenza B after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 99.63%.



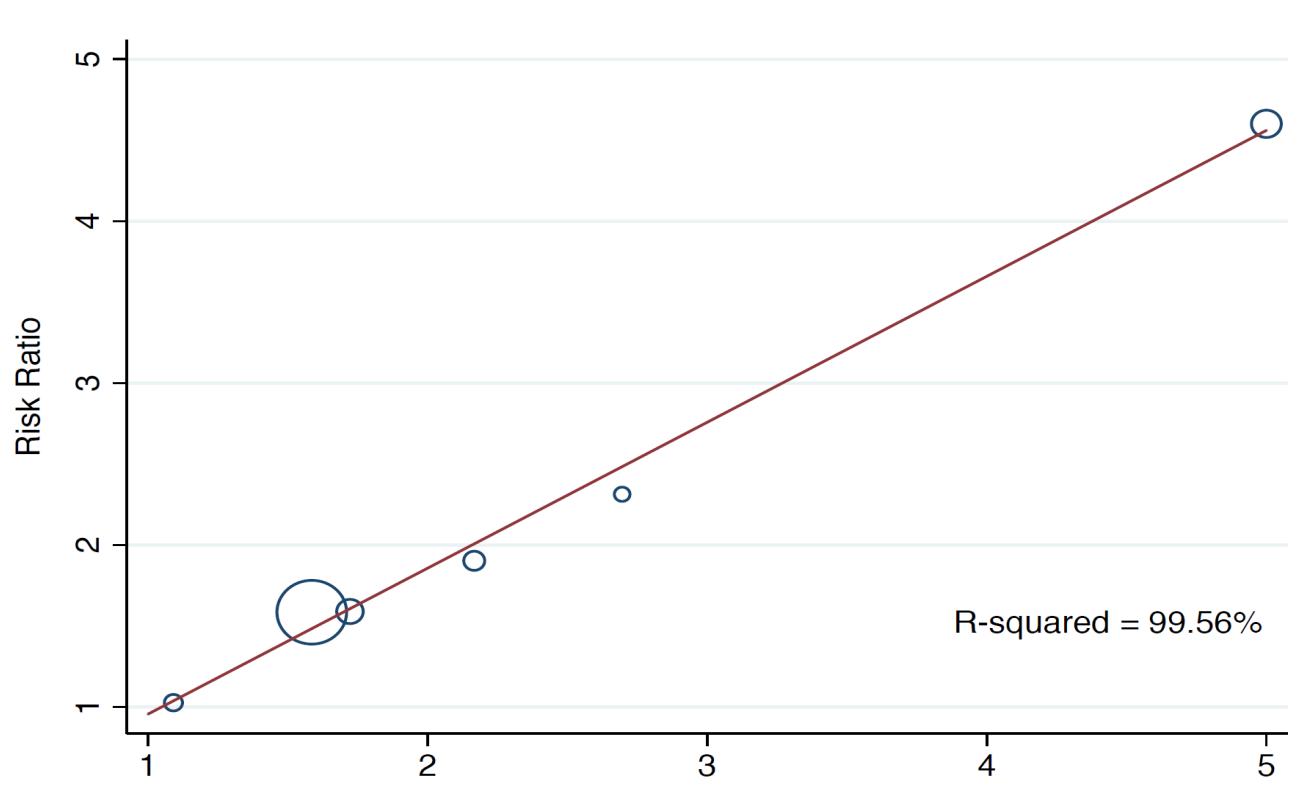
Supplementary Figure 19. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of RT-PCR-confirmed influenza among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



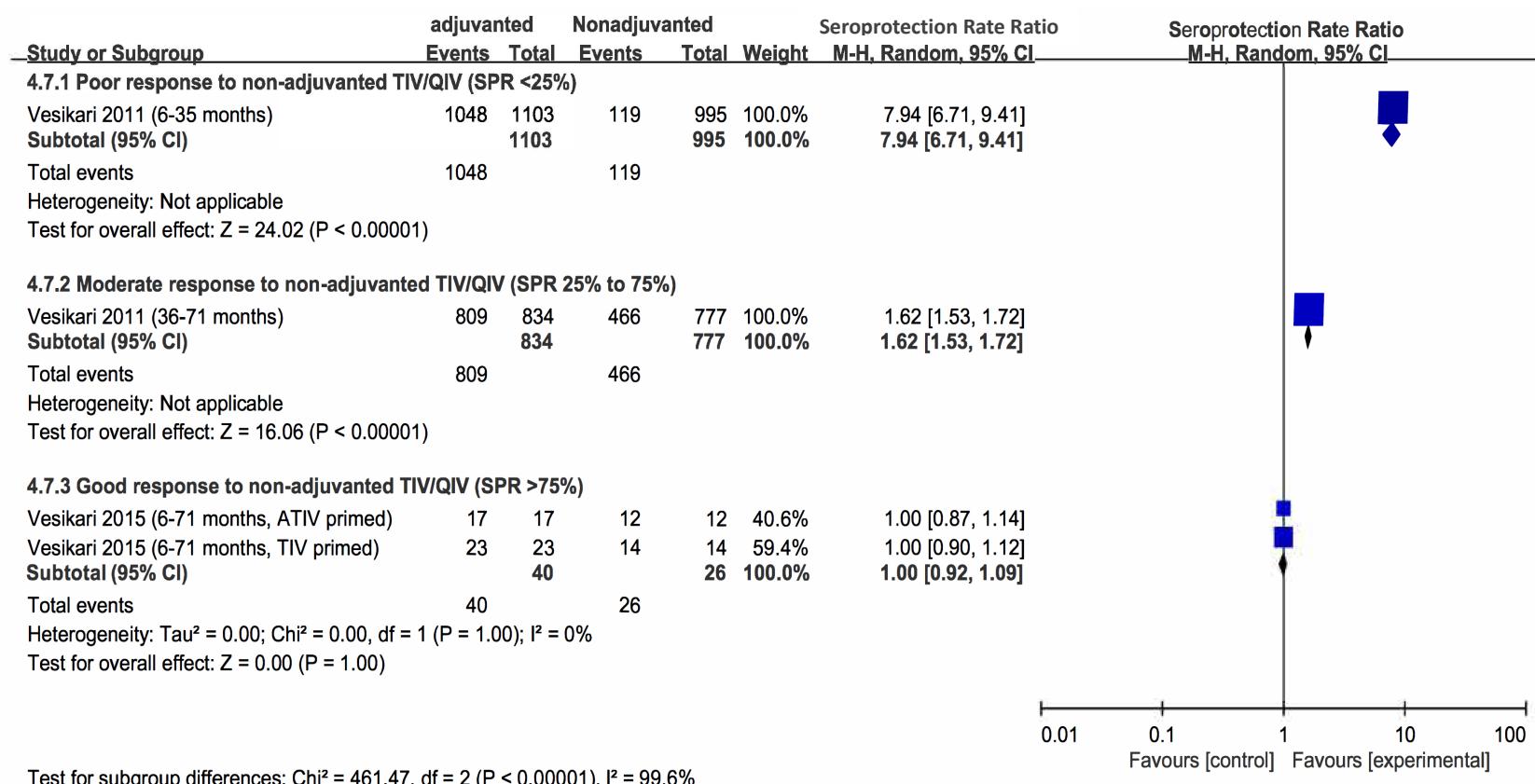
Supplementary Figure 20. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the ratios of the seroprotection rate (SPR) against H1N1, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



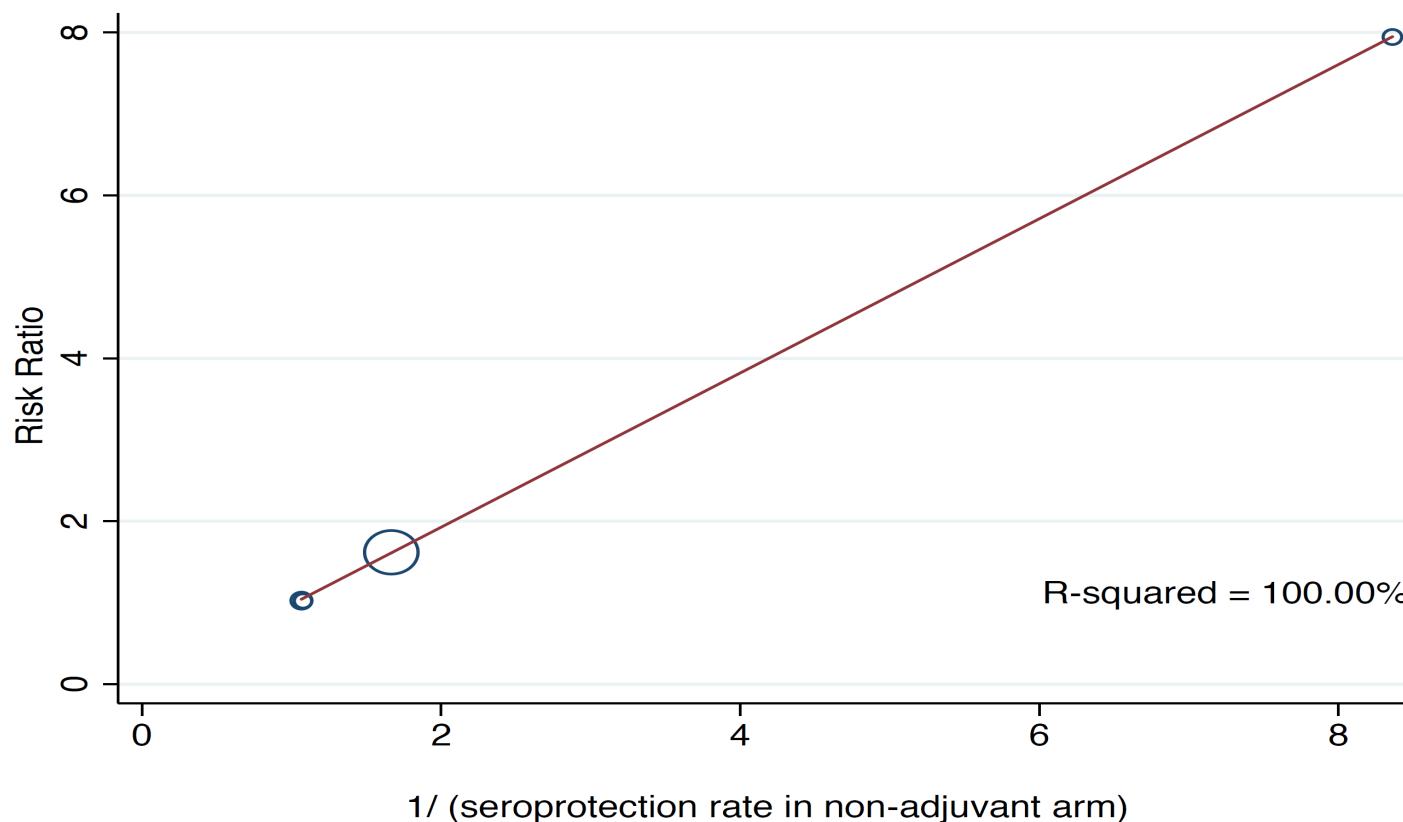
Supplementary Figure 21. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship (slope = 0.90, P <0.001) between the ratios of the seroprotection rate against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 99.56%.



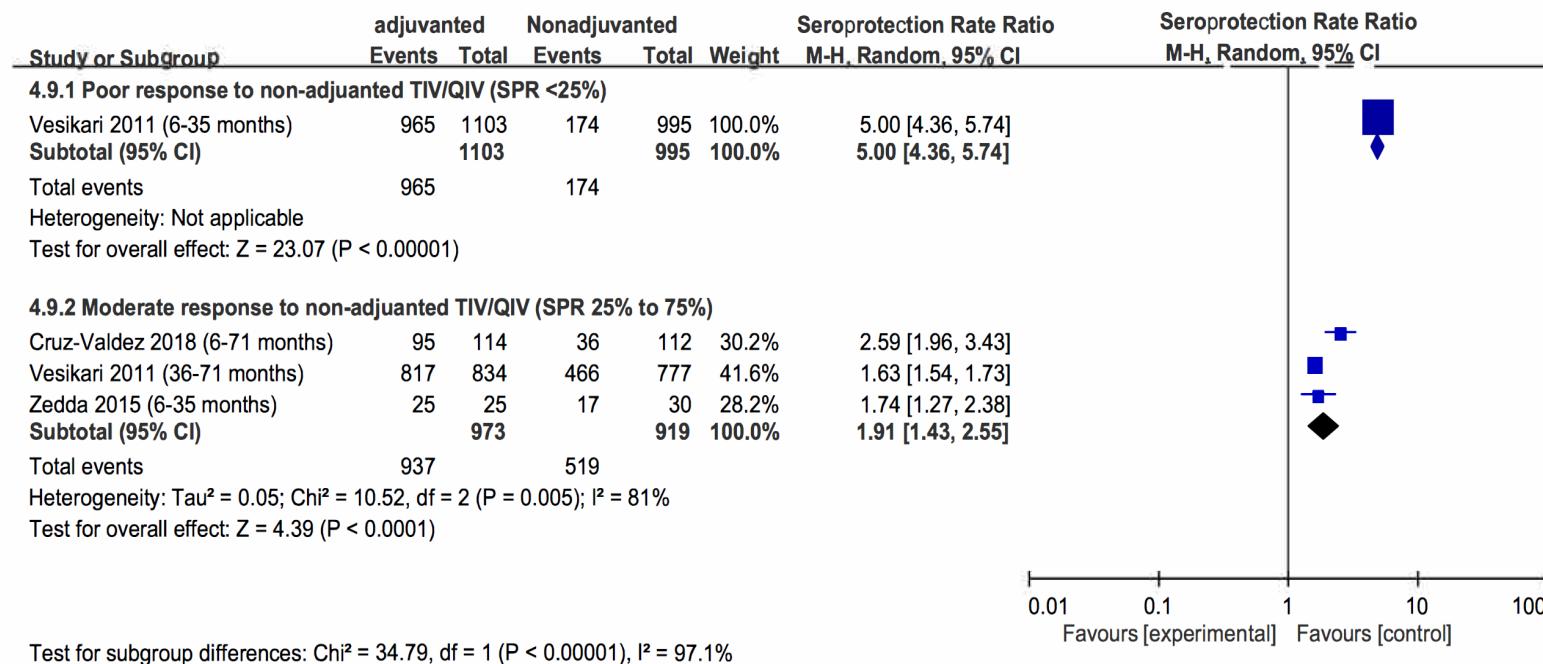
Supplementary Figure 22. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the ratios of the seroprotection rate (SPR) against H3N2, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the first dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



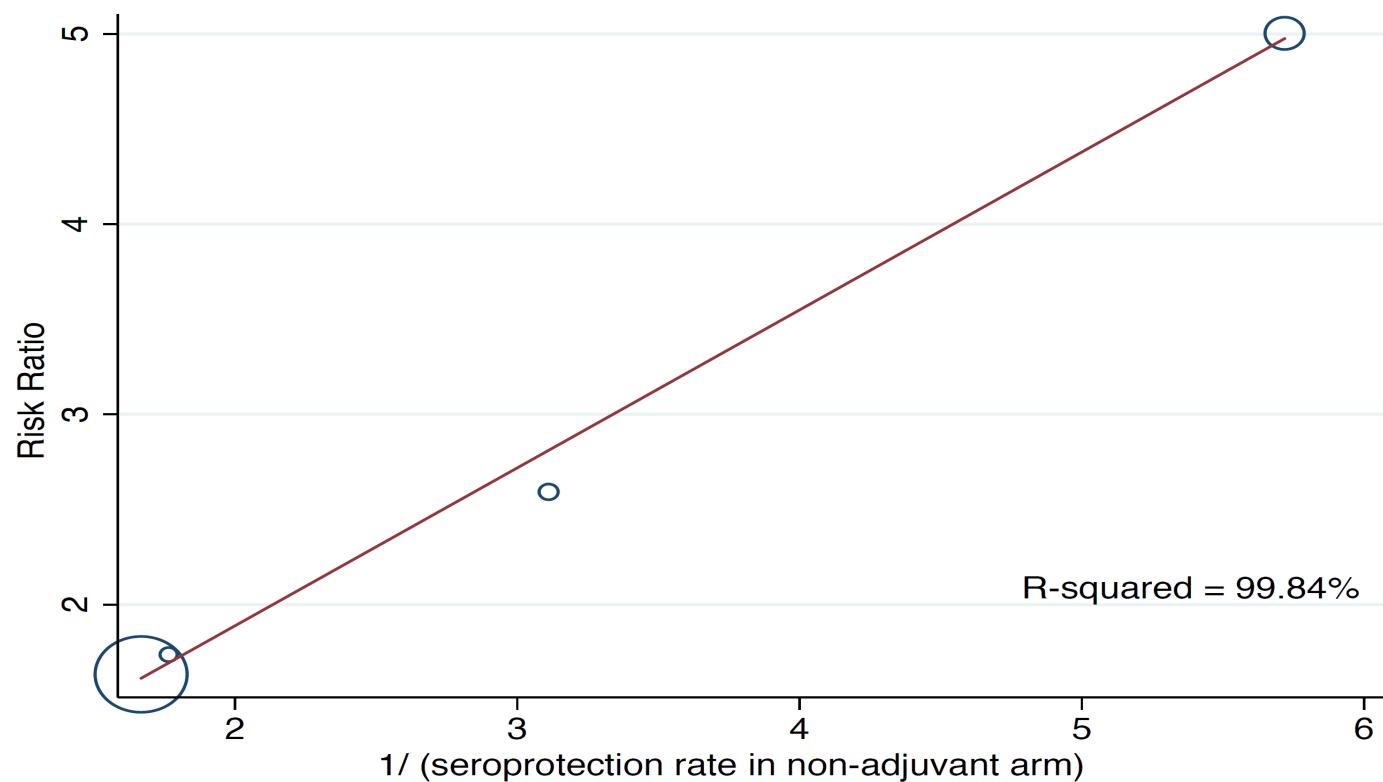
Supplementary Figure 23. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship (slope = 0.95, P <0.001) between the ratios of the seroprotection rate against H3N2 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 100%.



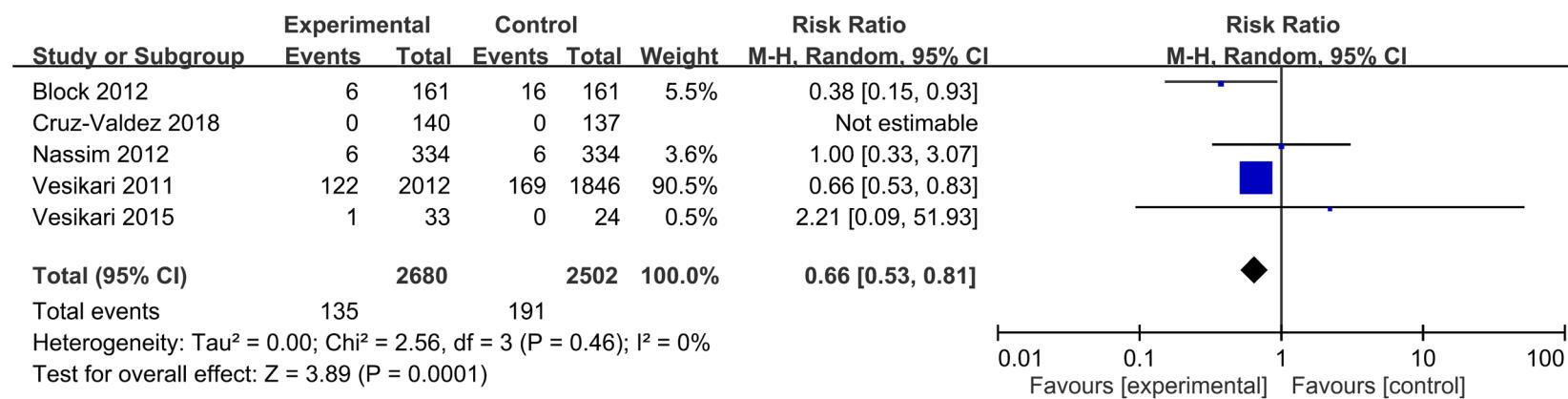
Supplementary Figure 24. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the ratios of the seroprotection rate (SPR) against influenza B, defined as a  $\geq 1:40$  haemagglutinin-inhibition (HI) titer, 21–28 days after the second dose among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



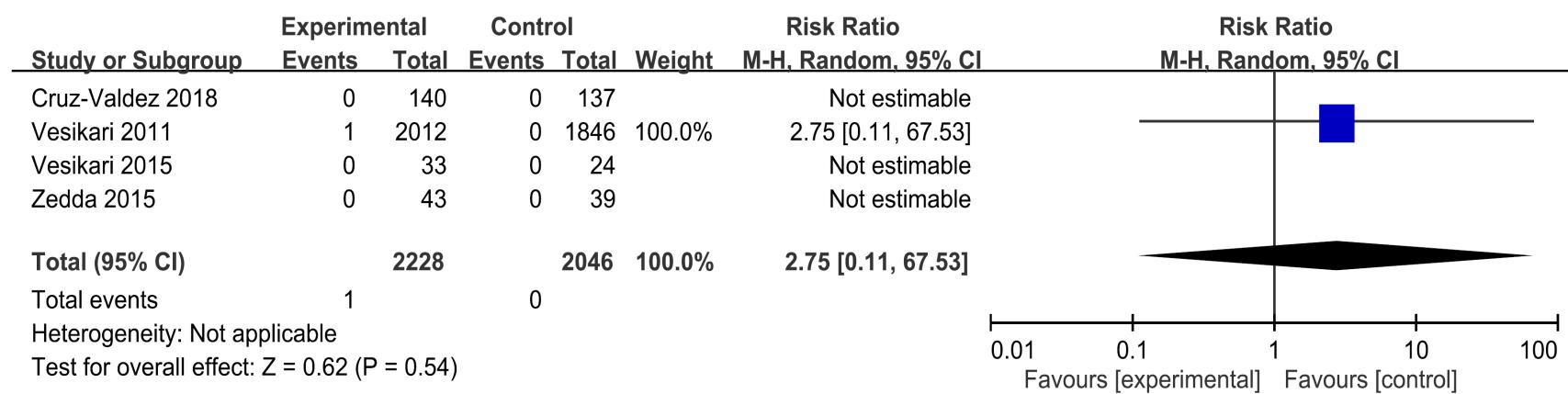
Supplementary Figure 25. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): meta-regression showing a linear relationship (slope = 0.83,  $P < 0.001$ ) between the ratios of the seroprotection rate against influenza B after the second dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 99.84%.



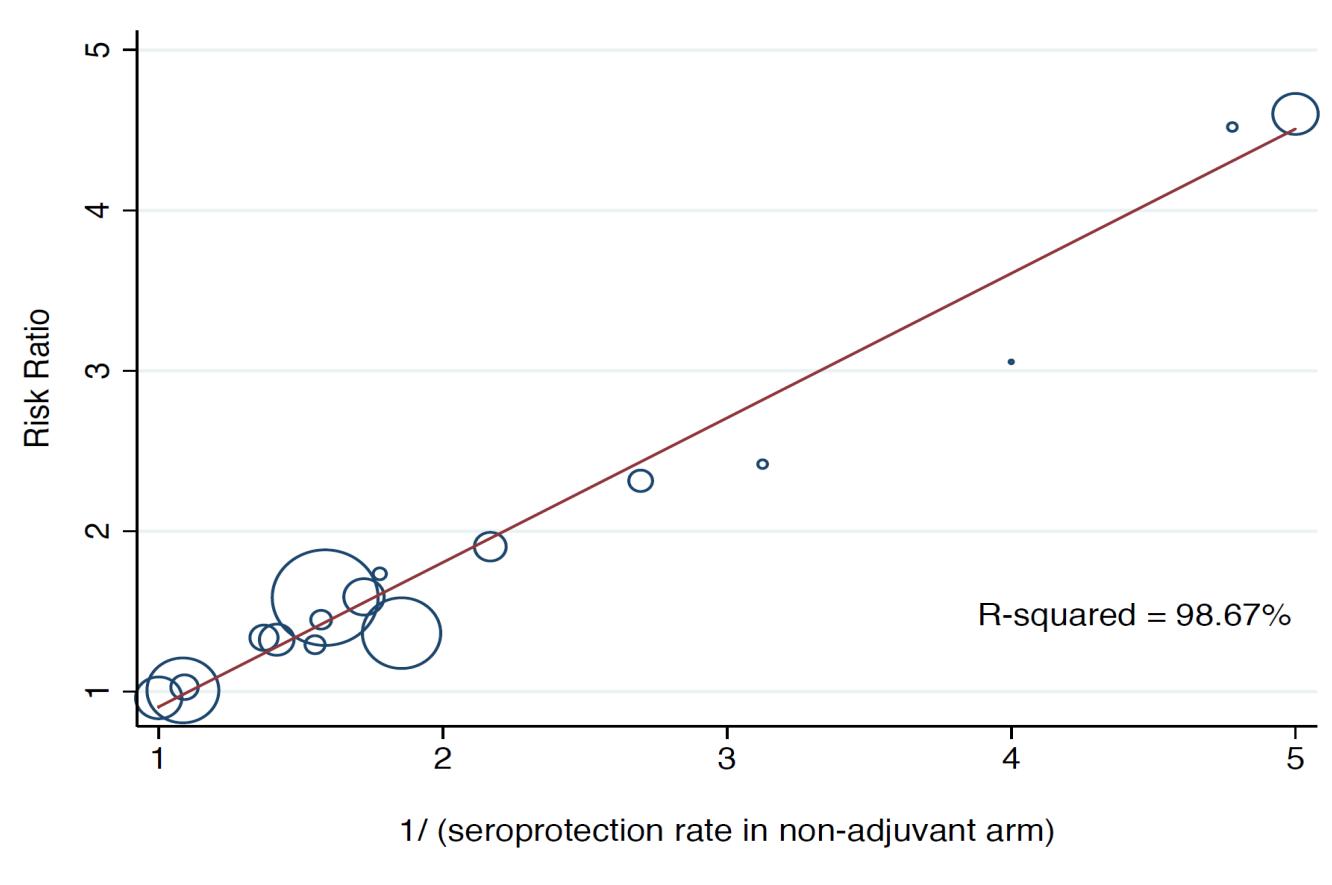
Supplementary Figure 26. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of serious adverse events during the follow-up time after the vaccinations among children who received adjuvanted versus non-adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



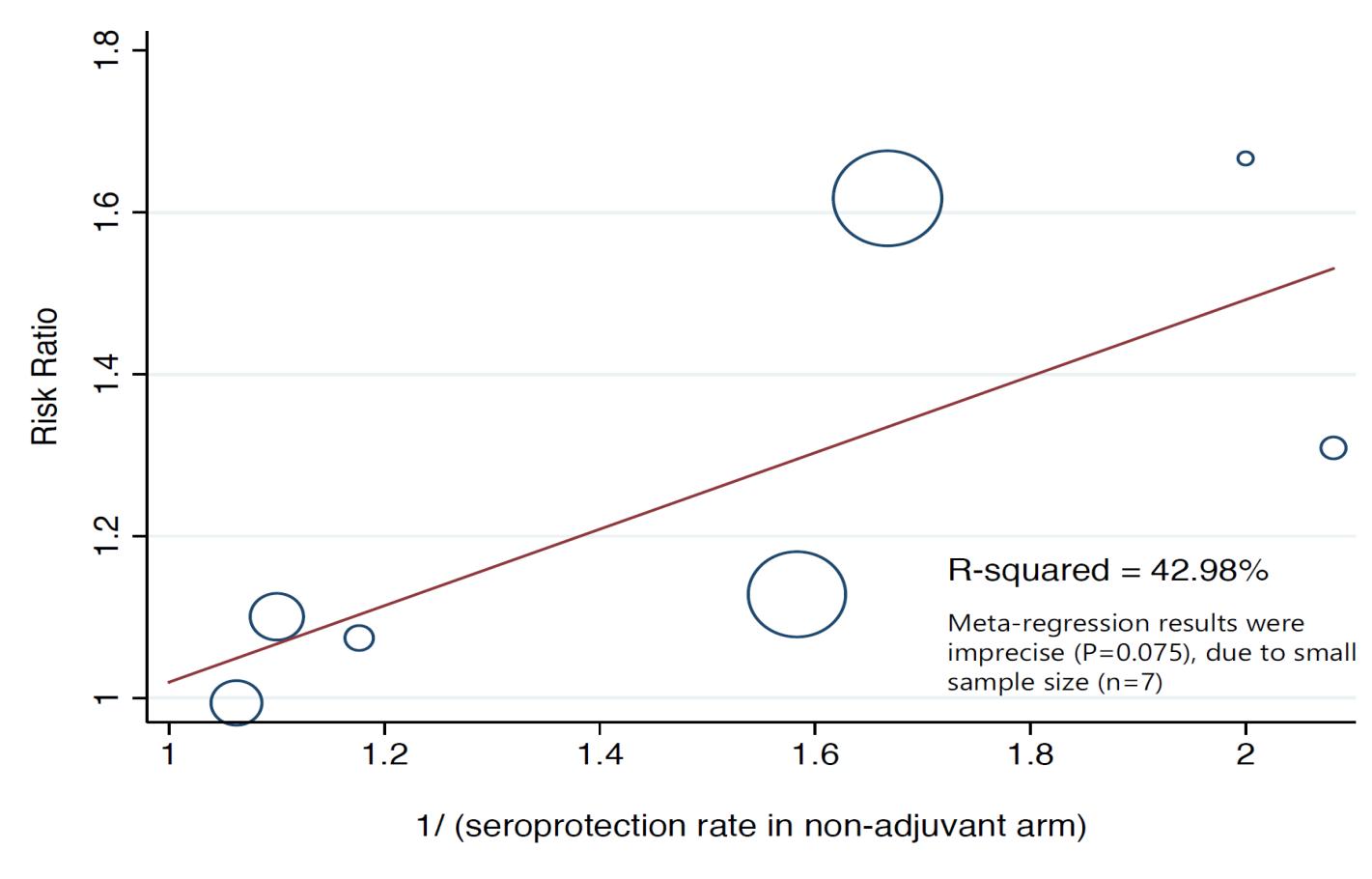
Supplementary Figure 27. Sensitivity analysis by excluding the 12 trials which did not compare the same vaccine with or without adjuvants (using adjuvanted and non-adjuvanted vaccines from different manufacturers, or using antigen-sparing design with reduced antigen dose in adjuvanted vaccines): forest plot showing the risk ratios of neurological events during the follow-up time after the vaccinations among children who received adjuvanted versus non- adjuvanted trivalent vaccines (TIV) or quadrivalent vaccines (QIV).



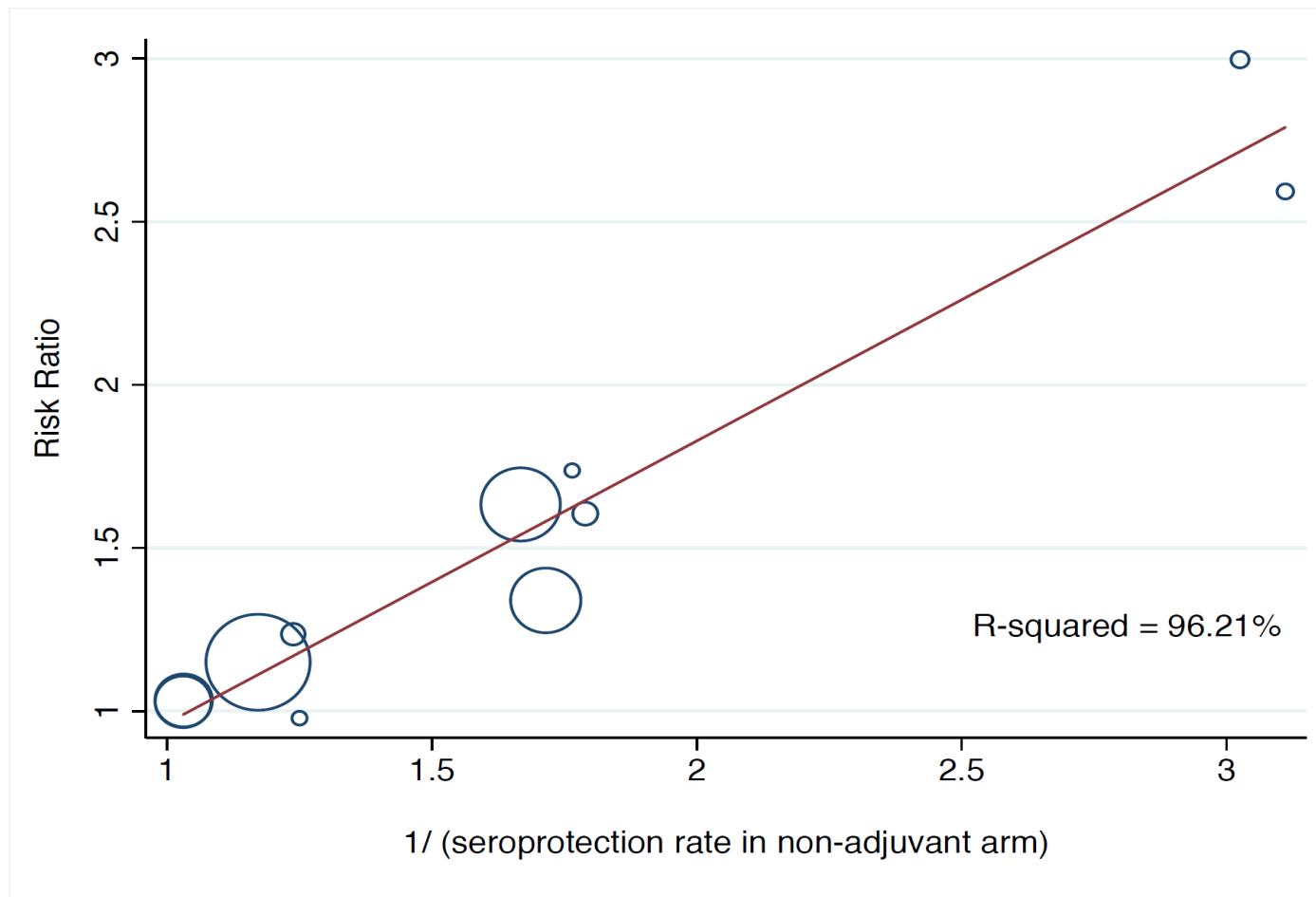
Supplementary Figure 28. Sensitivity analysis by excluding 2 data points (both reported in Diallo 2018) with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression still showed a linear relationship (slope = 0.90, P <0.001) between the ratios of seroprotection rates against H1N1 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 98.67%.



Supplementary Figure 29. Sensitivity analysis by excluding 2 data points (Vesikari 2011 and Della Cioppa 2011) with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression results became imprecise (slope = 0.47, P=0.075) between the ratios of seroprotection rates against H3N2 after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an R<sup>2</sup> of 42.98%, after the sample size decreased to only seven.



Supplementary Figure 30. Sensitivity analysis by excluding 2 data points (Vesikari 2011 and Della Cioppa 2011), with an inverse of seroprotection rate in non-adjuvanted arm larger than 5: Meta-regression still showed a linear relationship (slope = 0.86,  $P < 0.001$ ) between the ratios of seroprotection rates against influenza B after the first dose and the inverse of seroprotection rate in non-adjuvanted arm, with an  $R^2$  of 96.21%.



## Supplementary References

1. Vesikari T, Pellegrini M, Karvonen A, et al. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. *Pediatr Infect Dis J.* 2009;28(7):563-571.
2. Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59-adjuvanted influenza vaccine (FLUAD) in children: safety and immunogenicity following a second year seasonal vaccination. *Vaccine.* 2009;27(45):6291-6295.
3. Arguedas A, Soley C, Abdnour A, et al. Assessment of the safety, tolerability and kinetics of the immune response to A/H1N1v vaccine formulations with and without adjuvant in healthy pediatric subjects from 3 through 17 years of age. *Hum Vaccin.* 2011;7(1):58-66.
4. Della Cioppa G, Vesikari T, Sokal E, Lindert K, Nicolay U. Trivalent and quadrivalent MF59-adjuvanted influenza vaccine in young children: a dose- and schedule-finding study. *Vaccine.* 2011;29(47):8696-8704.
5. Vesikari T, Knuf M, Wutzler P, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *N Eng J Med.* 2011;365(15):1406-1416.
6. Block SL, Ruiz-Palacios GM, Guerrero ML, Beygo J, Sales V, Holmes SJ. Dose-range study of MF59-adjuvanted versus nonadjuvanted monovalent A/H1N1 pandemic influenza vaccine in six- to less than thirty-six-month-old children. *Pediatr Infect Dis J.* 2012;31(7):e92-98.
7. Langley JM, Reich D, Aggarwal N, et al. Randomized, multicenter trial of a single dose of AS03-adjuvanted or unadjuvanted H1N1 2009 pandemic influenza vaccine in children 6 months to <9 years of age: safety and immunogenicity. *Pediatr Infect Dis J.* 2012;31(8):848-858.
8. Nassim C, Christensen S, Henry D, Holmes S, Hohenboken M, Kanessa-Thasan N. Identification of antigen and adjuvant doses resulting in optimal immunogenicity and antibody persistence up to 1 year after immunization with a pandemic A/H1N1 influenza vaccine in children 3 to < 9 years of age. *Pediatr Infect Dis J.* 2012;31(4):e59-65.
9. Nolan T, Bravo L, Ceballos A, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. *Vaccine.* 2014;32(46):6146-6156.
10. Nolan T, Roy-Ghanta S, Montellano M, et al. Relative efficacy of AS03-adjuvanted pandemic influenza A(H1N1) vaccine in children: results of a controlled, randomized efficacy trial. *J Infect Dis.* 2014;210(4):545-557.
11. Knuf M, Leroux-Roels G, Rumke H, et al. Immunogenicity and safety of cell-derived MF59-adjuvanted A/H1N1 influenza vaccine for children. *Hum Vaccin Immunother.* 2015;11(2):358-376.
12. Solares AR, Aragon CG, Pivaral RU, et al. Safety and immunogenicity profiles of an adjuvanted seasonal influenza vaccine in Guatemalan children. *J Infect Dev Ctries.* 2014;8(9):1160-1168.
13. Vesikari T, Forsten A, Arora A, Tsai T, Clemens R. Influenza vaccination in children primed with MF59-adjuvanted or non-adjuvanted seasonal influenza vaccine. *Hum Vaccin Immunother.* 2015;11(8):2102-2112.

14. Zedda L, Forleo-Neto E, Vertruyen A, et al. Dissecting the immune response to MF59-adjuvanted and nonadjuvanted seasonal influenza vaccines in children less than three years of age. *Pediatr Infect Dis J.* 2015;34(1):73-78.
15. Vesikari T, Kirstein J, Devota Go G, et al. Efficacy, immunogenicity, and safety evaluation of an MF59-adjuvanted quadrivalent influenza virus vaccine compared with non-adjuvanted influenza vaccine in children: a multicentre, randomised controlled, observer-blinded, phase 3 trial. *Lancet Respir Med.* 2018;6(5):345-356.
16. Cruz-Valdez A, Valdez-Zapata G, Patel SS, et al. MF59-adjuvanted influenza vaccine (FLUAD) elicits higher immune responses than a non-adjuvanted influenza vaccine (Fluzone): A randomized, multicenter, Phase III pediatric trial in Mexico. *Hum Vaccin Immunother.* 2018;14(2):386-395.
17. Diallo A. *et al.* Immunogenicity and safety of MF59-adjuvanted and full-dose unadjuvanted trivalent inactivated influenza vaccines among vaccine-naïve children in a randomized clinical trial in rural Senegal. *Vaccine.* 36, 6424-6432 (2018).
18. Waddington CS, Walker WT, Oeser C, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. *BMJ.* 2010;340:c2649.