

# Comparative efficacy and safety of vaccines to prevent seasonal influenza: a systematic review and network meta-analysis

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## Search strategy

### MEDLINE (PUBMED)

#1 "Influenza, Human"[MeSH]  
#2 "Influenzavirus A"[MeSH]  
#3 "Influenzavirus B"[MeSH]  
#4 influenza\*[Text Word] OR flu[Text Word]  
#5 #1 OR #2 OR #3 OR #4  
#6 "Vaccines"[MeSH]  
#7 "Immunization"[MeSH]  
#8 (vaccin\*[Text Word] OR immuni\*[Text Word] OR inocula\*[Text Word])  
#9 #6 OR #7 OR #8  
#10 #5 AND #9  
#11 "Influenza Vaccines"[MeSH]  
#12 #10 OR #11  
#13 "Randomized Controlled Trial" [Publication Type]  
#14 "Controlled Clinical Trial" [Publication Type]  
#15 randomized[Title/Abstract]  
#16 placebo[Title/Abstract]  
#17 "drug therapy" [Subheading]  
#18 randomly[Title/Abstract]  
#19 trial[Title/Abstract]  
#20 groups[Title/Abstract]  
#21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20  
#22 ("Animals"[MeSH]) NOT "Humans"[MeSH]  
#23 #21 NOT #22  
#24 #12 AND #23

### EMBASE

#1 'influenza vaccine'/de  
#2 'influenza'/exp  
#3 'influenza virus a'/exp OR 'influenza virus b'/exp  
#4 flu:ab,ti OR influenza\*:ab,ti  
#5 #2 OR #3 OR #4  
#6 'vaccine'/de OR 'acellular vaccine'/de OR 'dna vaccine'/de OR 'inactivated vaccine'/de OR 'live vaccine'/de OR  
'subunit vaccine'/  
de OR 'virus vaccine'/de OR 'virosome vaccine'/de OR 'recombinant vaccine'/de  
#7 'immunization'/de OR 'vaccination'/de OR 'active immunization'/de OR 'immunoprophylaxis'/de OR 'mass  
immunization'/de  
#8 vaccin\*:ab,ti OR immuni\*:ab,ti OR inocul\*:ab,ti  
#9 #6 OR #7 OR #8  
#10 #5 AND #9  
#11 #1 OR #10  
#12 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp  
#13 random\*:ab,ti OR placebo\*:ab,ti OR factorial\*:ab,ti OR assign\*:ab,ti OR allocat\*:ab,ti OR volunteer\*:ab,ti OR  
(singl\* OR doubl\*) NEAR/3 (blind\* OR mask\*):ab,ti  
#14 #12 OR #13  
#15 #11 AND #14  
[1-1-2017]/sd NOT [14-2-2018]/sd AND [embase]/lim

### Cochrane central (Trials)

#1 MeSH descriptor: [Influenza, Human] explode all trees  
#2 MeSH descriptor: [Influenzavirus A] explode all trees  
#3 MeSH descriptor: [Influenzavirus B] explode all trees  
#4 influenza\* or flu  
#5 #1 or #2 or #3 or #4  
#6 MeSH descriptor: [Vaccines] explode all trees  
#7 MeSH descriptor: [Immunization] explode all trees  
#8 vaccin\* or immuni\* or inocula\*  
#9 #6 or #7 or #8  
#10 #5 and #9  
#11 MeSH descriptor: [Influenza Vaccines] explode all trees

- #12 #10 or #11
- #13 MeSH descriptor: [Randomized Controlled Trial] explode all trees
- #14 MeSH descriptor: [Controlled Clinical Trial] explode all trees
- #15 randomized
- #16 placebo
- #17 MeSH descriptor: [Drug Therapy] explode all trees
- #18 randomly
- #19 trial
- #20 groups
- #21 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20
- #22 #12 and #21

### **Inclusion criteria details**

We included only vaccines and doses licensed by regulatory authorities, namely

-Standard dose Inactivated vaccines, intramuscular: adults and elderly: virion, sub unit or split trivalent or quadrivalent vaccine containing 15 µg di HA per strains (TIV: 45 µg total, QIV: 60 µg total); children 6-36 months: 7,5 µg/strain; if never vaccinated before, two doses one month apart

-High- dose inactivated vaccines: 60 µg per strain; TIV: 180 µg; QIV 240 µg total. Vaccines with doses between 15 and 60 µg per strains were considered as standard dose (including vaccines prepared with the DNA recombinant technique)

-Adjuvanted vaccines: we included virosomal or liposome adjuvanted (one node) and MF59 or AS03 with or without IL2 (another node), both TIV or QIV. Vaccines adjuvanted using other methods (e.g TLR ligand or polyoxidonium) were excluded

-Recombinant trivalent inactivated (rHA): we included any dose

-Intradermal inactivated vaccines: we included only doses of 9 or 15 µg per strains; also QIV intradermal (doses of 9 or 15 µg per strains) were included in a separate node

-Trivalent live attenuated nasal spray

-Quadrivalent live attenuated nasal spray

## **Box 1. Summary of the different types of seasonal influenza vaccines available**

### Inactivated influenza vaccines (IIVs)

Consist of viruses killed through the use of different chemical compounds in production processes based on different technologies. IIVs are injectable and include: i) whole virion IIVs, containing whole viral particles; ii) split IIVs, in which the virus is inactivated with disrupting agents, yielding surface and internal antigens; iii) subunit IIVs, containing only surface antigens – hemagglutinin (HA) and neuraminidase (NA) - purified from other viral components. Among these, split and subunit IIVs are more commonly used due to improved tolerability. For split and subunit IIVs, the standard antigen dose corresponds to 15 µg of HA per viral strain. To enhance the vaccine-induced immune response, two types of vaccines were specifically developed: formulations that include the use of adjuvants (such as AS03 or MF59, oil-in-water emulsions) or virosomes/liposomes (vesicles with phospholipid membranes incorporating viral antigens), and high-dose (HD) influenza vaccines containing an amount of antigen four times higher than the standard dose (60 µg of HA per strain).

Most IIVs are administered intramuscularly (IM); intradermal (ID) preparations that enhance the immune response thanks to the simultaneous stimulation of innate and adaptive immunity are also available.

IIVs can be produced in eggs or in cell-cultures. Egg-based IIVs have been licensed in the US and Europe for use in adults and children six months and older, with the MF59-adjuvanted or high dose vaccines licensed for use in the elderly. Cell-based IIVs for individuals who are allergic to eggs are licensed in the US, and are under evaluation in Europe.

### Live-attenuated influenza vaccines (LAIVs)

Containing active whole viral particles; those currently available are made of temperature-sensitive viruses that can survive and replicate only at the low temperature of the upper respiratory tract (cold-adapted); they are administered intranasally (IN). LAIVs are licensed for persons aged 2 to 59 years old and are recommended for healthy, non-pregnant individuals who do not have chronic medical conditions, due to the relative lack of data in the other populations.

### Recombinant influenza vaccines (RIVs)

Recombinant technologies have the added benefit of substantially reducing production times compared with egg-based and cell-based technologies, as production can begin once a virus genome has been sequenced rather than starting with a live virus. A recombinant-HA expressed in insect cells using baculovirus vectors was licensed for use in adults aged 18–49 years old in the US.

## Nodes in the network

Label	Vaccine
placebo	placebo/no vaccine
3-IIV	trivalent inactivated intramuscular
3-IIV HD	trivalent inactivated high dose intramuscular
3-IIV ID	trivalent inactivated intradermal
3-IIV MF59/AS03-adj	trivalent inactivated adjuvanted with MF59/AS03 intramuscular
3-IIV vir/lip-adj	trivalent inactivated adjuvanted with Virosome/liposome intramuscular
3-RIV	trivalent recombinant intramuscular
4-IIV	quadrivalent inactivated intramuscular
4-IIV HD	quadrivalent inactivated high dose intramuscular
4-IIV ID	quadrivalent inactivated intradermal
4-IIV MF59/AS03-adj	quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular
4-IIV vir/lip-adj	quadrivalent inactivated adjuvanted with virosome/liposome intramuscular
4-RIV	quadrivalent recombinant intramuscular
3-LAIV	trivalent live attenuated intranasal
4-LAIV	quadrivalent live attenuated intranasal

## References of excluded studies

References	Reasons for exclusion
1. Agarkhedkar S, Chhatwal J, Kompithra RZ, Lalwani SK, Narayan A, Muninarayanaswam V, et al. Immunogenicity and safety of an intramuscular split-virion quadrivalent inactivated influenza vaccine in individuals aged $\geq 6$ months in India. <i>Human vaccines &amp; immunotherapeutics</i> . 2019;15(4):973-7.	No relevant outcome
2. Airey J, Albano FR, Sawlwin DC, et al. Immunogenicity and safety of a quadrivalent inactivated influenza virus vaccine compared with a comparator quadrivalent inactivated influenza vaccine in a pediatric population: a phase 3, randomized noninferiority study. <i>Vaccine</i> . 2017;35(20):2745-2752.	No relevant comparator
3. Ambati A, Boas LS, Ljungman P, et al. Evaluation of pretransplant influenza vaccination in hematopoietic SCT: a randomized prospective study. <i>Bone marrow transplantation</i> . Jun 2015;50(6):858-864.	No relevant outcome
4. Ansaldi F, Bacilieri S, Durando P, Sticchi L, Valle L, Montomoli E, et al. Cross-protection by MF59-adjuvanted influenza vaccine: neutralizing and haemagglutination-inhibiting antibody activity against A(H3N2) drifted influenza viruses. <i>Vaccine</i> . 2008;26(12):1525-9.	No relevant outcome
5. Ansaldi F, Zancolli M, Durando P, Montomoli E, Sticchi L, Del Giudice G, et al. Antibody response against heterogeneous circulating influenza virus strains elicited by MF59- and non-adjuvanted vaccines during seasons with good or partial matching between vaccine strain and clinical isolates. <i>Vaccine</i> . 2010;28(25):4123-9.	No relevant outcome
6. Arakane R, Annaka R, Takahama A, et al. Superior immunogenicity profile of the new intradermal influenza vaccine compared to the standard subcutaneous vaccine in subjects 65 years and older: a randomized controlled phase III study. <i>Vaccine</i> . 2015;33(48):6650-6658.	No relevant comparator
7. Arakane R, Nakatani H, Fujisaki E, Takahama A, Ishida K, Yoshiike M, et al. Immunogenicity and safety of the new intradermal influenza vaccine in adults and elderly: A randomized phase 1/2 clinical trial. <i>Vaccine</i> . 2015;33(46):6340-50.	No vaccine of interest
8. Baldo V, Menegon T, Bonello C, Floreani A, Trivello R. Comparison of three different influenza vaccines in institutionalised elderly. <i>Vaccine</i> . 2001;19(25-26):3472-3475. Baldo V, Baldovin T, Pellegrini M, et al. Immunogenicity of three different influenza vaccines against homologous and heterologous strains in nursing home elderly residents. <i>Clinical &amp; developmental immunology</i> . 2010;2010:517198.	No relevant outcome
9. Banzhoff A, Kaniok W, Muszer A. Effectiveness of an influenza vaccine used in Poland in the 1998-1999 influenza season. <i>Immunological investigations</i> . May 2001;30(2):103-113.	Secondary analysis of already included studies
10. Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. <i>Journal of infectious diseases</i> . 2000;181(3):1133-1137.	No vaccine of interest
11. Belshe RB, Gruber WC. Safety, efficacy and effectiveness of cold-adapted, live, attenuated, trivalent, intranasal influenza vaccine in adults and children. <i>Philosophical transactions of the royal society of london. Series B, biological sciences</i> . 2001;356(1416):1947-1951.	Secondary analysis of already included studies
12. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. <i>The New England journal of medicine</i> . Nov 25 2004;351(22):2286-2294.	Secondary analysis of already included studies
13. Bernstein DI, Guptill J, Naficy A, Nachbagauer R, Berlanda-Scorza F, Feser J, et al. Immunogenicity of chimeric haemagglutinin-based, universal influenza virus vaccine candidates: interim results of a randomised, placebo-controlled, phase 1 clinical trial. <i>The Lancet Infectious diseases</i> . 2020;20(1):80-91.	No vaccine of interest
14. Boyce TG, Hsu HH, Sannella EC, et al. Safety and immunogenicity of adjuvanted and unadjuvanted subunit influenza vaccines administered intranasally to healthy adults. <i>Vaccine</i> . Sep 15 2000;19(2-3):217-226.	No vaccine of interest
15. Branagan A, Duffy E, Foster C, et al. Two dose series of high-dose influenza vaccine is associated with longer duration of serologic immunity in patients with plasma cell disorders. <i>Blood</i> . 2017;130.	No relevant outcome
16. Burgess T, Richard S, Collins L, Colombo R, Ganesan A, Geaney C, et al. Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): Influenza-like-illness rates in year 1. <i>Open forum infectious diseases</i> . 2019;6:S990. Burgess T, Richard S, Collins L, Colombo R, Ganesan A, Geaney C, et al. Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): Methods. <i>Open forum infectious diseases</i> . 2019;6:S969.	No parallel RCT
17. Caldera F, Saha S, Wald A, Grimes I, Hillman L, Zhang Y, et al. Randomized trial evaluating the immunogenicity of high dose vs. standard dose influenza vaccine in IBD patients on anti-tnf monotherapy. <i>Gastroenterology</i> . 2018;154(6):S-69-.	Secondary analysis of already included studies
18. Camilloni B, Basileo M, Di Martino A, Donatelli I, Iorio AM. Antibody responses to intradermal or intramuscular MF59-adjuvanted influenza vaccines as evaluated in elderly institutionalized volunteers during a season of partial mismatching between vaccine and circulating A(H3N2) strains. <i>Immunity &amp; ageing : I &amp; A</i> . 2014;11:10.	No relevant outcome



19.	Castro M, Dozor A, Fish J, et al. The safety of inactivated influenza vaccine in adults and children with asthma. <i>New England Journal of Medicine</i> . 2001;345(21):1529-1536.	No parallel RCT
20.	Celik A, Orselik O. Effects of influenza vaccination in patients with heart failure. <i>Herz</i> . 2017;42(3):325-326.	No parallel RCT
21.	Chuaychoo B, Kositanont U, Rittayamai N, et al. The immunogenicity of the intradermal injection of seasonal trivalent influenza vaccine containing influenza A(H1N1) pdm09 in COPD patients soon after a pandemic. <i>Human vaccines &amp; immunotherapeutics</i> . Jul 2 2016;12(7):1728-1737.	No relevant comparator
22.	Chuaychoo B, Wongsurakiat P, Nana A, Kositanont U, Maranetra KN. The immunogenicity of intradermal influenza vaccination in COPD patients. <i>Vaccine</i> . 2010;28(24):4045-51.	No vaccine of interest
23.	Chumakov MP, Beregovskii NA, Linev MB, et al. [Use of highly purified subvirion trivalent flue vaccine ("Grippovak") in groups with a high risk of complications]. <i>Zhurnal mikrobiologii, epidemiologii, i immunobiologii</i> . Mar 1992(3):55-57.	No parallel RCT
24.	Ciszewski A, Billinska ZT, Brydak LB. Influenza vaccination in secondary prevention from coronary ischemic events in Coronary Artery Disease (FLUCAD). <i>ACC Cardiosource Review Journal</i> . 2008;17(4):34.	No relevant outcome
25.	Claeys C, Drame M, Garcia-Sicilia J, Zaman K, Carmona A, Tran PM, et al. Assessment of an optimized manufacturing process for inactivated quadrivalent influenza vaccine: a phase III, randomized, double-blind, safety and immunogenicity study in children and adults. <i>BMC infectious diseases</i> . 2018;18(1).	No relevant comparator
26.	Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. <i>The Journal of infectious diseases</i> . Feb 1991;163(2):300-304.	No parallel RCT
27.	Colombo R, Richard S, Schofield C, Collins L, Ganesan A, Geaney C, et al. Pragmatic assessment of influenza vaccine effectiveness in the DOD (PAIVED): immunogenicity sub-study. <i>Open forum infectious diseases</i> . 2019;6:S971-S2.	No parallel RCT
28.	Conne P, Gauthey L, Vernet P, et al. Immunogenicity of trivalent subunit versus virosome-formulated influenza vaccines in geriatric patients. <i>Vaccine</i> . 1997;15(15):1675-1679.	No relevant outcome
29.	Cook Q, Burks AW. Safety and immunogenicity of a recombinant influenza vaccine: a randomized trial. <i>Pediatrics</i> . 2018;142:S273-S4.	Secondary analysis of already included studies
30.	Cools HJM, Gussekloo J, Remmerswaal JEM, Remarque EJ, Kroes ACM. Benefits of increasing the dose of influenza vaccine in residents of long-term care facilities: A randomized placebo-controlled trial. <i>Journal of Medical Virology</i> . 2009;81(5):908-914.	No relevant outcome
31.	Cooper C, Thorne A, Klein M, Conway B, Boivin G, Haase D, et al. Immunogenicity is not improved by increased antigen dose or booster dosing of seasonal influenza vaccine in a randomized trial of HIV infected adults. <i>PloS one</i> . 2011;6(3):e17758.	No vaccine of interest
32.	Cordero E, Roca-Oporto C, Bulnes-Ramos A, Aydillo T, Gavaldà J, Moreno A, et al. Two Doses of Inactivated Influenza Vaccine Improve Immune Response in Solid Organ Transplant Recipients: Results of TRANSGRIPE 1-2, a Randomized Controlled Clinical Trial. <i>Clinical infectious diseases : an official publication of the Infectious Diseases Society of America</i> . 2017;64(7):829-38.	No vaccine of interest
33.	Danier J, Rivera L, Claeys C, Dbaibo G, Jain VK, Kosalaraksa P, et al. Clinical Presentation of Influenza in Children 6 to 35 Months of Age: Findings from a Randomized Clinical Trial of Inactivated Quadrivalent Influenza Vaccine. <i>Pediatric Infectious Disease Journal</i> . 2019;38(8):866-72.	Secondary analysis of already included studies
34.	Dbaibo G, Amanullah A, Claeys C, Izu A, Jain VK, Kosalaraksa P, et al. Quadrivalent Influenza Vaccine Prevents Illness and Reduces Healthcare Utilization Across Diverse Geographic Regions During Five Influenza Seasons: A Randomized Clinical Trial. <i>The Pediatric infectious disease journal</i> . 2020;39(1):e1-e10.	Secondary analysis of already included studies
35.	de B, Zanasi A, Ragusa S, Gluck R, Herzog C. An open-label comparison of the immunogenicity and tolerability of intranasal and intramuscular formulations of virosomal influenza vaccine in healthy adults. <i>Clinical therapeutics</i> . Jan 2002;24(1):100-111.	No relevant comparator
36.	Della Cioppa G, Nicolay U, Lindert K, et al. A dose-ranging study in older adults to compare the safety and immunogenicity profiles of MF59(R)-adjuvanted and non-adjuvanted seasonal influenza vaccines following intradermal and intramuscular administration. <i>Human vaccines &amp; immunotherapeutics</i> . 2014;10(6):1701-1710.	No relevant comparator
37.	Diallo A, Diop OM, Diop D, Niang MN, Sugimoto JD, Ortiz JR, et al. Effectiveness of Seasonal Influenza Vaccination in Children in Senegal During a Year of Vaccine Mismatch: A Cluster-randomized Trial. <i>Clinical infectious diseases : an official publication of the Infectious Diseases Society of America</i> . 2019;69(10):1780-8.	No parallel RCT
38.	Donatelli I, Zannolli R, Fuiano L, Biasio LR. Influenza vaccine in immunogenically naive healthy infants. <i>European journal of pediatrics</i> . Nov 1998;157(11):949-950.	No relevant comparator

39.	Durrer P, Gluck U, Spyr C, et al. Mucosal antibody response induced with a nasal virosome-based influenza vaccine. <i>Vaccine</i> . Oct 1 2003;21(27-30):4328-4334.	No vaccine of interest
40.	Edwards KM, Dupont WD, Westrich MK, Plummer Jr WD, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. <i>Journal of Infectious Diseases</i> . 1994;169(1):68-76.	No vaccine of interest
41.	El'shina GA, Masalin Iu M, Shervali VI, et al. [The trivalent polymer-subunit influenza vaccine Grippol studied in a controlled epidemiological trial (1)]. <i>Voenno-meditsinskii zhurnal</i> . Aug 1996;317(8):57-60.	No vaccine of interest
42.	Esposito S, Fling J, Chokeyphaibulkit K, de Bruijn M, Obery J, Zhang B, et al. Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Seasonal Influenza Vaccine in Young Children at High Risk of Influenza-associated Complications: A Phase III, Randomized, Observer-blind, Multicenter Clinical Trial. <i>The Pediatric infectious disease journal</i> . 2020;39(8):e185-e91.	Not relevant comparator
43.	Esposito S, Marchisio P, Ansaldi F, et al. A randomized clinical trial assessing immunogenicity and safety of a double dose of virosomal-adjuvanted influenza vaccine administered to unprimed children aged 6-35 months. <i>Vaccine</i> . Aug 31 2010;28(38):6137-6144.	No relevant outcome
44.	Esposito S, Marchisio P, Bosis S, et al. Clinical and economic impact of influenza vaccination on healthy children aged 2-5 years. <i>Vaccine</i> . Jan 30 2006;24(5):629-635.	No relevant outcome
45.	Esposito S, Marchisio P, Cavagna R, et al. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. <i>Vaccine</i> . Jul 4 2003;21(23):3162-3168.	No relevant comparator
46.	Eun BW, Lee TJ, Lee J, Kim KH, Kim DH, Jo DS, et al. A Randomized, Double-blind, Active-controlled Phase III Trial of a Cell Culture-derived Quadrivalent Inactivated Influenza Vaccine in Healthy South Korean Children and Adolescents 6 Months to 18 Years of Age. <i>The Pediatric infectious disease journal</i> . 2019;38(9):e209-e15.	No vaccine of interest
47.	Forrest BD, Pride MW, Dunning AJ, et al. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. <i>Clinical and vaccine immunology: CVI</i> . Jul 2008;15(7):1042-1053.	No relevant outcome
48.	Fritz Verhees RA, Thijs C, Ambergen T, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: 25 years follow-up of a randomized controlled trial. No impact on long-term mortality. <i>PLoS one</i> . 2019;14(5).	No parallel RCT
49.	Gaughran F, Walwyn R, Lambkin-Williams R, et al. Flu: effect of vaccine in elderly care home residents: a randomized trial. <i>Journal of the American Geriatrics Society</i> . Dec 2007;55(12):1912-1920.	No relevant comparator
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### Characteristics of included studies

REF	AUTHOR	YEAR	INTERVENTIONS	N. PATIENTS RANDOMISED	AGE	COMORBIDITY/ SPECIAL GROUPS	SETTING	FUNDING SOURCE	CONTINENT	COUNTRY	CENTER
<b>STUDIES INCLUDED IN THE NETWORK META-ANALYSES</b>											
1	Abadoglu	2004	trivalent inactivated IM	86	18 -60 years	chronic respiratory disease	outpatients	not reported	Asia	Turkey	not reported
			no vaccine	42							
3	Anh	2016	trivalent inactivated IM	30	18 -60 years	healthy subjects	outpatients	government/ private no profit	Asia	Vietnam	single center
			placebo	30							
2	Allsup	2004	trivalent inactivated IM	552	61 years and older	healthy subjects	outpatients	government/ private no profit	Europe	UK	no reported
			placebo	177							
5	Ansaldi	2012	trivalent inactivated IM	26	18 -60 years	imunodepression (any cause)	outpatients	not reported	Europe	Italy	not reported
			trivalent inactivated intradermal	28							
4	Ansaldi	2013	trivalent inactivated intradermal	250	61 years and older	healthy subjects	outpatients	not reported	Europe	Italy	multi-center
			trivalent inactivated adjuvanted virosome/liposome	250							
6	Arnou	2010	trivalent inactivated intradermal	1803	18 -60 years	healthy subjects	outpatients	industry	Europe	France, Italy, Belgium, Lithuania	multi-center
			trivalent inactivated IM	452							

7	Arnou	2009	trivalent inactivated IM	1089	61 years and older	healthy subjects	outpatients	industry	Europe	France, Italy, Belgium, Lithuania	multi-center
			trivalent inactivated intradermal	2618							
8	Ashkenazi	2006	trivalent live attenuated nasal spray	1101	<5 years	chronic respiratory disease	outpatients	not reported	Multi-Continent	Belgium, Czech Republic, Finland, Germany, Italy, Poland, Spain, Switzerland, UK, Israel	multi-center
			trivalent inactivated (subunit or split) IM	1086							
9	Auewarakul	2006	trivalent inactivated intradermal	400	18 -60 years	healthy subjects	outpatients	not reported	Asia	Thailand	not reported
			trivalent inactivated IM	100							
10	Baldo	2007	trivalent inactivated adjuvanted MF59/AS03 IM	128	18 -60 years	multicomorbidity	outpatients	government/ private no profit	Europe	Italy	not reported
			trivalent inactivated IM	128							
11	Baluch	2013	trivalent inactivated) intradermal	114	18 -60 years	imunodepression (any cause)	outpatients	industry	North America	Canada	not reported
			trivalent inactivated IM	115							
12	Barrett	2011	trivalent inactivated IM	3626	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	Usa	multi-center
			placebo	3624							

13	Bart	2016	quadrivalent inactivated IM	1335	18 -60 years	healthy subjects	outpatients	industry	North America	Usa	multi-center
			trivalent inactivated IM	1345							
14	Baxter	2011	trivalent inactivated recombinant	300	18 -60 years	healthy subjects	outpatients	not reported	North America	Usa	multi-center
			trivalent inactivated IM	302							
15	Belongia	2020	trivalent inactivated high doses (subunit or split) IM	29	61 years and older	healthy subjects	outpatients	government/ private no profit	North America	Usa	single center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	30							
			quadrivalent inactivated recombinant	30							
20	Belshe	1992	trivalent live attenuated nasal spray	32	mixed aged children	healthy subjects	outpatients	not reported	North America	Usa	not reported
			placebo	17							
18	Belshe	1998	trivalent live attenuated nasal spray	1070	<5 years	healthy subjects	outpatients	government/ private no profit	North America	Usa	multi-center
			placebo	532							
17	Belshe	2000	trivalent live attenuated nasal spray	917	<5 years	healthy subjects	outpatients	government/ private no profit	North America	Usa	multi-center
			placebo	441							

16	Belshe	2007	trivalent live attenuated nasal spray	4179	<5 years	healthy subjects	outpatients	not reported	Multi-Continent	USA (49% Of Subjects), Europe And Middle East (45% Of Subjects), Asia (6% Of Subjects)	multi-center
			trivalent inactivated IM	4173							
19	Belshe b	2007	trivalent inactivated intradermal	30	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	Usa	single center
			trivalent inactivated IM	31							
21	Ben-Yehuda	2003	trivalent inactivated IM	33	≥61 years	multicomorbidity	long- term care facilities	government/ private no profit	Asia	Israel	not reported
			trivalent inactivated adjuvanted virosome/liposome	48							
22	Ben-Yehuda b	2003	trivalent inactivated IM	37	18 -60 years	healthy subjects	outpatients	not reported	Asia	Israel	not reported
			trivalent inactivated adjuvanted virosome/liposome	36							
26	Beran	2009	trivalent inactivated IM	4137	18 -60 years	healthy subjects	outpatients	industry	Europe	Czech Republic	not reported
			placebo	2066							

24	Beran a	2013	trivalent inactivated IM	105	18 -60 years	healthy subjects	outpatients	industry	Europe	Czech Republic	single center
			trivalent inactivated adjuvanted MF59/AS03 IM	105							
			quadrivalent inactivated IM	105							
			quadrivalent inactivated adjuvanted MF59/AS03	105							
25	Beran b	2009	trivalent inactivated IM	5103	18 -60 years	healthy subjects	outpatients	industry	Europe	Czech Republic, Finland	multi-center
			placebo	2549							
23	Beran c cohort 1	2009	trivalent inactivated IM	547	18 -60 years	healthy subjects	outpatients	industry	Europe	Belgium, Czech Republic, Lithuania	multi-center
			trivalent inactivated intradermal	544							
	Beran c cohort 2		trivalent inactivated IM	410							
			trivalent inactivated (subunit or split) intradermal	418							
27	Bergen	2004	trivalent live attenuated nasal spray	6473	18 -60 years	healthy subjects	outpatients	not reported	Not Reported	Not Reported	not reported
			placebo	3216							
28	Block	2012	quadrivalent inactivated IM	1385	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi-center
			trivalent inactivated IM	927							

29	Block	2011	quadrivalent inactivated IM	1200	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			T/LAIV-B/Yamagata	299							
			T/LAIV-B/Victoria	301							
30	Boonnak	2017	trivalent inactivated IM	111	≥61 years	multicomorbidity	outpatients	government/ private no profit	not reported	not reported	not reported
			trivalent inactivated intradermal	111							
31	Bracco Neto cohort 1	2009	trivalent live attenuated nasal spray	944	<5 years	healthy subjects	outpatients	industry	Multi-continent	South Africa, Brazil, Argentina	multi-center
			placebo	941							
	Bracco Neto cohort 2	2009	placebo	342							
			trivalent live attenuated nasal spray	338							
32	Brady	2018	trivalent live attenuated nasal spray	124	18 -60 years	pregnant women	outpatients	government/ private no profit	North America	USA	multi center
			trivalent inactivated (subunit or split) IM	124							
33	Bridges cohort 1	2000	trivalent inactivated) IM	595	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	not reported
			placebo	589							
	Bridges cohort 2	2000	trivalent inactivated IM	587	18 -60 years	healthy subjects	outpatients	government/ private no profit			
			placebo	604							



34	Brooks	2016	trivalent live attenuated nasal spray	1174	<5 years	healthy subjects	outpatients	government/ private no profit	Africa	Bangladesh	multi-center
			placebo	587							
35	Bueving	2004	trivalent inactivated IM	347	6-17 years	chronic respiratory disease	outpatients	government/ private no profit	Europe	Holland	not reported
			placebo	349							
36	Cadorna-Carlos	2015	quadrivalent inactivated IM	1648	18 -60 years	healthy subjects	outpatients	not reported	Oceania	Philippines, Australia	multi center
			trivalent inactivated IM	56							
			quadrivalent inactivated IM	329	6-17 years	healthy subjects	outpatients				
			trivalent inactivated IM	55							
37	Caldera	2019	trivalent inactivated high doses (subunit or split) IM	25	18 -60 years	immunodepression (any cause)	outpatients	government/ private no profit	North America	USA	multi center
			quadrivalent inactivated (subunit or split) IM	15							
38	Carr	2011	trivalent inactivated IM	27	mixed aged children	cancer	outpatients	industry	North America	USA	not reported
			trivalent live attenuated nasal spray	28							
39	Chan	2014	trivalent inactivated IM	50	≥61 years	multicomorbidity	inpatients	government/ private no profit	Asia	Hong Kong	single center
			trivalent inactivated intradermal	50							

40	Chang	2019	quadrivalent inactivated high doses IM	1777	61 years and older	multicomorbidity	outpatients	industry	North America	USA	multi center
			trivalent inactivated high doses (subunit or split) IM	893				industry		USA	
41	Chi	2010	trivalent inactivated IM	65	≥61 years	multicomorbidity	outpatients	government/ private no profit	North America	Washington	not reported
			trivalent inactivated intradermal	63							
43	Chiu	2007	trivalent inactivated IM	56	mixed aged children	healthy subjects	outpatients	government/ private no profit	Asia	Hong Kong	not reported
			trivalent inactivated intradermal	56							
42	Chiu	2009	trivalent inactivated IM	63	<5 years	healthy subjects	outpatients	government/ private no profit	Asia	Hong Kong	not reported
			trivalent inactivated intradermal	63							
44	Choi	2018	trivalent inactivated (IM	100	adult and elderly	healthy subjects	outpatients	industry	Asia	Republic of Korea	multi center
			quadrivalent inactivated IM	200							
45	Choi	2017	trivalent inactivated) IM	751	adult and elderly	healthy subjects	outpatients	industry	Asia	Republic of Korea	multi center
			quadrivalent inactivated IM	752							

47	Chuaychoo	2019	trivalent inactivated (subunit or split) IM	39	61 years and older	chronic respiratory disease	outpatients	government/ private no profit	Asia	Bangkok, Thailand	single center
		2019	trivalent inactivated (subunit or split) intradermal ID	41	61 years and older	chronic respiratory disease	outpatients	government/ private no profit		Bangkok, Thailand	
48	Claeys	2018	quadrivalent inactivated (subunit or split) IM	6006	<5 years	healthy subjects	outpatients	industry	Multi continent	Europe, Central America, and Asia	multi center
		2018	pneumococcal conjugate vaccine (PCV), hepatitis A vaccine, or varicella vaccine.	6012							
49	Colmegna	2020	trivalent inactivated high doses (subunit or split) IM	139	adult and elderly	immunodepression (any cause)	outpatients	industry	North America	Canada	multi center
		2020	quadrivalent inactivated (subunit or split) IM	140							
49	Colombo	2001	trivalent inactivated IM	177	<5 years	healthy subjects	outpatients	government/ private no profit	Europe	Italy	not reported
			no vaccine	167							
51	Couch	2007	trivalent inactivated IM	208	≥61 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent inactivated high doses IM	206							
52	Cowling	2010	trivalent inactivated IM	71	6-17 years	healthy subjects	outpatients	government/ private no profit	Asia	Hong Kong	not reported
			placebo	48							
53	Cowling	2014	trivalent inactivated IM	479	6-17 years	healthy subjects	outpatients	government/ private no profit	Asia	Hong Kong	multi center
			placebo	317							

54	Cowling	2020	quadrivalent inactivated (subunit or split) IM	508	61 years and older	multicomorbidity	outpatients	government/ private no profit	Asia	Hong Kong	single center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	508	61 years and older	multicomorbidity	outpatients	government/ private no profit		Hong Kong	
			trivalent inactivated high doses (subunit or split) IM	510	61 years and older	multicomorbidity	outpatients	government/ private no profit		Hong Kong	
			quadrivalent inactivated recombinant	335	61 years and older	multicomorbidity	outpatients	government/ private no profit		Hong Kong	
55	Cruz-Valdez	2018	trivalent inactivated IM	143	<5 years	healthy subjects	outpatients	industry	South America	Mexico	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	144							
57	De Bruijn	2006	trivalent inactivated IM	129	adult and elderly	healthy subjects	outpatients	not reported	not reported	not reported	not reported
			trivalent inactivated adjuvanted virosome/liposome	127							
			trivalent inactivated adjuvanted MF59/AS03 IM	130							
56	De Bruijn	2007	trivalent inactivated IM	129	≥61 years	healthy subjects	outpatients	not reported	Europe	Germany, Sweden, Lithuania, Bulgaria	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	130							
			trivalent inactivated adjuvanted virosome/liposome	127							

58	De Donato	1999	trivalent inactivated adjuvanted MF59/AS03 IM	106	≥61 years	healthy subjects	outpatients	not reported	Europe	Italy	not reported
			trivalent inactivated IM	105							
59	De Villiers	2009	trivalent live attenuated nasal spray	1620	≥61 years	multicomorbidity	outpatients	industry	Africa	Republic of South Africa	multi center
			placebo	1622							
61	Desheva	2002	trivalent live attenuated nasal spray	184	<5 years	healthy subjects	outpatients	not reported	Asia	Russia	not reported
			placebo	72							
62	Diallo 2018	2018	trivalent inactivated (subunit or split) IM	119	<5 years	healthy subjects	outpatients	government/ private no profit	Africa	Senegal	single center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	118	<5 years	healthy subjects	outpatients	government/ private no profit		Senegal	
			placebo/no intervention	59	<5 years	healthy subjects	outpatients	government/ private no profit		Senegal	
63	DiazGranados	2013	trivalent inactivated IM	3055	≥61 years	multicomorbidity	outpatients	industry	North America	USA	multi center
			trivalent inactivated high doses IM	6117							
64	DiazGranados	2014	trivalent inactivated IM	15998	≥61 years	multicomorbidity	outpatients	industry	North America	USA, Canada	multi center
			trivalent inactivated high doses IM	15991							
65	DiazGranados	2015	trivalent inactivated high doses IM	148	18 -60 years	healthy subjects	outpatients	industry	North America	USA, Canada	multi center
			trivalent inactivated IM	152							

66	Domachowske	2013	trivalent inactivated IM	1823	mixed aged children	healthy subjects	outpatients	industry	Multi-continent	Czech Republic, France, Germany, Philippines, USA	multi center
			quadrivalent inactivated (subunit or split) IM	915							
67	Dunkle	2017	quadrivalent inactivated IM	4505	adult and elderly	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			quadrivalent inactivated recombinant	4498							
69	Dunkle b	2017	quadrivalent inactivated IM	339	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			quadrivalent inactivated recombinant	1011							
68	Dunkle	2018	quadrivalent inactivated recombinant	108	6-17 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated (subunit or split) IM	111	6-17 years						
70	Durando cohort 1	2008	trivalent inactivated adjuvanted MF59/AS03 IM	81	18 -60 years	healthy subjects	outpatients	industry	Europe	Italy	multi center
			trivalent inactivated IM	80							
	Durando cohort 2		trivalent inactivated adjuvanted MF59/AS03 IM	46	18 -60 years	imunodepression (any cause)	outpatients	industry			
			trivalent inactivated IM	49							
71	Englund	2010	trivalent inactivated IM	915	<5 years	healthy subjects	outpatients	not reported	North America	USA	multi center
			placebo	460							

72	Esposito	2010	trivalent inactivated IM	91	<5 years	cancer	outpatients	government/ private no profit	Europe	Italy	multi center
			no vaccine	91							
73	Esposito	2011	trivalent inactivated IM	37	6-17 years	healthy subjects	outpatients	government/ private no profit	Europe	Italy	not reported
			trivalent inactivated intradermal	75							
74	Esposito	2014	trivalent inactivated IM	30	6-17 years	imunodepression (any cause)	outpatients	government/ private no profit	Europe	Italy	not reported
			trivalent inactivated adjuvanted virosome/liposome	30							
75	Essink	2019	quadrivalent inactivated adjuvanted MF5quadrivalent inactivated intradermal/ASplacebo/no intervention trivalent inactivated (subunit or split) intradermal ID	889	61 years and older	healthy subjects+multicomortibity	outpatients	industry	North America	20 centers usa	multi center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	889	61 years and older	healthy subjects+multicomortibity	outpatients	industry		20 centers usa	
76	Evison	2009	trivalent inactivated IM	151	18 -60 years	imunodepression (any cause)	outpatients	industry	Europe	Switzerland	not reported
			trivalent inactivated adjuvanted virosome/liposome	153							
77	Falsey	2009	trivalent inactivated IM	1288	≥61 years	multicomortibity	outpatients	industry	North America	USA	multi center
			trivalent inactivated high doses IM	2588							

79	Fleming	2006	trivalent live attenuated nasal spray	1114	6-17 years	chronic respiratory disease	outpatients	industry	Multi-continent	Belgium, Finland, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, UK	multi center
			trivalent inactivated IM	1115							
80	Forrest	2011	trivalent inactivated IM	1501	≥61 years	healthy subjects	outpatients	industry	Africa	Republic of South Africa	multi center
			trivalent live attenuated nasal spray	1508							
81	Frenck	2011	trivalent inactivated IM	398	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent inactivated intradermal	394							
83	Frey	2010	trivalent inactivated IM	7504	18 -60 years	healthy subjects	outpatients	industry	Multi-continent	USA, Finland, Poland	multi center
			placebo	3900		healthy subjects	outpatients	industry			
82	Frey	2003	trivalent inactivated IM	151	18 -60 years	healthy subjects	outpatients	Not reported	North America	USA	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	150							



84	Frey	2014	trivalent inactivated IM	3552	≥61 years	healthy subjects	outpatients	industry	Multi-continent	Colombia, Panama, Philippines, USA	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	3552							
85	Gabutti	2005	trivalent inactivated IM	19	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	Europe	Italy	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	18							
86	Gasparini	2001	trivalent inactivated IM	104	≥61 years	healthy subjects	outpatients	not reported	Europe	Italy	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	204							
87	Giaquinta	2014	trivalent inactivated IM	15	3-17 years	solid organ transplantation	outpatients	industry	North America	USA	multi center
			trivalent inactivated high doses IM	23							
89	Gorse b	2013	trivalent inactivated IM	495	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			trivalent inactivated intradermal	755							
90	Gorse	2015	trivalent inactivated intradermal	1683	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated intradermal	1672							
88	Gorse	2013	trivalent inactivated IM	1428	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			trivalent inactivated intradermal	2864							

91	Govaert	1993	quadrivalent inactivated IM	927	≥61 years	multicomorbidity	outpatients	government/ private no profit	Europe	Netherlands	multi center
			placebo	911							
92	Greenberg	2014	trivalent inactivated IM	1461	6-17 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	2902		healthy subjects	outpatients	industry			
94	Greenberg	2017	trivalent inactivated IM	450	≥61 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	225							
93	Greenberg	2013	trivalent inactivated IM	380	adult and elderly	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	190							
95	Hakim	2016	trivalent inactivated) IM	42	6-17 years	cancer +imunodepression (any cause)	outpatients	government/ private no profit	North America	USA	single center
			trivalent inactivated high doses IM	41							
96	Halasa	2011	trivalent live attenuated nasal spray	10	6-17 years	imunodepression (any cause)	outpatients	industry	North America	USA	multi center
			placebo	10							
97	Halasa	2016	trivalent inactivated IM	15	18 -60 years	transplantation	outpatients	industry	North America	USA	single center
			trivalent inactivated high doses IM	29							

98	Hartvickson	2015	trivalent inactivatedIM	1174	6-17 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	1159							
99	Hobermann cohort 1	2003	trivalent inactivated IM	278	<5 years	healthy subjects	outpatients	industry	North America	USA	single center
			placebo	139							
	Hobermann cohort 2	2003	trivalent inactivated IM	253	<5 years	healthy subjects	outpatients				
			placebo	123							
100	Hoft	2011	trivalent inactivated IM	14	<5 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent live attenuated nasal spray	13							
101	Holland	2008	trivalent inactivated IM	368	≥61 years	multicomorbidity	outpatients	industry	Oceania	Australia, New Zealand	multi center
			trivalent inactivated intradermal	370							
102	Hoon Han cohort 1	2013	trivalent inactivated IM	60	18 -60 years	healthy subjects	outpatients	not reported	Asia	South Korea	multi center
			trivalent inactivatedintradermal	60							
	Hoon Han cohort 2	2013	trivalent inactivated IM	60	≥61 years	healthy subjects	outpatients				
			trivalent inactivated intradermal	60							

103	Hu	2019 b	quadrivalent inactivated (subunit or split) IM	1160	<5 years	healthy subjects	outpatients	industry	Asia	China	multi center
			trivalent inactivated (subunit or split) IM	1160	<5 years						
104	Hui	2006	trivalent inactivated IM	65	≥61 years	healthy subjects	outpatients	government/ private no profit	Asia	Hong Kong	multi center
			placebo	63							
105	Hung	2012	trivalent inactivated (subunit or split) intradermal ID	133	61 years and older	multicomorbidity	outpatients	government/ private no profit	Asia	Hong Kong	single center
			trivalent inactivated (subunit or split) IM	66							
106	Hurwitz	2000	trivalent inactivated (subunit or split) IM	76	<5 years	healthy subjects	outpatients	industry	North America	10 US Navy–affiliated day care centers	multi center
			hepatitis A vaccine	74							
108	Jackson cohort 1	2010	trivalent inactivated IM	1734	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			placebo	1756							
	Jackson cohort 1+2	2010	trivalent inactivated IM	3783	18 -60 years	healthy subjects	outpatients				
			placebo	3828							
	Jackson cohort 2	2010	trivalent inactivated IM	2048	18 -60 years	healthy subjects	outpatients				
			placebo	2073							

109	Jamshe	2019	trivalent inactivated (subunit or split) IM	51	18 -60 years	cancer	outpatients	industry+government/ private no profit	North America	USA	single center
			trivalent inactivated high doses (subunit or split) IM	54	18 -60 years						
110	Jeffs	2015	trivalent inactivated IM	24	18 -60 years	immunosuppression in autoimmune vasculitis	outpatients	government/ private no profit	Oceania	Australia	not reported
			no vaccine	7							
			trivalent inactivated IM	53	18 -60 years	healthy subjects	outpatients				
			no vaccine	14							
111	Kanra	2004	trivalent inactivated IM	228	<5 years	healthy subjects	outpatients	industry	Multi-continent	Germany, Italy, Turkey.	multi center
			trivalent inactivated recombinant	224							
112	Keitel	2006	placebo	50	≥61 years	healthy subjects	outpatients	government/ private no profit	North America	USA	single center
			trivalent inactivated IM	51							
			trivalent inactivated high doses IM	50							
114	Keitel	2009	trivalent inactivated IM	434	≥61 years	healthy subjects	outpatients	not reported	not reported	not reported	multi center
			trivalent inactivated recombinant	436							

113	Keitel cohort 1	1997	placebo	298	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent inactivated IM	300							
	Keitel cohort 2	1997	placebo	241	18 -60 years	healthy subjects	outpatients				
			trivalent inactivated IM	457							
	Keitel cohort 3	1997	placebo	253	18 -60 years	healthy subjects	outpatients				
			trivalent inactivated IM	577							
	Keitel cohort 4	1997	placebo	217	18 -60 years	healthy subjects	outpatients				
			trivalent inactivated IM	723							
	Keitel cohort 5	1997	placebo	145	18 -60 years	healthy subjects	outpatients				
			trivalent inactivated IM	789							
115	Khajedaluae	2018	trivalent inactivated (subunit or split) IM	500	<5 years	healthy subjects	outpatients	not reported	Asia	Iran	multi center
			placebo/no intervention	500	<5 years						

116	Khan	1996	trivalent inactivated IM	168	6-17 years	healthy subjects	outpatients	not reported	Asia	Russia	not reported
			placebo	187							
			trivalent live attenuated	200							
117	Kieninger	2013	trivalent inactivated IM	1620	adult and elderly	healthy subjects	outpatients	industry	Multi-continent	Germany, Romania, Spain, Korea, Taiwan , USA	multi center
			quadrivalent inactivated IM	3036							
118	King cohort 1	2000	trivalent live attenuated nasal spray	27	18 -60 years	healthy subjects	outpatients	not reported	North America	USA	multi center
			placebo	27	18 -60 years						
	King cohort 2	2000	trivalent live attenuated nasal spray	28	18 -60 years	imunodepression (any cause)	outpatients				
			placebo	29	18 -60 years						
119	King	1998	trivalent live attenuated nasal spray	234	mixed aged children	healthy subjects	outpatients	industry	North America	USA	multi center
			placebo	122							
120	Kositantont	2004	trivalent inactivated IM	61	≥61 years	chronic respiratory disease	outpatients	government/ private no profit	Asia	Thailand	single center
			placebo	62							
121	Kumar	2016	trivalent inactivated IM	34	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	North America	Canada	single center
			trivalent inactivated adjuvanted MF59/AS03 IM	34							

122	Lan	2019	trivalent inactivated (subunit or split) IM	740	18 -60 years	healthy subjects	outpatients	government/ private no profit	Asia	Vietnam	not reported
			placebo/no intervention	148							
124	Langley	2014	trivalent inactivated IM	302	<5 years	healthy subjects	outpatients	industry	Multi-continent	Canada, Dominican Republic, Honduras	multi center
			quadrivalent inactivated IM	299							
123	Langley	2013	trivalent inactivated IM	1861	mixed aged children	healthy subjects	outpatients	industry	Multi-continent	Canada, USA, Mexico, Spain, Taiwan	multi center
			quadrivalent inactivated IM	932							
125	Leroux-Roels	2008	trivalent inactivatedIM	390	18 -60 years	healthy subjects	outpatients	industry	Europe	Belgium, Germany, Switzerland	multi center
			trivalent inactivated intradermal	588							
127	Levin	2008	trivalent inactivated IM	121	6-17 years	imunodepression (any cause)	outpatients	government/ private no profit	North America	USA	not reported
			trivalent live attenuated nasal spray	122							
128	Levin	2016	trivalent inactivated intradermal	60	≥61 years	healthy subjects	outpatients	industry	Europe	Germany, Belgium	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	63							
			trivalent inactivated adjuvanted virosome/liposome	63							



129	Li	2008	trivalent inactivated IM	200	≥61 years	healthy subjects	outpatients	industry	Asia	China	not reported
			trivalent inactivated adjuvanted MF59/AS03 IM	400							
130	Liebowitz	2020	quadrivalent inactivated (subunit or split) IM	72	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	not reported
			placebo/no intervention	36							
131	Li-Kim-Moy	2016	trivalent inactivated (subunit or split) IM	57	<5 years	healthy subjects	outpatients	industry+government/ private no profit	Oceania	Sydney, Australia	multi center
			hepatitis A vaccine	67							
132	Lum	2010	trivalent live attenuated nasal spray	819	<5 years	healthy subjects	outpatients	not reported	Multi-continent	Bangladesh, Belgium, Finland, Germany, Hong Kong, Lithuania, Malaysia, Mexico, Philippines, Poland, Singapore, South Korea, Thailand	multi center
			placebo	414							
135	Madhi	2011	trivalent inactivated IM	255	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	Africa	South Africa	single center
			placebo	251							
134	Madhi	2013	trivalent inactivated IM	206	mixed aged children	imunodepression (any cause)	outpatients	government/ private no profit	Africa	South Africa	single center
			placebo	204							

133	Madhi cohort 1	2014	trivalent inactivated IM	1062	18 -60 years	pregnant women	outpatients	government/ private no profit	Africa	South Africa	single center
			placebo	1054							
	Madhi cohort b	2014	trivalent inactivated) IM	100	18 -60 years	pregnant women+imunodepression (any cause)	outpatients	government/ private no profit			
			placebo	94							
136	Magnani	2005	trivalent inactivated IM	21	adult and elderly	imunodepression (any cause)	outpatients	not reported	Europe	Italy	single center
			trivalent inactivated adjuvanted MF59/AS03 IM	21							
			no vaccine	16							
138	Mallory (only study 2)	2018	quadrivalent live attenuated nasal spray	868	mixed aged children	healthy subjects+chronic respiratory disease	outpatients	industry	Asia	Japan	multi center
			placebo/no intervention	433							
137	Mallory	2020	trivalent live attenuated nasal spray	67	<5 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent live attenuated nasal spray	133							
139	Marchisio	2009	trivalent inactivated adjuvanted virosome/liposome	90	<5 years	healthy subjects	outpatients	government/ private no profit	Europe	Italy	not reported
			placebo	90							

140	McBride cohort 1	2016	trivalent inactivated IM	5032	18 -60 years	healthy subjects	outpatients	industry	Oceania	Australia , New Zealand	multi center
			placebo	2512							
	McBride cohort 2	2016	trivalent inactivated IM	5001	18 -60 years	healthy subjects	outpatients	industry			
			placebo	2499							
141	McElhane	2013	trivalent inactivated IM	21802	≥61 years	healthy subjects	outpatients	industry	Multi-continent	Belgium, Canada, Czech Republic, Estonia, France, Germany, Mexico, Norway, Poland, Romania, Russia, Taiwan, the Netherlands, UK, USA	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	21893		healthy subjects	outpatients	industry			
142	McKittrick	2013	trivalent inactivated IM	98	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	North America	USA	single center
			trivalent inactivated high doses IM	100							
143	McManus	2014	trivalent inactivated IM	16	6-17 years	cancer	outpatients	government/ private no profit	North America	USA	single center
			trivalent inactivated high doses (subunit or split) IM	34							

144	Mesa -Duque	2001	trivalent inactivated IM	247	18 -60 years	healthy subjects	outpatients	not reported	South America	Colombia	not reported
			placebo	246							
145	Minutello	1999	trivalent inactivated IM	46	≥61 years	healthy subjects	outpatients	not reported	Europe	Italy	single center
			trivalent inactivated adjuvanted MF59/AS03 IM	46							
146	Mixeu	2002	trivalent inactivated IM	405	18 -60 years	healthy subjects	outpatients	industry	South America	Brazil	single center
			placebo	408							
147	Miyazaki	1993	trivalent live attenuated nasal spray	19	6-17 years	chronic respiratory disease	inpatients	government/ private no profit	Asia	Japan	single center
			no vaccine	20							
148	Monto	2009	trivalent inactivated IM	814	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	single center
			trivalent live attenuated nasal spray	813							
			placebo	325							
149	Morelon	2010	trivalent inactivated IM	31	18 -60 years	imunodepression (any cause)	outpatients	industry	Europe	France	multi center
			trivalent inactivated intradermal	31							
150	Musto	1997	trivalent inactivated IM	25	18 -60 years	cancer	outpatients	not reported	Europe	Italy	single center
			no vaccine	25							

152	Natori a	2017	trivalent inactivated adjuvanted MF59/AS03 IM	35	adult and elderly	imunodepression (any cause)	outpatients	industry	not reported	not reported	not reported
			trivalent inactivated IM	38							
153	Natori b	2017	trivalent inactivated IM	85	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	not reported	not reported	not reported
			trivalent inactivated highIM	87							
155	Nichol	1999	trivalent live attenuated nasal spray	3041	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			placebo	1520							
154	Nichol	1995	trivalent inactivated IM	424	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	not reported
			placebo	425		healthy subjects	outpatients	government/ private no profit			
156	Noh	2019	quadrivalent inactivated high doses IM	30	18 -60 years	healthy subjects	outpatients	industry	Asia	KOREA	single center
			quadrivalent inactivated (subunit or split) IM	10							
157	Nolan	2014	trivalent inactivated IM	2964	<5 years	healthy subjects	outpatients	industry	Multi-continent	Argentina, Australia, Chile, Philippines, South Africa	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	3136							

159	Ohmit	2008	trivalent inactivated IM	818	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			placebo	338							
			trivalent live attenuated nasal spray	787							
158	Ohmit	2006	trivalent inactivated IM	522	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			placebo	206							
			trivalent live attenuated nasal spray	519							
160	Ortiz	2015	trivalent live attenuated nasal spray	150	<5 years	healthy subjects	outpatients	government/ private no profit	Africa	Bangladesh	single center
			placebo	150							
161	Pedroza	2009	trivalent inactivated) IM	132	6-17 years	chronic respiratory disease	outpatients	industry	South America	Mexico	single center
			placebo	31							
162	Pepin	2013	trivalent inactivated IM	449	adult and elderly	healthy subjects	outpatients	industry	Europe	France, Germany	multi center
			quadrivalent inactivated (subunit or split) IM	1116							
164	Pepin	2016	trivalent inactivated IM	355	<5 years	healthy subjects	outpatients	industry	Multi-continent	Poland, Finland, Mexico, Taiwan	multi center
			quadrivalent inactivated IM	887							

163	Pepin	2019	quadrivalent inactivated (subunit or split) IM	2721	<5 years	healthy subjects	outpatients	industry	Multi continent	Asia, Latin America, Europe, and Africa	multi center
			placebo/no intervention	2715							
			trivalent inactivated (subunit or split) IM	369							
165	Powers	1995	trivalent inactivated recombinant	77	18 -60 years	healthy subjects	outpatients	not reported	North America	USA	multi center
			trivalent inactivated IM	26							
			placebo	24							
166	Pregliasco	2001	trivalent inactivated IM	213	≥61 years	nr	long term care facilities	not reported	Europe	Italy	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	207							
			trivalent inactivated adjuvanted virosome/liposome	215							
168	Redding	2002	trivalent live attenuated nasal spray	24	6-17 years	chronic respiratory disease	outpatients	industry	North America	USA	multi center
			placebo	24							
169	Reid	1998	trivalent inactivated IM	17	18 -60 years	chronic respiratory disease	outpatients	not reported	not reported	not reported	not reported
			placebo	5							

170	Rodriguez Weber	2014	trivalent inactivated IM	301	<5 years	healthy subjects	outpatients	industry	South America	Mexico	multi center
			quadrivalent inactivated IM	298							
171	Rolfes	2017	trivalent inactivated (subunit or split) IM	2576	<5 years	healthy subjects	outpatients	government/ private no profit	Asia	Bangladesh	single center
			inactivated polio vaccine (IPV)	2593							
172	Rouphael	2017	trivalent inactivated IM	25	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	not reported
			trivalent inactivated intradermal	25							
			placebo	25							
173	Rudenko	2001	trivalent inactivated IM	95	≥61 years	multicomorbidity	long term care facilities	not reported	Asia	Russia	multi center
			trivalent live attenuated nasal spray	114							
			placebo	110							
174	Ruf	2004	trivalent inactivated IM	273	adult and elderly	healthy subjects	outpatients	not reported	Europe	Germany	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	275							
			trivalent inactivated adjuvanted virosome/liposome	272							
175	Safdar	2006	trivalent inactivated IM	6	18 -60 years	cancer	inpatients	not reported	North America	USA	not reported
			trivalent inactivated recombinant	21							



176	Sarkar	2020	trivalent inactivated (subunit or split) IM	155	mixed aged children	healthy subjects	outpatients	industry	Asia	India	multi center
			quadrivalent inactivated (subunit or split) IM	151							
177	Sarsenbayeva	2018	trivalent inactivated IM	22	18 -60 years	healthy subjects	outpatients	not reported	Asia	Kazakhstan	single center
			placebo	22							
178	Saxen	1999	trivalent inactivated IM	216	18 -60 years	healthy subjects	outpatients	not reported	Europe	Finland	multi center
			placebo	211							
179	Schaad	2000	trivalent inactivated IM	21	mixed aged children	chronic respiratory disease	outpatients	not reported	Europe	Switzerland	multi center
			trivalent inactivated adjuvanted virosome/liposome	43							
180	Scheifele	2013	trivalent inactivated IM	310	≥61 years	healthy subjects	outpatients	government/ private no profit	North America	Canada	multi center
			trivalent inactivated intradermal	306							
			trivalent inactivated adjuvanted virosome/liposome	306							
182	Seo	2014	trivalent inactivated) IM	113	≥61 years	healthy subjects	outpatients	government/ private no profit	Asia	South Korea	multi center
			trivalent inactivated intradermal	111							
			trivalent inactivated adjuvanted virosome/liposome	111							

181	Seo	2016	trivalent inactivated IM	28	18 -60 years	immunodepression (any cause)	outpatients	not reported	Asia	Republic of Korea	multi center
			trivalent inactivated intradermal	58							
184	Sharma	2018	trivalent inactivated (subunit or split) IM	174	adult and elderly	healthy subjects	long term care facilities	industry	Asia	India	multi center
			quadrivalent inactivated (subunit or split) IM	176	adult and elderly						
185	Sheldon	2013	trivalent live attenuated nasal spray	598	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent live attenuated nasal spray	1202							
186	Sindoni	2009	trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	96	61 years and older	multicomorbidity	long term care facilities	not reported	Europe	Italy	single center
			trivalent inactivated (subunit or split) IM	99	61 years and older	multicomorbidity	long term care facilities	not reported			
188	Solares	2014	trivalent inactivated IM	180	<5 years	healthy subjects	outpatients	industry	South America	Guatemala	multi center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	180							
189	Song	2007	trivalent inactivated (subunit or split) IM	198	adult and elderly	multicomorbidity	outpatients	not reported	Asia	Seoul, Korea	single center
			placebo/no intervention	113	adult and elderly						
190	Song	2019	quadrivalent inactivated (subunit or split) IM	648	adult and elderly	healthy subjects	outpatients	industry+government/private no profit	Asia	South Korea	multi center
			trivalent inactivated (subunit or split) IM	651							

192	Squarcione	2003	trivalent inactivated (subunit or split) IM	1076	61 years and older	healthy subjects	outpatients	not reported	Europe	Italy	single center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	1074	61 years and older						
194	Steinhoff cohort 1	2017	trivalent inactivated IM	1049	18 -60 years	pregnant women	outpatients	government/ private no profit	Asia	Nepal	multi center
			placebo	1041							
	Steinhoff cohort b	2017	trivalent inactivated) IM	798	18 -60 years						
			placebo	805							
195	Stevanovic	2017	trivalent inactivated IM	30	18 -60 years	healthy subjects	outpatients	government/ private no profit	Europe	Serbia	single center
			placebo	30							
196	Stevanovic	2020	trivalent inactivated (subunit or split) IM	320	18 -60 years	healthy subjects	outpatients	government/ private no profit	Asia	Serbia	multi center
			placebo/no intervention	160							
197	Strijbos	2019	trivalent inactivated (subunit or split) IM	24	adult and elderly	immunodepression (any cause)	outpatients	government/ private no profit	Europe	Netherlands	single center
			placebo/no intervention	23							
198	Swierkosz	1994	trivalent live attenuated nasal spray	17	mixed aged children	healthy subjects	outpatients	not reported	not reported	not reported	not reported
			placebo	5							

199	Tam cohort 1	2007	trivalent live attenuated nasal spray	1900	mixed aged children	healthy subjects	outpatients	industry	Multi-continent	China, Hong Kong, India, Malaysia, Philippines, Singapore, Taiwan, Thailand	multi center
			placebo	1274							
	Tam cohort b	2007	trivalent live attenuated nasal spray	1477							
			placebo	1470							
200	Tanaka	1993	trivalent live attenuated nasal spray	20	mixed aged children	chronic respiratory disease	inpatients	government/ private no profit	not reported	not reported	not reported
			placebo	25							
201	Tapia	2016	trivalent inactivated (subunit or split) IM	2108	18 -60 years	pregnant women	outpatients	government/ private no profit	Africa	Mali	multi center
			meningococcal vaccine	2085	18 -60 years	pregnant women	outpatients	government/ private no profit			
202	Tasker	1999	trivalent inactivated IM	55	18 -60 years	imunodepression (any cause)	outpatients	not reported	North America	USA	single center
			placebo	47							
203	Tinoco	2014	trivalent inactivated IM	431	adult and elderly	healthy subjects	outpatients	industry	Multi-continent	Canada, Mexico, USA	multi center
			quadrivalent inactivated IM	1272							
204	Treanor	1994	trivalent inactivated IM	30	≥61 years	multicomorbidity	outpatients	government/ private no profit	North America	USA	multi center
			placebo	11							

206	Treanor	2011	trivalent inactivated recombinant	2344	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			placebo	2304							
207	Treanor	2000	trivalent inactivated IM	33	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent live attenuated nasal spray	36							
			placebo	34							
205	Treanor	2005	trivalent inactivated IM	763	18 -60 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			placebo	193							
208	Treanor	2007	trivalent inactivated recombinant	306	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			placebo	154							
209	Treanor cohort 1	2017	trivalent inactivated IM	871	18 -60 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	870							
	Treanor cohort 2	2017	trivalent inactivated IM	871	≥61 years	healthy subjects	outpatients				
			quadrivalent inactivated IM	870							
210	Tsang	2014	trivalent inactivated IM	319	≥61 years	healthy subjects	outpatients	government/ private no profit	North America	USA	multi center
			trivalent inactivated high doses IM	320							
			trivalent inactivated intradermal	637							

211	Van Damme	2010	trivalent inactivated intradermal	398	≥61 years	multicomorbidity	outpatients	not reported	Europe	Belgium, France	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	397							
212	Van de Witte	2018	quadrivalent inactivated (subunit or split) IM	769	18 -60 years	healthy subjects	outpatients	industry	Europe	Belgium, Germany, Hungary, Latvia and Lithuania	multi center
			trivalent inactivated (subunit or split) IM	222	18 -60 years						
			quadrivalent inactivated (subunit or split) IM	769	61 years and older						
			trivalent inactivated (subunit or split) IM	220	61 years and older						
213	Vardeny	2020	trivalent inactivated high doses (subunit or split) IM	2630	61 years and older	multicomorbidity	inpatients	industry+government/private no profit	North America	US and Canada	multi center
			quadrivalent inactivated (subunit or split) IM	2630	61 years and older						
216	Vesikari	2008	trivalent live attenuated nasal spray	61	<5 years	healthy subjects	outpatients	industry	Europe	Finland	multi center
			placebo	59							
219	Vesikari	2009	trivalent inactivated IM	139	<5 years	healthy subjects	outpatients	industry	Europe	Finland	not reported
			trivalent inactivated adjuvante MF59/AS03 IM	130							

217	Vesikari	2011	trivalent inactivated IM	1773	<5 years	healthy subjects	outpatients	industry	Europe	Germany, Finland	multi center
			trivalent inactivated adjuvanted (subunit or split) MF59/AS03 IM	1941							
214	Vesikari cohort 1	2006	trivalent live attenuated nasal spray	1059	<5 years	healthy subjects	outpatients	industry	Multi-continent	Belgium, Finland, Israel, Spain, UK	multi center
			placebo	725							
	Vesikari cohort 2	2006	trivalent live attenuated nasal spray	658	<5 years	healthy subjects	outpatients				
			placebo	461							
215	Vesikari b	2006	trivalent live attenuated nasal spray	98	<5 years	healthy subjects	outpatients	industry	Europe	Finland	multi center
			placebo	99							
220	Vesikari b	2020	quadrivalent inactivated (subunit or split) IM	230	18 -60 years	pregnant women	outpatients	industry	Europe	Finland	multi center
			trivalent inactivated (subunit or split) IM	116	18 -60 years						
218	Vesikari a	2020	quadrivalent inactivated (subunit or split) IM	402	mixed aged children	healthy subjects	outpatients	industry	Europe	Estonia, Finland, Germany, Hungary, Lithuania, and Poland	multi center
			trivalent inactivated (subunit or split) IM	798	mixed aged children						

221	Victor	2016	trivalent live attenuated nasal spray	1174	<5 years	healthy subjects	outpatients	government/ private no profit	Africa	Senegal	single center
			placebo	587							
222	Volling	2019	trivalent inactivated high doses (subunit or split) IM	87	18 -60 years	healthy subjects	outpatients	industry	North America	Canada	single center
			trivalent inactivated (subunit or split) IM	83	18 -60 years						
223	Wang	2015	trivalent inactivated IM	156	<5 years	healthy subjects	outpatients	industry	North America	USA	multi center
			quadrivalent inactivated IM	158							
224	Wang cohort 1	2017	trivalent inactivated IM	916	mixed aged children	healthy subjects	outpatients	industry	Asia	China	single center
			quadrivalent inactivated IM	913							
	Wang cohort 2	2017	trivalent inactivated IM	460	18 -60 years	healthy subjects	outpatients	industry			
			quadrivalent inactivated IM	458							
	Wang cohort 3	2017	trivalent inactivated IM	456	≥61 years	healthy subjects	outpatients	industry			
			quadrivalent inactivated IM	458							
225	Wang	2020	trivalent live attenuated nasal spray	1000	mixed aged children	healthy subjects	outpatients	industry	Asia	China	multi center
			placebo/no intervention	1000	mixed aged children						



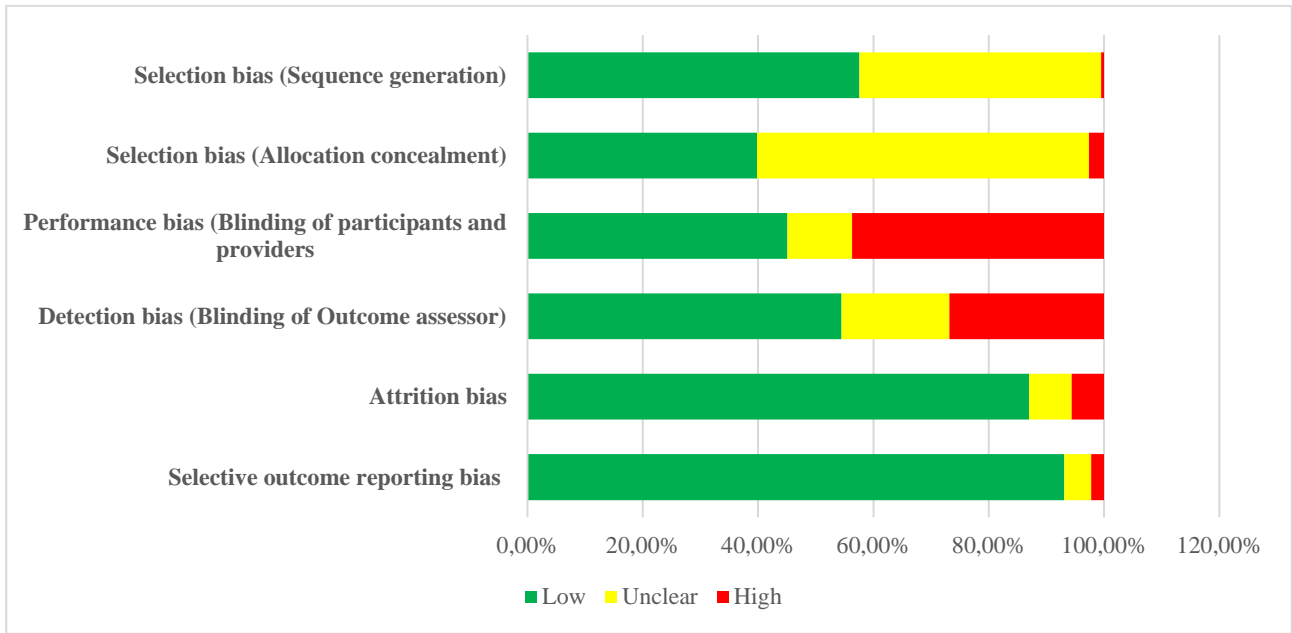
226	Ward b	2020	quadrivalent inactivated recombinant	5077	18 -60 years	healthy subjects	outpatients	industry	Multi continent	Asia, Europe, and North America	multi center
			placebo/no intervention	5083	18 -60 years						
			quadrivalent inactivated recombinant	6396	61 years and older						
			quadrivalent inactivated (subunit or split) IM	6398	61 years and older						
227	Weingarten 1988	1988	trivalent inactivated (subunit or split) IM	91	18 -60 years	healthy subjects	outpatients	not reported	North America	USA	single center
			placebo/no intervention	88	18 -60 years						
228	Wilde cohort 1	1999	trivalent inactivated (subunit or split) IM	52	18 -60 years	healthy subjects	outpatients	industry+government/ private no profit	North America	USA	multi center
	cohort 1		meningococcal vaccine	50	18 -60 years						
	cohort 2		trivalent inactivated (subunit or split) IM	51	18 -60 years						
	cohort 2		pneumococcal vaccine	52	18 -60 years						
	cohort 3		trivalent inactivated (subunit or split) IM	78	18 -60 years						
	cohort 3		placebo/no intervention	78	18 -60 years						
229	Wongsurakiat	2004	trivalent inactivated IM	62	adult and elderly	chronic respiratory disease	outpatients	government/ private no profit	Asia	Thailand	single center
			placebo	63							

230	Zaman	2018	trivalent inactivated (subunit or split) IM	172	18 -60 years	pregnant women	outpatients	government/ private no profit	Asia	Bangladesh	not reported
			pneumococcal vaccine	168	18 -60 years						
231	Zedda	2015	trivalent inactivated IM	41	<5 years	healthy subjects	outpatients	not reported	Europe	Belgium	multi center
			trivalent inactivated adjuvanted MF59/AS03 IM	43							
<b>Studies included in the systematic review but not in the network meta-analyses due to not reporting outcome data</b>											
60	Della Cioppa	2011	17 study groups		<5 years	healthy subjects	outpatients	industry	Europe	Finland, Belgium	multi center
46	Chu	2020	quadrivalent inactivated (subunit or split) IM	1160	mixed aged children; adult and elderly	healthy subjects	outpatients	not reported	Asia	China	multi center
			trivalent inactivated (subunit or split) IM	1160							
78	Fayyaz Jahani	2012	trivalent inactivated IM	70	<5 years	chronic respiratory disease	outpatients	not reported	not reported	not reported	not reported
			placebo	70							
107	Izikson	2013	trivalent inactivated recombinant	3384	18 -60 years	healthy subjects	outpatients	not reported	not reported	not reported	not reported
			placebo	2458							
126	Leung	2014	trivalent inactivated IM	73 tot	18 -60 years	multicomorbidity	outpatients	not reported	not reported	not reported	not reported
			trivalent inactivated intradermal								

151	Nace	2015	trivalent inactivated IM	110	≥61 years	healthy subjects	outpatients	industry	North America	Pennsylvania	multi center
			trivalent inactivated high doses IM	95							
167	Principi	2003	trivalent inactivated adjuvanted virosome/liposome	202	<5 years	chronic respiratory disease	inpatients	not reported	Europe	Italy	not reported
			no vaccine	101							
183	Sesay	2018	quadrivalent inactivated adjuvanted virosome/liposome	836	18 -60 years	healthy subjects	outpatients	industry	Europe	Belgium, France, Germany, Poland	multi center
			trivalent inactivated IM	278							
			quadrivalent inactivated adjuvanted virosome/liposome	834	≥61 years						
			trivalent inactivated) IM	277							
187	Sleigh	2000	trivalent inactivated IM	19	18 -60 years	chronic fatigue syndrome	outpatients	government/ private no profit	not reported	not reported	not reported
			placebo	21							
191	Souza	2010	trivalent inactivated IM	47	mixed aged children; adult and elderly	sickle cell disease	outpatients	government/ private no profit	South America	Brazil	Souza
			trivalent inactivated adjuvanted virosome/liposome	43							

193	Stapleton	2020	trivalent inactivated IM	25	18 -60 years	imunodepression (any cause)	outpatients	government/ private no profit	North America	USA	single center
			trivalent inactivated high doses IM	26							

### Cochrane risk of bias results across studies



## Cochrane risk of bias in individual studies

Author-Year	Selection bias (random sequence generation)	Selection bias (allocation concealment)	Performance bias (blinding of participants and personnel)	Detection bias (blinding of outcome assessor)	Attrition bias	Selective outcome reporting bias
Abadoglu 2004	Unclear	Unclear	Unclear	Unclear	Low	Low
Allsup 2004	Low	Low	Low	Low	Low	Low
Anh 2016	Unclear	Low	Low	Unclear	Low	Low
Ansaldi 2012	Low	Unclear	High	High	Low	Low
Ansaldi 2013	Unclear	Unclear	High	High	Low	Low
Arnou 2009	Low	Low	High	High	Low	Low
Arnou 2010	Low	Low	High	High	Low	Low
Ashkenazi 2006	Low	Low	High	High	Low	Low
Auewarakul 2006	Unclear	Unclear	High	High	Low	Low
Baldo 2007	Low	Unclear	Low	Low	Low	Low
Baluch 2013	Low	Low	High	High	Low	Low
Barrett 2011	Low	Low	Low	Low	Low	Low
Bart 2016	Low	Low	Low	Low	Low	Low
Baxter 2011	Unclear	Unclear	High	High	Low	Low
Belongia 2020	Low	high	high	High	Low	High
Belshe 1992	Unclear	Unclear	Low	Low	Low	Low
Belshe 1998	Low	Low	Low	Low	Low	Low
Belshe 2000	Unclear	Unclear	Low	Low	Unclear	Low
Belshe 2007	Low	Low	Low	Low	Low	Low
Belshe 2007 b	Low	Unclear	High	High	Low	Low
Ben-Yehuda 2003	Unclear	Unclear	Low	Unclear	Low	Low
Ben-Yehuda b 2003	Unclear	Unclear	Unclear	Unclear	Low	Low
Beran 2009	Low	Low	Low	Low	Low	Low
Beran 2009 b	Unclear	Unclear	Low	Low	Low	High
Beran 2009 c	Low	Low	High	High	Low	Low
Beran 2013	Low	Low	Low	Low	Low	Low
Bergen 2004	Unclear	Unclear	Low	Low	Low	Low
Block 2011	Unclear	Unclear	Low	Low	Low	Low
Block 2012	Low	Low	Low	Low	Low	Low
Boonnak 2017	Unclear	Unclear	High	High	Low	Low
Bracco Neto 2009	Unclear	Unclear	Low	Low	Low	Low
Brady 2018	unclear	unclear	Low	low	Low	Low

Bridges 2000	Low	Low	Low	Low	Low	Low
Brooks 2016	Low	Low	Low	Low	Low	Low
Bueving 2004	Low	Low	Low	Low	Low	Low
Cadorna-Carlos 2015	Low	Low	High	High	Low	Low
Caldera 2020	Low	unclear	Low	Low	Low	Low
Carr 2011	Low	Unclear	High	High	Low	Low
Chan 2014	Low	Unclear	High	High	Low	Low
Chang 2019	Low	Unclear	high	Low	Low	Low
Chi 2010	Low	Unclear	High	High	Low	Low
Chiu 2007	Low	High	High	High	Low	Low
Chiu 2009	Low	Unclear	High	High	Low	Low
Choi 2017	Low	Low	Low	Low	Low	Low
Choi 2018	Unclear	Unclear	High	High	Low	Low
Chu 2020	Low	Low	Low	Low	Low	Low
Chuaychoo 2020	Low	unclear	high	High	unclear	Low
Claeys 2018	Low	Low	high	Low	High	Low
Colmegna 2020l	Low	Low	high	Low	Low	Low
Colombo 2001	Low	Unclear	High	High	Low	Low
Couch 2007	Unclear	High	High	Unclear	Low	Low
Cowling 2010	Low	Low	Low	Low	Low	Low
Cowling 2014	Low	Low	Low	Low	Low	Low
Cowling 2020	Low	Low	high	Low	High	Low
Cruz-Valdez 2017	Low	Unclear	High	High	Low	Low
De Bruijn 2006	Unclear	Unclear	High	High	Low	Low
De Bruijn 2007	Low	Unclear	High	High	Low	Low
De Donato 1999	Unclear	Unclear	High	Unclear	Unclear	Low
De Villiers 2009	Low	Unclear	Low	Low	Low	Low
Della Cioppa 2011	Unclear	Unclear	Unclear	Unclear	Low	Low
Desheva 2002	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Diallo 2018	Low	unclear	Low	Low	High	Low
DiazGranados 2013	Low	Low	Low	Low	Low	Low
DiazGranados 2014	Low	Low	Low	Low	Low	Low
DiazGranados 2015	Low	Low	High	Low	Low	Low
Domachowske 2013	Low	Low	Low	Low	Low	Low
Dunkle 2017	Low	Low	Low	Low	Low	Low
Dunkle 2017 b	Low	Low	High	Low	Low	Low
Dunkle 2018	unclear	high	high	Low	Low	High

Durando 2008	Unclear	Unclear	High	High	Low	Low
Englund 2010	Low	Low	Low	Low	Low	Low
Esposito 2010	Unclear	Unclear	High	High	Low	Low
Esposito 2011	Low	Low	High	High	Low	Low
Esposito 2014	Low	Unclear	High	Unclear	Low	Low
Essink 2020	Low	Low	Low	Low	Low	Low
Evison 2009	Low	Unclear	Low	Low	Low	Low
Falsey 2009	Low	Unclear	Low	Low	Low	Low
Fayyaz Jahani 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Fleming 2006	Unclear	Low	High	High	Low	Low
Forrest 2011	Unclear	Unclear	High	High	Low	Low
Frenck 2011	Unclear	Unclear	High	High	Low	Low
Frey 2003	Unclear	Unclear	High	Unclear	Low	Low
Frey 2010	Unclear	Low	High	Low	Low	Low
Frey2014	Unclear	Low	High	Unclear	Low	Low
Gabutti 2005	Unclear	Unclear	Unclear	Unclear	High	Low
Gasparini 2001	Unclear	Unclear	Low	Low	Low	Low
Giaquinta 2014	Unclear	Unclear	Low	Low	Low	Low
Gorse 2013	Unclear	Unclear	High	High	Low	Low
Gorse 2013 b	Low	Low	High	High	Low	Low
Gorse 2015	Unclear	Low	Low	Low	Unclear	Low
Govaert 1993	Low	Low	Low	Low	Low	Low
Greenberg 2013	Unclear	Low	High	High	Low	Low
Greenberg 2014	Unclear	Low	High	Unclear	High	Low
Greenberg 2017	Unclear	Low	Low	Low	Low	Low
Hakim 2016	Low	Unclear	High	High	Low	Low
Halasa 2011	Unclear	Unclear	Low	Low	Low	Low
Halasa 2016	Low	Unclear	High	High	Low	Low
Hartvickson 2015	Unclear	Low	Low	Low	Low	Low
Hobermann 2003	Low	Low	High	Unclear	Low	Low
Hoft 2011	Unclear	Unclear	High	High	Low	Low
Holland 2008	Low	Unclear	High	High	Low	Low
Hoon Han 2013	Unclear	Unclear	High	High	Low	Low
Hu 2020	Low	Low	Low	Low	Low	Low
Hui 2006	Low	Unclear	High	Unclear	Low	Low
Hung 2009	unclear	unclear	high	High	High	Low
Hurwitz 2000	unclear	unclear	high	unclear	High	Low



Izikson 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jackson 2010	Low	Low	High	Unclear	Low	Low
Jamshed 2019	unclear	Low	Low	Low	Low	Low
Jeffs 2015	Low	Unclear	High	High	Low	Low
Kanra 2004	Unclear	Unclear	High	High	Low	Low
Keitel 1997	Unclear	Unclear	Low	Low	Unclear	Low
Keitel 2006	Unclear	Unclear	Unclear	Unclear	Low	Low
Keitel 2009	Unclear	Unclear	Low	Low	Low	Low
Khajedaluae 2018	high	high	high	High	Low	Low
Khan 1996	Low	Unclear	Low	Low	Low	Low
Kieninger 2013	Low	Low	Low	Low	Low	Low
King 1998	Low	Unclear	Low	Low	Low	Low
King 2000	Unclear	Unclear	Unclear	Unclear	Low	Low
Kositantont 2004	Unclear	Unclear	Unclear	Unclear	Low	Low
Kumar 2016	Low	Low	High	Low	Low	Low
Lan 2019	unclear	unclear	unclear	unclear	Low	Low
Langley 2013	Low	Low	Low	Low	Low	Low
Langley 2014	Low	Low	Low	Low	Low	Low
Leroux-Roels	Unclear	Unclear	High	High	Low	Low
Leung 2014	Unclear	Unclear	High	High	Unclear	Low
Levin 2008	Unclear	Unclear	High	High	Low	Low
Levin 2016	Unclear	Unclear	High	High	Low	Low
Li 2008	Low	Unclear	High	Unclear	Low	Low
Liebowitz 2020	Low	Low	Low	Low	Low	Low
Li-Kim-Moy 2016	Low	unclear	high	Low	Low	Low
Lum 2010	Low	Low	Low	Low	Low	Low
Madhi 2011	Low	Low	Low	Low	Low	Low
Madhi 2013	Low	Low	Low	Low	Low	Low
Madhi 2014	Low	Unclear	Low	Low	Unclear	Low
Magnani 2005	Unclear	Unclear	High	High	Low	Low
Mallory 2018	unclear	unclear	unclear	unclear	Low	Low
Mallory 2020	unclear	unclear	unclear	unclear	Low	low
Marchisio 2009	Unclear	Unclear	High	High	Low	Low
McBride 2016	Low	Unclear	High	Low	Low	Low
McElhaney	Low	Unclear	High	Low	Low	Low
McKittrick 2013	Low	Low	Low	Low	Low	Low
McManus 2014	Unclear	Unclear	Low	Low	Unclear	Unclear

Mesa –Duque 2001	Low	Low	Low	Low	Unclear	low
Minutello 1999	Unclear	Unclear	High	Unclear	Low	Low
Mixeu 2002	Unclear	Unclear	Low	Low	Low	Low
Miyazaki 1993	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Monto 2009	Unclear	Unclear	Low	Low	Low	Low
Morelon 2010	Low	Unclear	High	High	Low	Low
Musto 1995	Unclear	Unclear	High	High	Unclear	Unclear
Nace 2015	Low	Unclear	High	High	High	High
Natori 2017	Low	Unclear	High	Low	Low	Low
Natori 2018	Low	Low	High	Low	High	Unclear
Nichol 1995	Low	Unclear	Low	Low	Low	Low
Nichol 1999	Low	Low	Low	Low	Low	Low
Noh 2019	Low	Low	high	Low	Low	Low
Nolan 2014	Unclear	Low	High	Unclear	Low	Low
Ohmit 2006	Low	Unclear	Low	Low	Low	Low
Ohmit 2008	Unclear	Unclear	Low	Low	Low	Low
Ortiz 2015	Unclear	Unclear	Low	Low	Low	Low
Pedroza 2009	Unclear	Unclear	Unclear	Low	Low	Low
Pepin 2013	Low	Low	Low	Low	Low	Low
Pepin 2016	Low	Low	Low	Low	Low	Low
Pepin 2019	Low	Low	high	High	High	Low
Powers 1995	Unclear	Unclear	Low	Low	Unclear	Unclear
Pregliasco 2001	Unclear	Unclear	High	Unclear	Unclear	Low
Principi 2003	Unclear	Unclear	High	High	Unclear	Unclear
Redding 2002	Low	Unclear	Low	Low	Low	Low
Reid 1998	Unclear	Unclear	Low	Low	Low	Unclear
Rodriguez Weber 2014	Low	Low	Unclear	Unclear	Low	Low
Rolfes 2017	Low	Low	Low	Low	Low	Low
Rouphael 2017	Low	Unclear	High	High	Low	Low
Rudenko 2001	Unclear	Unclear	Low	Low	Low	Low
Ruf2004	Unclear	Unclear	High	High	Low	Low
Safdar 2006	Unclear	Unclear	Unclear	Unclear	Low	Low
Sarkar 2020	Low	unclear	high	unclear	Low	Low
Sarsenbayeva 2018	Low	Low	Low	Low	Low	Low
Saxen 1999	Unclear	Unclear	Unclear	Unclear	Low	Low
Schaad 2000	Unclear	Unclear	High	High	Low	Low
Scheifele 2013	Low	Unclear	High	Low	Low	Low

Seo 2014	Unclear	Unclear	High	High	Low	Low
Seo 2016	Unclear	Unclear	High	High	Low	Low
Sesay 2018	Low	Low	Low	Low	Low	Low
Sharma 2018	Low	unclear	high	unclear	Low	Low
Sheldon 2013	Low	Low	Unclear	Unclear	Low	Low
Sindoni 2009	Low	unclear	unclear	unclear	Low	Low
Sleigh 2000	Low	Low	Low	Low	Low	Low
Solares 2014	Unclear	Unclear	High	Unclear	Low	Low
Song 2007	Low	unclear	high	Low	High	Low
Song 2019	Low	unclear	Low	Low	Low	Low
Souza 2010	Unclear	Unclear	High	High	High	Low
Squarcion 2003	unclear	unclear	high	high	Low	Low
Stapleton 2020	Low	Low	Low	Low	Low	Low
Steinhoff 2017	Low	Low	High	Low	Low	Low
Stevanovic 2018	Unclear	Low	Low	Low	Low	Low
Stevanovic 2020	unclear	unclear	Low	Low	Low	Low
Strijbos 2019	Low	unclear	high	Low	Low	Low
Swierkosz 1994	Unclear	Unclear	Low	Low	Unclear	Low
Tam 2007	Low	Low	Low	Low	Low	Low
Tanaka 1993	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Tapia 2016	Low	Low	Low	Low	Low	Low
Tasker 1999	Low	Low	Low	Low	Low	Low
Tinoco 2014	Low	Low	Low	Low	Low	Low
Treanor 1994	Unclear	Unclear	Unclear	Unclear	Low	Low
Treanor 2000	Unclear	Unclear	Low	Low	Low	Low
Treanor 2005	Low	Unclear	Low	Low	Low	Low
Treanor 2007	Low	Unclear	Low	Low	Low	Low
Treanor 2011	Low	Unclear	Low	Low	Low	Low
Treanor 2017	Low	Low	Low	Low	Low	Low
Tsang 2014	Unclear	Low	High	High	Low	Low
Van Damme 2010	Low	Low	High	High	Low	Low
van de Witte 2018	Low	Low	Low	Low	Low	Low
Vardeny 2020	Low	Low	unclear	Low	Low	Low
Vesikari 2006	Low	Low	Low	Low	Low	Low
Vesikari 2006 b	Unclear	Unclear	Low	Low	Low	Low
Vesikari 2008	Unclear	Unclear	Low	Low	Low	Low
Vesikari 2009	Low	Unclear	Unclear	Low	Low	Unclear

Vesikari 2011	Unclear	Unclear	Unclear	Unclear	Low	Low
Vesikari 2020	Low	Low	Low	Low	Low	Low
Vesikari 2020 b	Low	unclear	high	Low	Low	Low
Victor 2016	Low	Low	Low	Low	Low	Low
Volling 2019	Low	high	Low	Low	Low	High
Wang 2015	Low	Unclear	High	Unclear	Low	Low
Wang 2017	Low	Low	Low	Low	Low	Low
Wang 2020	Low	Low	Low	Low	Low	Low
Ward 2020	Low	Low	high	Low	Low	Low
Weingarten 1988	Low	unclear	Low	Low	Low	Low
Wilde 1999	Low	Low	Low	Low	Low	Low
Wongsurakiat 2004	Low	Low	Low	Low	Low	Low
Zaman 2008	Low	Low	Low	Low	High	Low
Zedda	Unclear	Unclear	Unclear	Unclear	Low	Low

## Pairwise meta-analyses

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
<b>All adults and the elderly</b>							
placebo vs 3-IIV	Infl Lab Conf	31	74282	0.42 (0.36, 0.49)	48.86%	-0.03 (-0.04, -0.02)	<b>89.52%</b>
placebo vs 3-RIV	Infl Lab Conf	3	5209	0.28 (0.09, 0.89)	57.40%	-0.03 (-0.05, 0.00)	46.52%
placebo vs 4-IIV	Infl Lab Conf	2	1946	0.52 (0.39, 0.69)	0.00%	-0.13 (-0.33, 0.08)	<b>78.77%</b>
placebo vs 3-LAIV	Infl Lab Conf	6	6590	0.58 (0.48, 0.71)	0.00%	-0.04 (-0.06, -0.01)	66.82%
3-IIV vs 3-IIV HD	Infl Lab Conf	3	41333	0.76 (0.64, 0.90)	0.00%	-0.00 (-0.01, 0.00)	<b>79.88%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Infl Lab Conf	2	43768	0.91 (0.68, 1.22)	6.58%	-0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-RIV	Infl Lab Conf	3	1575	1.10 (0.51, 2.37)	6.64%	0.00 (-0.01, 0.02)	3.96%
3-IIV vs 3-LAIV	Infl Lab Conf	7	7923	1.63 (1.24, 2.15)	0.00%	0.01 (0.00, 0.02)	42.14%
4-RIV vs 4-IIV	Infl Lab Conf	2	21797	0.80 (0.62, 1.03)	52.84%	-0.01 (-0.01, 0.00)	69.41%
placebo vs 3-IIV	Systemic AE	30	43713	1.18 (1.06, 1.31)	68.17%	0.03 (0.01, 0.05)	<b>84.43%</b>
placebo vs 3-IIV ID	Systemic AE	2	97	4.93 (0.81, 30.09)	0.00%	0.26 (-0.08, 0.61)	<b>76.09%</b>
placebo vs 3-RIV	Systemic AE	3	5209	0.97 (0.86, 1.09)	0.00%	-0.00 (-0.02, 0.02)	0.00%
placebo vs 4-IIV	Systemic AE	2	1946	0.64 (0.19, 2.16)	<b>90.52%</b>	-0.12 (-0.41, 0.17)	<b>90.17%</b>
placebo vs 3-LAIV	Systemic AE	7	5384	1.23 (1.12, 1.35)	0.00%	0.06 (0.03, 0.08)	0.00%
3-IIV vs 3-IIV HD	Systemic AE	10	6016	1.21 (1.10, 1.34)	16.90%	0.06 (0.03, 0.09)	11.39%
3-IIV vs 3-IIV ID	Systemic AE	24	19330	1.01 (0.94, 1.09)	38.07%	0.01 (-0.01, 0.03)	44.23%
3-IIV vs 3-IIV MF59/AS03-adj	Systemic AE	23	57933	1.25 (1.13, 1.39)	35.76%	0.02 (0.01, 0.04)	74.54%
3-IIV vs 3-IIV vir/lip-adj	Systemic AE	7	1940	0.83 (0.65, 1.05)	0.00%	-0.02 (-0.06, 0.02)	67.30%
3-IIV vs 3-RIV	Systemic AE	4	1602	0.97 (0.77, 1.22)	0.00%	0.00 (-0.03, 0.04)	0.00%

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
3-IIV vs 4-IIV	Systemic AE	18	23154	1.03 (0.98, 1.08)	0.00%	0.01 (-0.00, 0.02)	0.00%
3-IIV vs 3-LAIV	Systemic AE	6	6151	1.13 (1.05, 1.22)	0.00%	0.04 (0.01, 0.06)	0.00%
3-IIV HD vs 4-IIV	Systemic AE	3	6318	1.00 (0.86, 1.16)	0.00%	-0.00 (-0.01, 0.01)	0.00%
3-IIV ID vs 3-IIV MF59/AS03-adj	Systemic AE	4	1766	0.93 (0.78, 1.11)	0.00%	0.00 (-0.02, 0.02)	0.00%
3-IIV ID vs 3-IIV vir/lip-adj	Systemic AE	2	623	0.93 (0.50, 1.72)	0.00%	-0.00 (-0.04, 0.03)	0.00%
3-IIV MF59/AS03-adj vs 3-IIV vir/lip-adj	Systemic AE	5	1605	0.74 (0.54, 1.02)	29.26%	-0.04 (-0.14, 0.05)	<b>91.23%</b>
3-IIV MF59/AS03-adj vs 4-IIV	Systemic AE	2	1226	0.84 (0.64, 1.10)	0.00%	-0.04 (-0.24, 0.16)	<b>88.45%</b>
4-IIV MF59/AS03-adj vs 3-IIV MF59/AS03-adj	Systemic AE	2	1988	1.10 (0.92, 1.31)	0.00%	0.01 (-0.02, 0.04)	0.00%
4-RIV vs 4-IIV	Systemic AE	4	23990	1.07 (0.95, 1.20)	28.40%	0.01 (-0.04, 0.05)	<b>97.67%</b>
3-LAIV vs 4-LAIV	Systemic AE	2	3600	0.99 (0.92, 1.07)	0.00%	-0.00 (-0.04, 0.03)	0.00%
placebo vs 3-IIV	Local AE	30	39906	2.78 (2.26, 3.43)	<b>92.89%</b>	0.26 (0.20, 0.32)	<b>98.09%</b>
placebo vs 3-IIV ID	Local AE	2	97	2.48 (0.63, 9.70)	0.00%	0.10 (-0.03, 0.24)	0.00%
placebo vs 3-RIV	Local AE	3	5209	3.81 (2.66, 5.47)	57.62%	0.25 (0.14, 0.37)	<b>85.81%</b>
placebo vs 4-IIV	Local AE	2	1946	3.86 (0.89, 16.81)	61.03%	0.19 (-0.00, 0.37)	<b>89.36%</b>
placebo vs 3-LAIV	Local AE	7	9875	1.76 (1.65, 1.87)	0.00%	0.18 (0.16, 0.21)	37.44%
3-IIV vs 3-IIV HD	Local AE	9	5915	1.48 (1.34, 1.63)	13.63%	0.12 (0.08, 0.16)	49.15%
3-IIV vs 3-IIV ID	Local AE	25	19551	1.54 (1.31, 1.82)	<b>93.38%</b>	0.16 (-0.01, 0.32)	<b>99.72%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Local AE	21	57818	1.84 (1.60, 2.12)	<b>76.25%</b>	0.13 (0.09, 0.17)	<b>94.88%</b>
3-IIV vs 3-IIV vir/lip-adj	Local AE	7	1940	1.36 (1.05, 1.74)	37.19%	0.08 (-0.01, 0.17)	<b>88.89%</b>
3-IIV vs 3-RIV	Local AE	4	1602	0.61 (0.33, 1.10)	<b>79.89%</b>	-0.08 (-0.18, 0.02)	<b>75.32%</b>
3-IIV vs 4-IIV	Local AE	19	24857	1.14 (1.08, 1.21)	53.35%	0.04 (0.02, 0.06)	<b>84.27%</b>

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
3-IIV vs 3-LAIV	Local AE	5	6082	1.25 (0.69, 2.25)	<b>98.00%</b>	0.04 (-0.13, 0.21)	<b>97.57%</b>
3-IIV HD vs 4-IIV	Local AE	3	6318	0.99 (0.81, 1.20)	0.00%	-0.00 (-0.01, 0.01)	0.00%
3-IIV ID vs 3-IIV MF59/AS03-adj	Local AE	4	1766	1.03 (0.56, 1.90)	<b>86.66%</b>	-0.03 (-0.15, 0.08)	<b>92.71%</b>
3-IIV ID vs 3-IIV vir/lip-adj	Local AE	2	623	0.50 (0.39, 0.64)	0.00%	-0.26 (-0.61, 0.09)	<b>94.94%</b>
3-IIV MF59/AS03-adj vs 3-IIV vir/lip-adj	Local AE	5	1605	0.57 (0.45, 0.73)	39.04%	-0.15 (-0.34, 0.04)	<b>96.67%</b>
3-IIV MF59/AS03-adj vs 4-IIV	Local AE	2	1226	1.02 (0.86, 1.21)	0.00%	-0.00 (-0.02, 0.01)	0.00%
4-IIV MF59/AS03-adj vs 3-IIV MF59/AS03-adj	Local AE	2	1988	1.07 (0.92, 1.23)	0.00%	0.01 (-0.05, 0.06)	29.05%
4-RIV vs 4-IIV	Local AE	4	23990	1.04 (0.80, 1.35)	<b>96.54%</b>	0.01 (-0.05, 0.07)	<b>97.12%</b>
3-LAIV vs 4-LAIV	Local AE	2	3600	0.95 (0.73, 1.24)	<b>88.64%</b>	-0.01 (-0.11, 0.08)	<b>87.90%</b>
placebo vs 3-IIV	ILI	27	42312	0.81 (0.74, 0.90)	73.74%	-0.04 (-0.06, -0.02)	<b>81.33%</b>
placebo vs 3-RIV	ILI	2	4749	0.77 (0.62, 0.96)	0.00%	-0.02 (-0.03, -0.00)	0.00%
placebo vs 4-IIV	ILI	2	1946	0.79 (0.63, 0.98)	0.00%	-0.05 (-0.16, 0.05)	41.94%
placebo vs 3-LAIV	ILI	2	7803	0.95 (0.90, 1.00)	0.00%	-0.02 (-0.03, 0.00)	0.00%
3-IIV vs 3-RIV	ILI	3	1575	0.98 (0.66, 1.46)	0.00%	-0.00 (-0.03, 0.02)	0.00%
placebo vs 3-IIV	Mortality	11	26844	1.16 (0.45, 3.01)	0.00%	0.00 (-0.00, 0.00)	0.00%
placebo vs 3-LAIV	Mortality	2	7803	0.57 (0.08, 3.97)	0.00%	-0.00 (-0.00, 0.00)	43.43%
3-IIV vs 3-IIV HD	Mortality	4	36165	1.00 (0.75, 1.33)	0.00%	0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Mortality	3	50867	0.89 (0.60, 1.32)	42.45%	-0.00 (-0.00, 0.00)	0.00%
3-IIV vs 4-IIV	Mortality	6	9362	1.67 (0.55, 5.04)	0.00%	0.00 (-0.00, 0.00)	0.00%
4-RIV vs 4-IIV	Mortality	2	21797	0.69 (0.39, 1.22)	0.00%	-0.00 (-0.00, 0.00)	0.00%
placebo vs 3-IIV	Hospitalization	11	4794	0.44 (0.25, 0.79)	0.00%	-0.01 (-0.02, 0.01)	<b>88.71%</b>

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
placebo vs 3-LAIV	Hospitalization	2	7803	0.78 (0.39, 1.58)	0.00%	-0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-IIV HD	Hospitalization	3	472	0.49 (0.23, 1.04)	0.00%	-0.03 (-0.08, 0.03)	69.04%
3-IIV vs 3-IIV MF59/AS03-adj	Hospitalization	3	43836	0.92 (0.70, 1.21)	0.00%	-0.00 (-0.00, 0.00)	0.00%
<b>The elderly (≥61 years)</b>							
placebo vs 3-IIV	Infl Lab Conf	3	453	0.58 (0.20, 1.67)	<b>80.51%</b>	-0.07 (-0.21, 0.07)	<b>75.49%</b>
placebo vs 3-LAIV	Infl Lab Conf	2	3466	0.57 (0.44, 0.75)	0.00%	-0.03 (-0.05, -0.02)	0.00%
3-IIV vs 3-IIV HD	Infl Lab Conf	2	41161	0.76 (0.64, 0.90)	0.00%	-0.00 (-0.01, 0.00)	<b>89.58%</b>
3-IIV vs 3-LAIV	Infl Lab Conf	2	3218	1.43 (0.81, 2.54)	0.00%	0.01 (-0.00, 0.01)	0.00%
placebo vs 3-IIV	Systemic AE	5	1124	0.88 (0.77, 1.01)	0.00%	-0.03 (-0.08, 0.03)	20.41%
placebo vs 3-LAIV	Systemic AE	2	3287	1.19 (1.06, 1.34)	0.00%	0.05 (0.02, 0.08)	0.00%
3-IIV vs 3-IIV HD	Systemic AE	4	5030	1.23 (1.05, 1.43)	30.67%	0.05 (0.01, 0.10)	44.15%
3-IIV vs 3-IIV ID	Systemic AE	10	6880	1.08 (0.98, 1.20)	4.39%	0.02 (0.00, 0.04)	0.13%
3-IIV vs 3-IIV MF59/AS03-adj	Systemic AE	12	55886	1.24 (1.06, 1.43)	57.91%	0.02 (0.00, 0.04)	<b>82.98%</b>
3-IIV vs 3-IIV vir/lip-adj	Systemic AE	3	765	0.93 (0.58, 1.50)	0.00%	0.01 (-0.02, 0.04)	27.71%
3-IIV vs 4-IIV	Systemic AE	4	4319	1.06 (0.92, 1.23)	0.00%	0.01 (-0.01, 0.03)	0.00%
3-IIV vs 3-LAIV	Systemic AE	2	3073	1.11 (0.99, 1.25)	0.00%	0.03 (-0.00, 0.06)	0.00%
3-IIV HD vs 4-IIV	Systemic AE	2	6278	0.97 (0.83, 1.13)	0.00%	-0.00 (-0.01, 0.01)	0.00%
3-IIV ID vs 3-IIV MF59/AS03-adj	Systemic AE	4	1766	0.93 (0.78, 1.11)	0.00%	0.00 (-0.02, 0.02)	0.00%
3-IIV ID vs 3-IIV vir/lip-adj	Systemic AE	2	623	0.93 (0.50, 1.72)	0.00%	-0.00 (-0.04, 0.03)	0.00%
3-IIV MF59/AS03-adj vs 3-IIV vir/lip-adj	Systemic AE	3	805	0.81 (0.40, 1.66)	38.54%	-0.03 (-0.23, 0.16)	<b>94.30%</b>
4-RIV vs 4-IIV	Systemic AE	2	13637	1.13 (1.06, 1.20)	0.00%	0.02 (-0.01, 0.05)	<b>90.01%</b>



Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
placebo vs 3-IIV	Local AE	4	1023	3.13 (1.68, 5.85)	8.69%	0.13 (0.05, 0.21)	63.61%
placebo vs 3-LAIV	Local AE	2	3287	1.82 (1.64, 2.03)	0.00%	0.12 (-0.03, 0.27)	<b>81.00%</b>
3-IIV vs 3-IIV HD	Local AE	3	4929	1.55 (1.33, 1.80)	47.38%	0.14 (0.09, 0.19)	50.80%
3-IIV vs 3-IIV ID	Local AE	11	7101	1.74 (1.38, 2.19)	73.46%	0.16 (0.00, 0.31)	<b>98.58%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Local AE	12	55886	1.89 (1.58, 2.26)	<b>76.08%</b>	0.10 (0.05, 0.14)	<b>95.82%</b>
3-IIV vs 3-IIV vir/lip-adj	Local AE	3	765	1.12 (0.73, 1.72)	0.00%	0.01 (-0.01, 0.02)	0.00%
3-IIV vs 4-IIV	Local AE	4	4319	1.22 (1.01, 1.46)	26.40%	0.03 (0.01, 0.04)	0.00%
3-IIV vs 3-LAIV	Local AE	2	3073	0.76 (0.04, 12.85)	<b>86.92%</b>	0.03 (-0.35, 0.42)	<b>95.88%</b>
3-IIV HD vs 4-IIV	Local AE	2	6278	0.98 (0.80, 1.21)	0.00%	-0.00 (-0.01, 0.01)	0.00%
3-IIV ID vs 3-IIV MF59/AS03-adj	Local AE	4	1766	1.03 (0.56, 1.90)	<b>86.66%</b>	-0.03 (-0.15, 0.08)	<b>92.71%</b>
3-IIV ID vs 3-IIV vir/lip-adj	Local AE	2	623	0.50 (0.39, 0.64)	0.00%	-0.26 (-0.61, 0.09)	<b>94.94%</b>
3-IIV MF59/AS03-adj vs 3-IIV vir/lip-adj	Local AE	3	805	0.60 (0.38, 0.97)	59.05%	-0.12 (-0.45, 0.21)	<b>97.13%</b>
4-RIV vs 4-IIV	Local AE	2	13637	0.84 (0.23, 3.02)	68.13%	0.03 (-0.09, 0.15)	<b>99.26%</b>
placebo vs 3-IIV	ILI	2	854	0.42 (0.19, 0.96)	0.00%	-0.07 (-0.32, 0.17)	<b>93.21%</b>
3-IIV vs 3-IIV HD	Mortality	2	35865	1.00 (0.75, 1.34)	0.00%	0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Mortality	2	50799	0.88 (0.57, 1.35)	65.16%	-0.00 (-0.00, 0.00)	4.85%
3-IIV vs 4-IIV	Mortality	2	1664	2.43 (0.12, 47.37)	0.00%	0.00 (-0.00, 0.01)	0.00%
placebo vs 3-IIV	Hospitalization	3	982	0.35 (0.13, 0.90)	0.00%	-0.05 (-0.22, 0.12)	<b>95.10%</b>
<b>Adults and the Elderly -Immunocompromised/cancer participants</b>							
placebo vs 3-IIV	Infl Lab Conf	3	802	0.24 (0.09, 0.64)	44.50%	-0.13 (-0.28, 0.02)	<b>90.06%</b>
placebo vs 3-IIV	Systemic AE	4	768	1.17 (0.88, 1.56)	0.00%	0.03 (-0.06, 0.12)	59.03%

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
3-IIV vs 3-IIV HD	Systemic AE	4	516	1.16 (0.86, 1.57)	31.63%	0.07 (-0.00, 0.13)	0.00%
3-IIV vs 3-IIV ID	Systemic AE	3	206	2.21 (0.58, 8.41)	59.08%	0.12 (0.04, 0.21)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Systemic AE	5	315	1.45 (0.78, 2.70)	0.00%	0.01 (-0.03, 0.05)	0.00%
placebo vs 3-IIV	Local AE	4	778	1.54 (0.78, 3.05)	47.10%	0.12 (-0.08, 0.31)	<b>87.45%</b>
3-IIV vs 3-IIV HD	Local AE	4	516	1.39 (0.97, 1.99)	0.00%	0.06 (-0.00, 0.12)	14.05%
3-IIV vs 3-IIV ID	Local AE	3	206	3.16 (1.07, 9.27)	<b>77.16%</b>	0.39 (0.29, 0.50)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Local AE	3	200	1.87 (1.02, 3.44)	0.00%	0.09 (-0.05, 0.24)	53.69%
placebo vs 3-IIV	ILI	4	852	0.68 (0.48, 0.95)	26.07%	-0.13 (-0.30, 0.04)	<b>85.35%</b>
placebo vs 3-IIV	Mortality	2	537	0.57 (0.07, 4.79)	0.00%	-0.00 (-0.02, 0.01)	0.00%
3-IIV vs 3-IIV HD	Mortality	2	300	1.00 (0.06, 15.84)	0.00%	0.00 (-0.02, 0.02)	0.00%
placebo vs 3-IIV	Hospitalization	3	658	0.42 (0.11, 1.61)	33.07%	-0.05 (-0.14, 0.04)	<b>91.29%</b>
3-IIV vs 3-IIV HD	Hospitalization	3	472	0.49 (0.23, 1.04)	0.00%	-0.03 (-0.08, 0.03)	69.04%
3-IIV vs 3-IIV MF59/AS03-adj	Hospitalization	2	141	0.83 (0.41, 1.67)	0.00%	-0.02 (-0.13, 0.09)	0.00%
<b>Adults and elderly with chronic respiratory diseases</b>							
placebo vs 3-IIV	Infl Lab Conf	2	248	0.59 (0.11, 3.31)	<b>88.74%</b>	-0.06 (-0.36, 0.23)	<b>87.81%</b>
placebo vs 3-IIV	ILI	2	253	0.50 (0.36, 0.68)	0.00%	-0.24 (-0.43, -0.05)	68.05%
placebo vs 3-IIV	Hospitalization	2	253	0.31 (0.08, 1.22)	0.00%	-0.05 (-0.10, 0.01)	0.00%
<b>All children</b>							
placebo vs 3-IIV	Infl Lab Conf	8	7561	0.60 (0.48, 0.76)	31.20%	-0.04 (-0.07, -0.01)	70.51%
placebo vs 4-IIV	Infl Lab Conf	2	17454	0.51 (0.46, 0.56)	0.00%	-0.05 (-0.06, -0.04)	26.82%
placebo vs 3-LAIV	Infl Lab Conf	11	17704	0.29 (0.18, 0.47)	<b>94.04%</b>	-0.09 (-0.13, -0.05)	<b>94.07%</b>

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
3-IIV vs 3-LAIV	Infl Lab Conf	3	12768	0.51 (0.40, 0.66)	50.43%	-0.03 (-0.05, -0.02)	61.23%
placebo vs 3-IIV	Systemic AE	5	5495	1.14 (0.69, 1.87)	<b>97.38%</b>	0.04 (-0.06, 0.15)	<b>93.57%</b>
placebo vs 3-LAIV	Systemic AE	20	21549	1.09 (1.03, 1.16)	0.00%	0.01 (-0.00, 0.02)	<b>79.33%</b>
3-IIV vs 3-IIV HD	Systemic AE	3	171	1.03 (0.32, 3.28)	61.36%	0.00 (-0.24, 0.24)	74.68%
3-IIV vs 3-IIV ID	Systemic AE	3	350	1.22 (0.73, 2.03)	41.44%	0.05 (-0.07, 0.17)	45.71%
3-IIV vs 3-IIV MF59/AS03-adj	Systemic AE	7	11051	1.17 (1.06, 1.30)	23.57%	0.04 (0.01, 0.07)	47.29%
3-IIV vs 3-IIV vir/lip-adj	Systemic AE	3	577	1.21 (0.92, 1.61)	0.00%	0.02 (-0.01, 0.06)	0.00%
3-IIV vs 4-IIV	Systemic AE	13	21378	0.97 (0.87, 1.08)	<b>84.87%</b>	-0.01 (-0.04, 0.02)	<b>81.37%</b>
3-IIV vs 3-LAIV	Systemic AE	6	13093	1.39 (0.97, 1.98)	<b>92.25%</b>	0.04 (0.02, 0.05)	10.57%
3-LAIV vs 4-LAIV	Systemic AE	2	2512	2.97 (0.86, 10.32)	0.00%	0.01 (0.00, 0.01)	0.00%
placebo vs 3-IIV	Local AE	5	5495	1.47 (0.92, 2.35)	<b>95.29%</b>	0.09 (-0.02, 0.20)	<b>90.90%</b>
placebo vs 3-LAIV	Local AE	19	21293	1.13 (1.08, 1.19)	55.59%	0.06 (0.03, 0.09)	<b>79.75%</b>
3-IIV vs 3-IIV HD	Local AE	3	171	1.07 (0.72, 1.59)	0.00%	0.00 (-0.14, 0.15)	3.78%
3-IIV vs 3-IIV ID	Local AE	3	350	1.68 (0.66, 4.26)	22.64%	0.04 (-0.07, 0.16)	<b>79.64%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Local AE	7	11051	1.24 (0.93, 1.66)	<b>94.33%</b>	0.06 (0.00, 0.12)	<b>86.48%</b>
3-IIV vs 3-IIV vir/lip-adj	Local AE	3	577	0.90 (0.61, 1.33)	0.00%	0.00 (-0.03, 0.04)	0.00%
3-IIV vs 4-IIV	Local AE	13	21323	1.02 (0.95, 1.09)	60.97%	0.01 (-0.01, 0.02)	55.23%
3-IIV vs 3-LAIV	Local AE	4	2512	2.12 (1.93, 2.32)	0.00%	0.34 (0.26, 0.42)	41.00%
placebo vs 3-IIV	Otitis Media	3	1137	1.02 (0.78, 1.34)	52.15%	0.00 (-0.08, 0.08)	68.34%
placebo vs 3-LAIV	Otitis Media	7	15737	0.59 (0.30, 1.16)	<b>83.25%</b>	-0.02 (-0.05, 0.01)	<b>92.19%</b>
placebo vs 3-IIV	ILI	6	2148	0.61 (0.44, 0.84)	63.49%	-0.09 (-0.15, -0.03)	73.80%

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
placebo vs 3-LAIV	ILI	7	12465	0.72 (0.57, 0.90)	70.61%	-0.07 (-0.12, -0.03)	<b>83.55%</b>
3-IIV vs 3-LAIV	ILI	3	10907	1.11 (0.98, 1.26)	0.00%	0.01 (-0.00, 0.02)	0.00%
placebo vs 3-IIV	Mortality	3	8663	0.90 (0.11, 7.43)	0.00%	0.00 (-0.00, 0.00)	0.00%
placebo vs 4-IIV	Mortality	2	17454	1.17 (0.10, 13.37)	58.11%	0.00 (-0.00, 0.00)	69.21%
placebo vs 3-LAIV	Mortality	3	4994	1.51 (0.25, 9.21)	0.00%	0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Mortality	3	10101	0.28 (0.05, 1.49)	0.00%	-0.00 (-0.00, 0.00)	66.59%
3-IIV vs 4-IIV	Mortality	4	7008	1.32 (0.13, 13.50)	0.00%	0.00 (-0.00, 0.00)	0.00%
placebo vs 3-IIV	Hospitalization	5	7372	1.03 (0.59, 1.78)	45.59%	-0.00 (-0.01, 0.01)	64.60%
placebo vs 4-IIV	Hospitalization	2	17454	1.00 (0.23, 4.39)	0.00%	-0.00 (-0.00, 0.00)	0.00%
placebo vs 3-LAIV	Hospitalization	3	12254	1.02 (0.58, 1.80)	17.61%	-0.00 (-0.00, 0.00)	19.06%
3-IIV vs 3-LAIV	Hospitalization	3	12768	1.08 (0.85, 1.36)	0.00%	0.00 (-0.01, 0.01)	57.09%
<b>Young children (up to 5 years)</b>							
placebo vs 3-IIV	Infl Lab Conf	6	6646	0.65 (0.51, 0.82)	31.95%	-0.04 (-0.08, -0.01)	62.63%
placebo vs 4-IIV	Infl Lab Conf	2	17454	0.51 (0.46, 0.56)	0.00%	-0.05 (-0.06, -0.04)	26.82%
placebo vs 3-LAIV	Infl Lab Conf	8	15620	0.30 (0.18, 0.51)	<b>95.74%</b>	-0.09 (-0.12, -0.05)	<b>90.87%</b>
3-IIV vs 3-LAIV	Infl Lab Conf	2	10539	0.45 (0.38, 0.54)	0.00%	-0.04 (-0.05, -0.03)	46.54%
placebo vs 3-IIV	Systemic AE	3	4636	1.37 (0.69, 2.73)	<b>98.74%</b>	0.09 (-0.09, 0.26)	<b>96.91%</b>
placebo vs 3-LAIV	Systemic AE	16	19436	1.09 (1.03, 1.16)	0.00%	0.01 (-0.00, 0.03)	<b>83.58%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Systemic AE	7	11051	1.17 (1.06, 1.30)	23.57%	0.04 (0.01, 0.07)	47.29%
3-IIV vs 4-IIV	Systemic AE	6	8166	0.93 (0.74, 1.16)	<b>92.18%</b>	-0.03 (-0.11, 0.05)	<b>89.48%</b>
3-IIV vs 3-LAIV	Systemic AE	3	10566	1.87 (0.83, 4.20)	<b>94.46%</b>	0.03 (0.03, 0.04)	0.00%

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
placebo vs 3-IIV	Local AE	3	4636	1.30 (0.76, 2.23)	<b>95.60%</b>	0.05 (-0.07, 0.17)	<b>90.43%</b>
placebo vs 3-LAIV	Local AE	15	19180	1.13 (1.07, 1.19)	62.51%	0.05 (0.02, 0.09)	<b>82.22%</b>
3-IIV vs 3-IIV MF59/AS03-adj	Local AE	7	11051	1.24 (0.93, 1.66)	<b>94.33%</b>	0.06 (0.00, 0.12)	<b>86.48%</b>
3-IIV vs 4-IIV	Local AE	6	8166	0.96 (0.81, 1.14)	74.47%	-0.01 (-0.06, 0.04)	<b>81.96%</b>
3-IIV vs 3-LAIV	Local AE	2	2214	3.30 (0.83, 13.05)	59.08%	0.45 (0.19, 0.71)	71.52%
placebo vs 3-IIV	Otitis Media	3	1137	1.02 (0.78, 1.34)	52.15%	0.00 (-0.08, 0.08)	68.34%
placebo vs 3-LAIV	Otitis Media	5	5999	0.33 (0.13, 0.81)	<b>87.06%</b>	-0.03 (-0.04, -0.02)	0.00%
placebo vs 3-IIV	ILI	3	878	0.58 (0.33, 1.01)	<b>79.09%</b>	-0.14 (-0.30, 0.02)	<b>87.12%</b>
3-IIV vs 3-LAIV	ILI	2	10539	1.11 (0.97, 1.26)	0.00%	0.01 (-0.00, 0.02)	0.00%
placebo vs 3-IIV	Mortality	3	8663	0.90 (0.11, 7.43)	0.00%	0.00 (-0.00, 0.00)	0.00%
placebo vs 4-IIV	Mortality	2	17454	1.17 (0.10, 13.37)	58.11%	0.00 (-0.00, 0.00)	69.21%
placebo vs 3-LAIV	Mortality	2	2994	1.09 (0.12, 9.79)	0.00%	0.00 (-0.00, 0.00)	0.00%
3-IIV vs 3-IIV MF59/AS03-adj	Mortality	3	10101	0.28 (0.05, 1.49)	0.00%	-0.00 (-0.00, 0.00)	66.59%
placebo vs 3-IIV	Hospitalization	5	7372	1.03 (0.59, 1.78)	45.59%	-0.00 (-0.01, 0.01)	64.60%
placebo vs 4-IIV	Hospitalization	2	17454	1.00 (0.23, 4.39)	0.00%	-0.00 (-0.00, 0.00)	0.00%
placebo vs 3-LAIV	Hospitalization	2	2565	1.51 (0.67, 3.41)	0.00%	0.00 (-0.01, 0.01)	50.70%
3-IIV vs 3-LAIV	Hospitalization	2	10539	1.09 (0.86, 1.38)	0.00%	0.00 (-0.00, 0.01)	0.00%
<b>All children with chronic respiratory diseases</b>							
placebo vs 3-LAIV	Infl Lab Conf	2	84	0.17 (0.05, 0.58)	0.00%	-0.32 (-0.49, -0.15)	17.33%
3-IIV vs 3-LAIV	Infl Lab Conf	2	4416	0.58 (0.40, 0.82)	40.53%	-0.03 (-0.04, -0.01)	0.00%
placebo vs 3-LAIV	ILI	2	84	0.23 (0.08, 0.64)	0.00%	-0.35 (-0.51, -0.19)	0.00%

Comparison	Outcome	N. studies	N. patients	RR (95% CI)	I <sup>2</sup> RR	ARD (95%CI)	I <sup>2</sup> ARD
3-IIV vs 3-LAIV	Hospitalization	2	4416	0.89 (0.31, 2.54)	10.39%	-0.00 (-0.00, 0.00)	0.00%
placebo vs 3-LAIV	Exacerb Chronon Disease	2	93	2.76 (0.26, 29.54)	0.00%	0.03 (-0.06, 0.12)	27.84%
<b>All children immunocompromised/cancer</b>							
3-IIV vs 3-IIV HD	Systemic AE	3	171	1.03 (0.32, 3.28)	61.36%	0.00 (-0.24, 0.24)	74.68%
3-IIV vs 3-LAIV	Systemic AE	2	298	1.07 (0.73, 1.56)	0.00%	0.02 (-0.08, 0.12)	0.00%
3-IIV vs 3-IIV HD	Local AE	3	171	1.07 (0.72, 1.59)	0.00%	0.00 (-0.14, 0.15)	3.78%
3-IIV vs 3-LAIV	Local AE	2	298	2.27 (1.62, 3.19)	0.00%	0.28 (0.18, 0.39)	0.00%

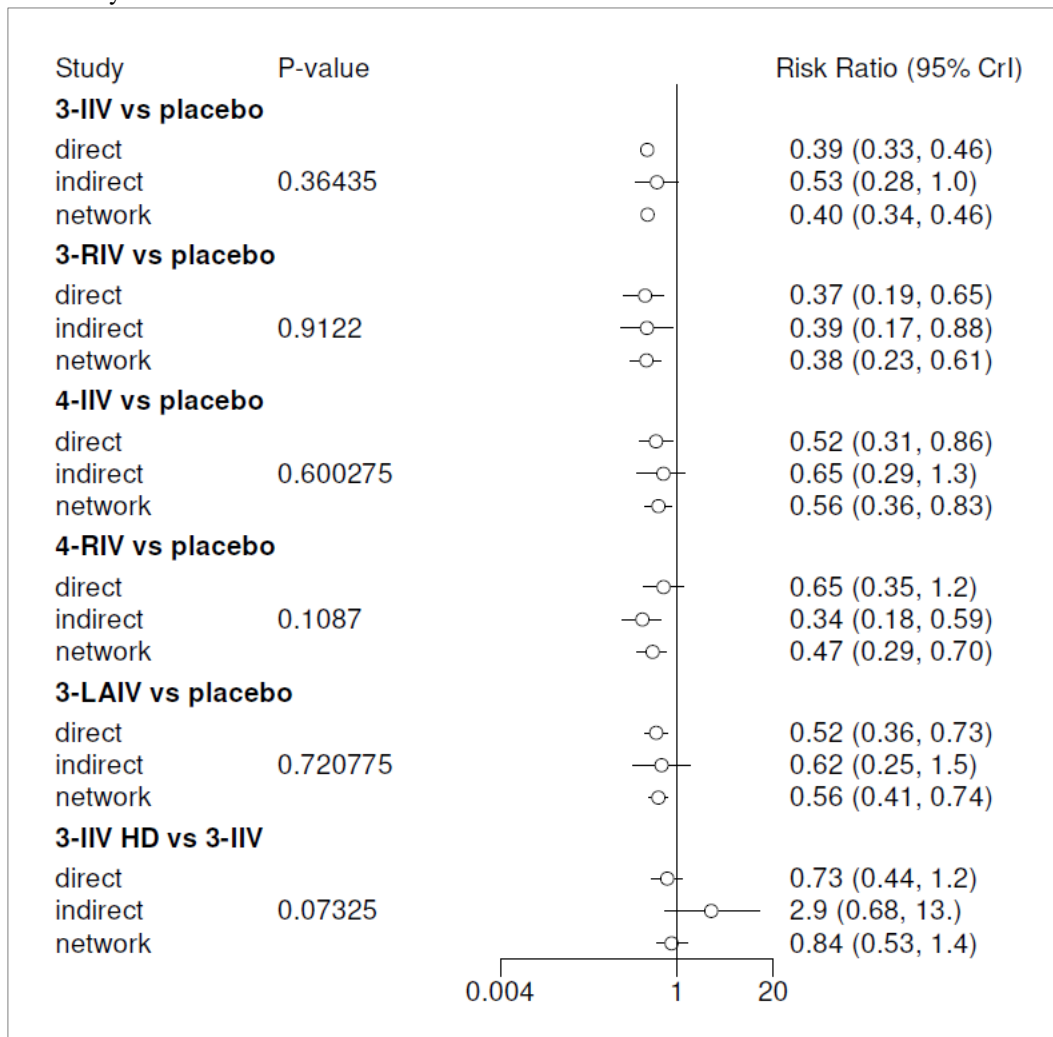
I<sup>2</sup> values exceeding 75 % are highlighted

#### Abbreviations

**Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Adults and the elderly: Inconsistency in networks of laboratory- confirmed influenza and any systemic adverse event outcomes**

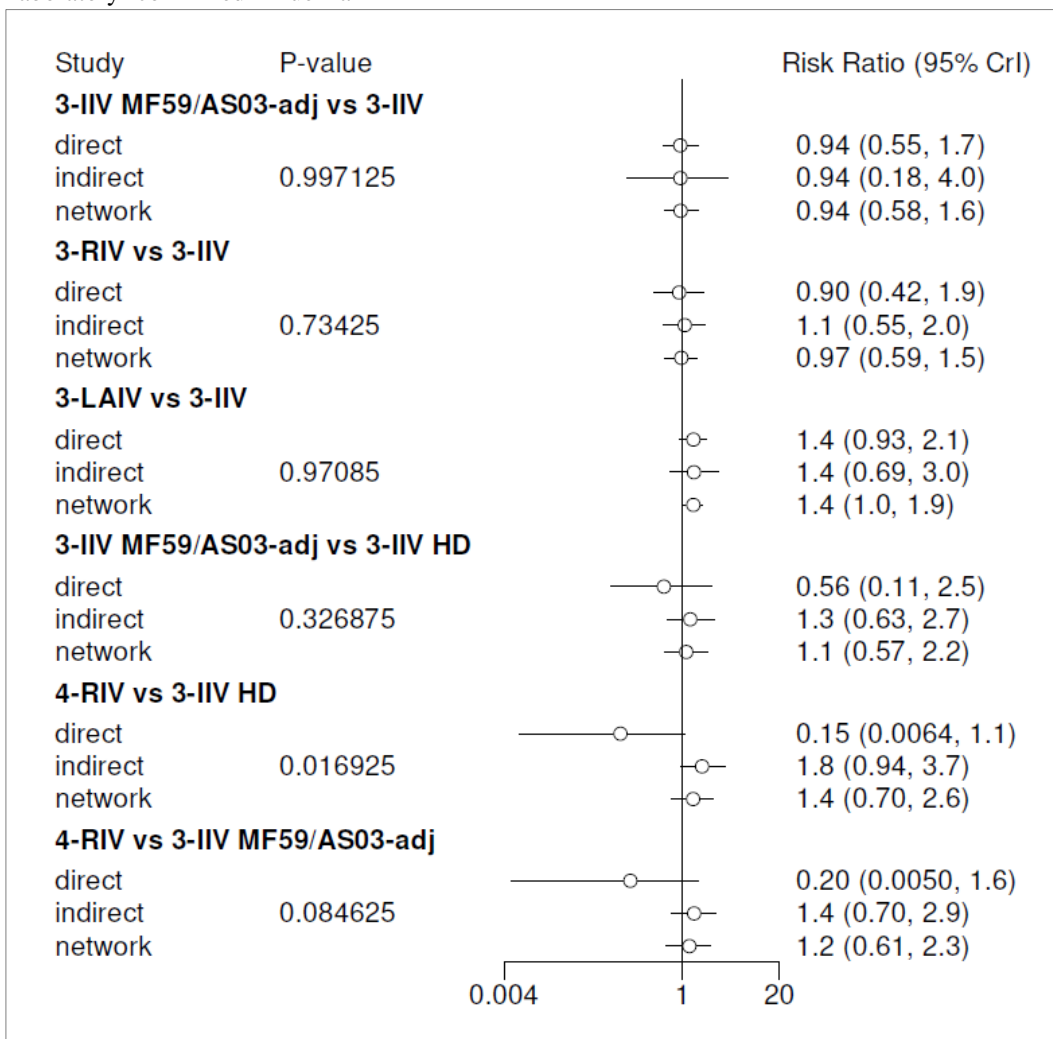
Laboratory- confirmed influenza \*



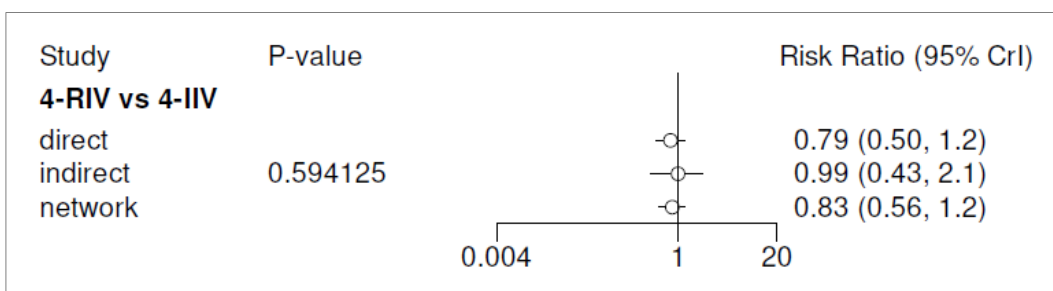
OR <1 favors experimental vaccine compared to placebo or 3-IIV

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Laboratory- confirmed influenza\*



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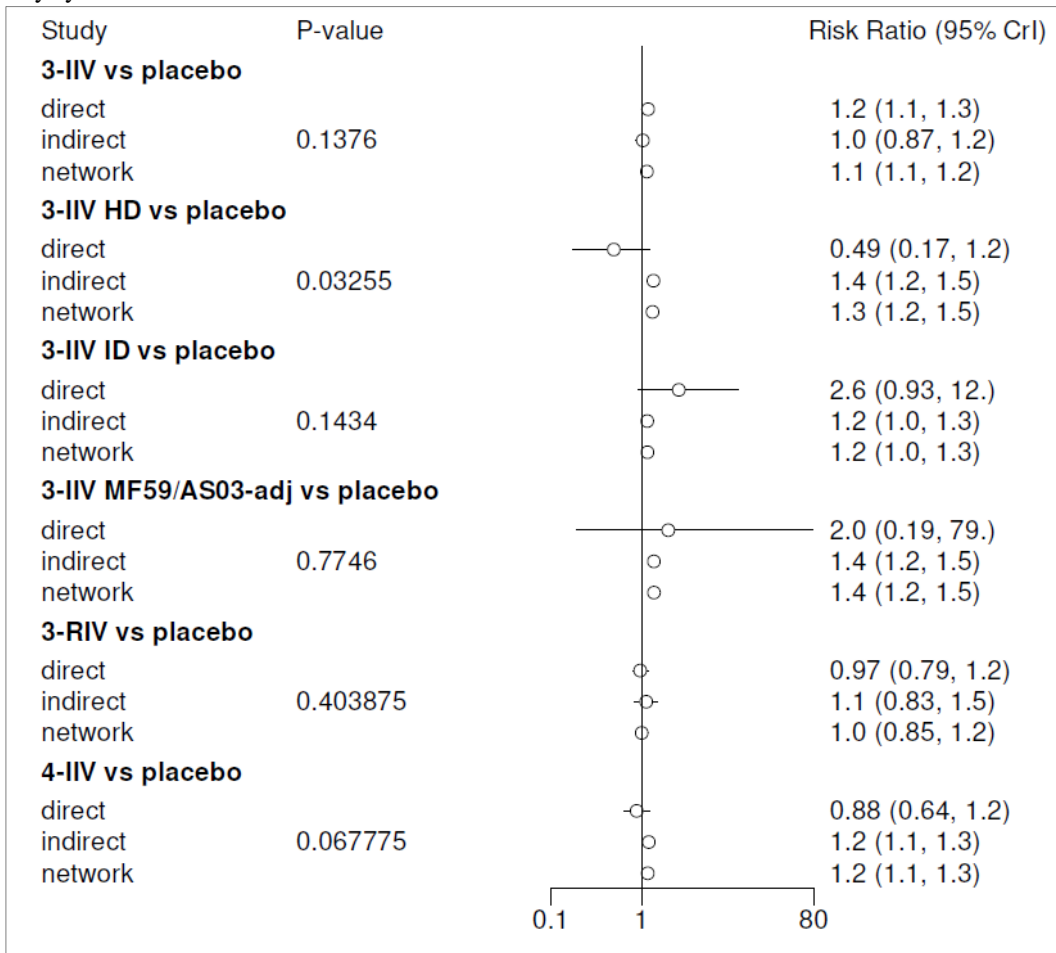


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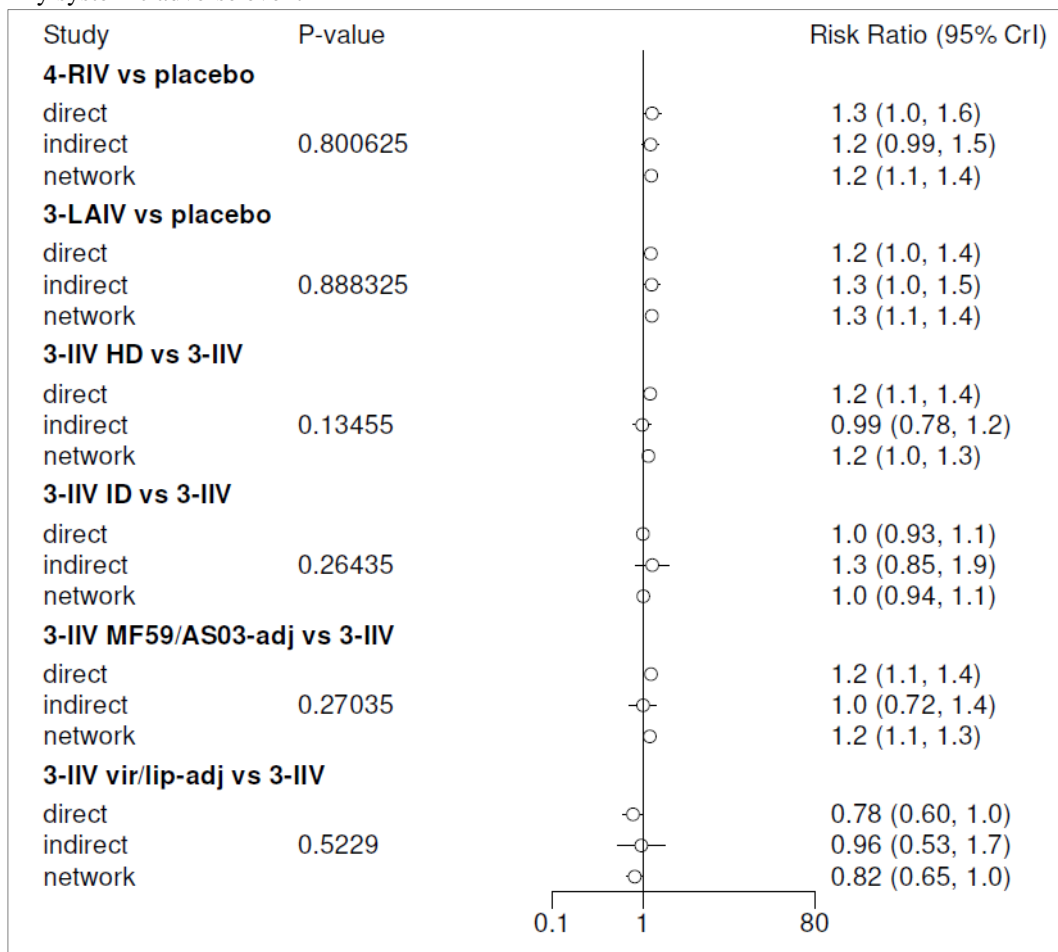
Any systemic adverse event\*



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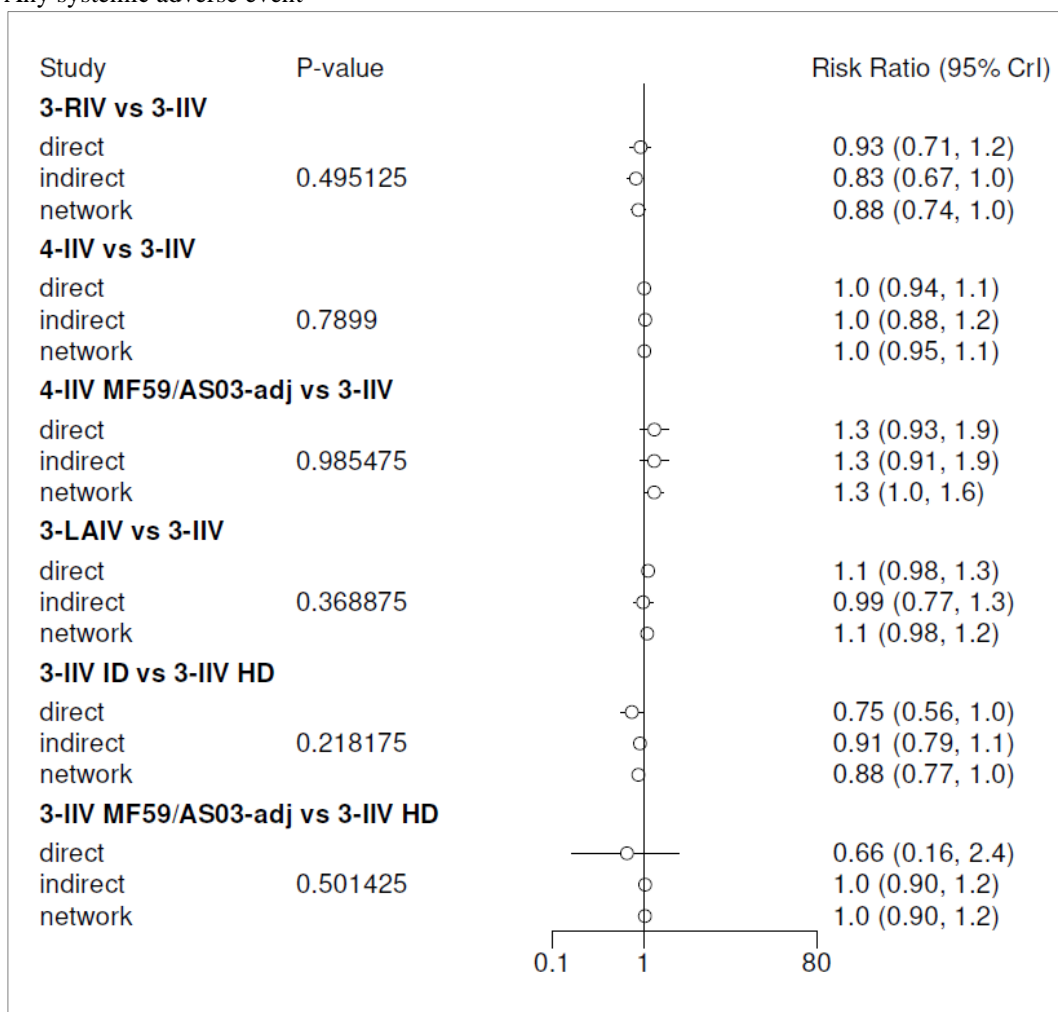
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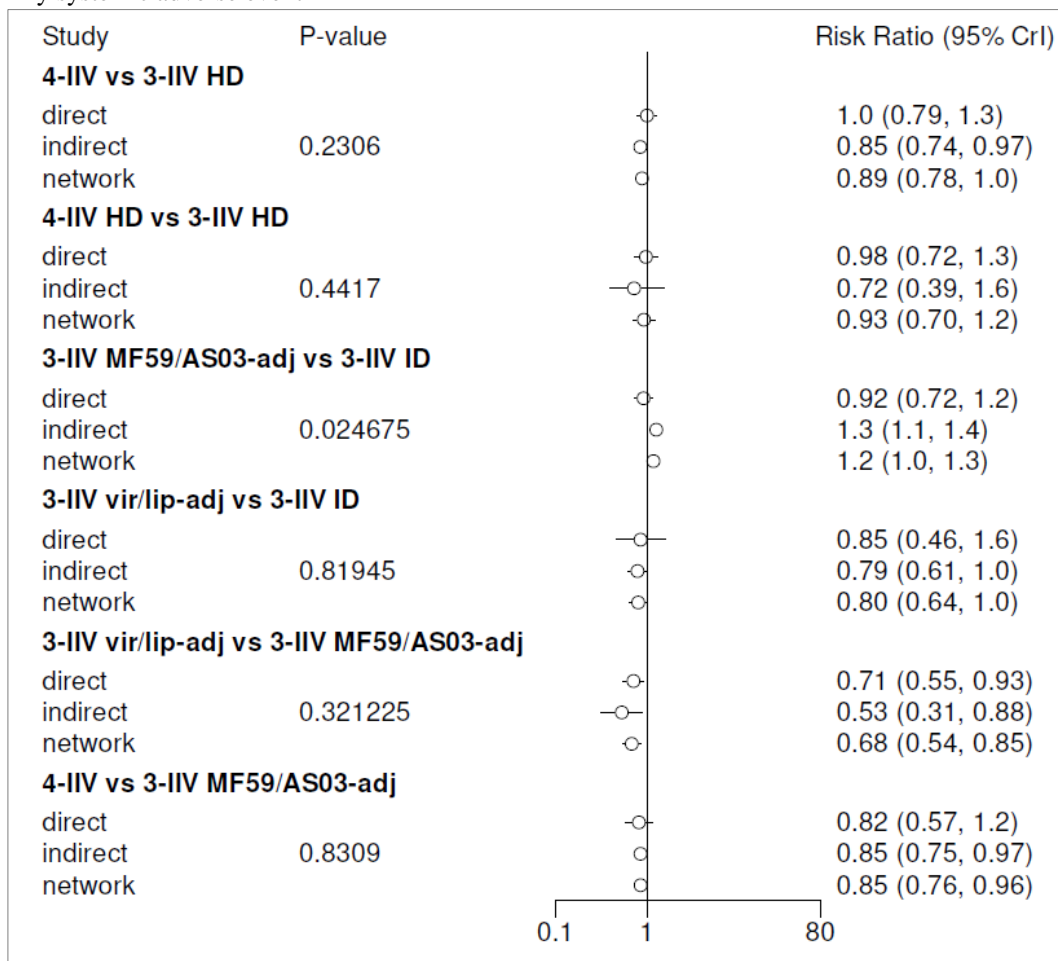
Any systemic adverse event\*



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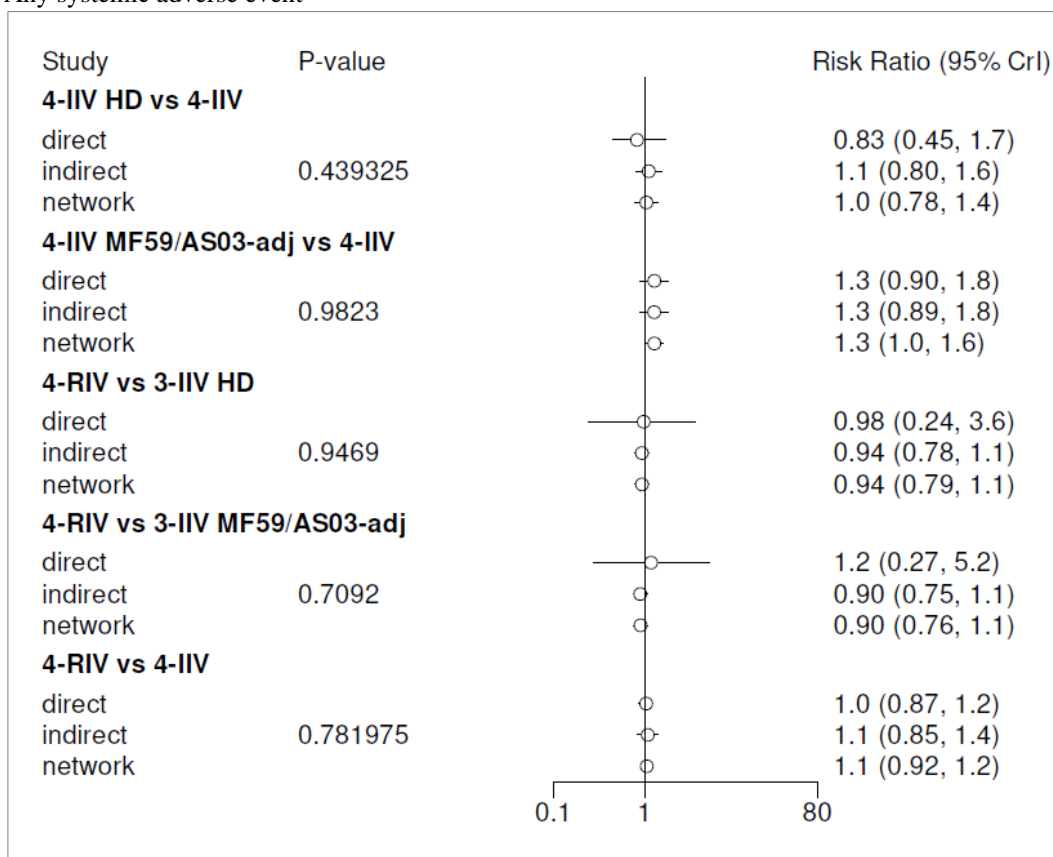
Any systemic adverse event\*



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Any systemic adverse event\*

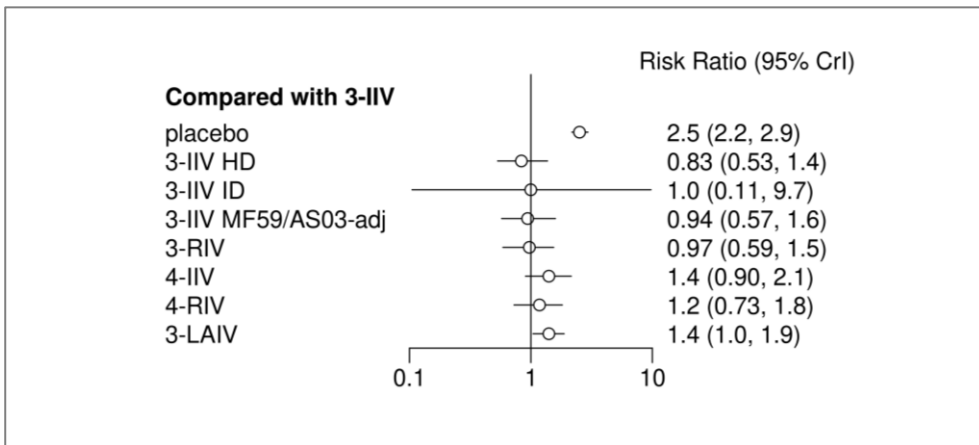


OR <1 favors experimental vaccine compared to placebo or 3-IIV

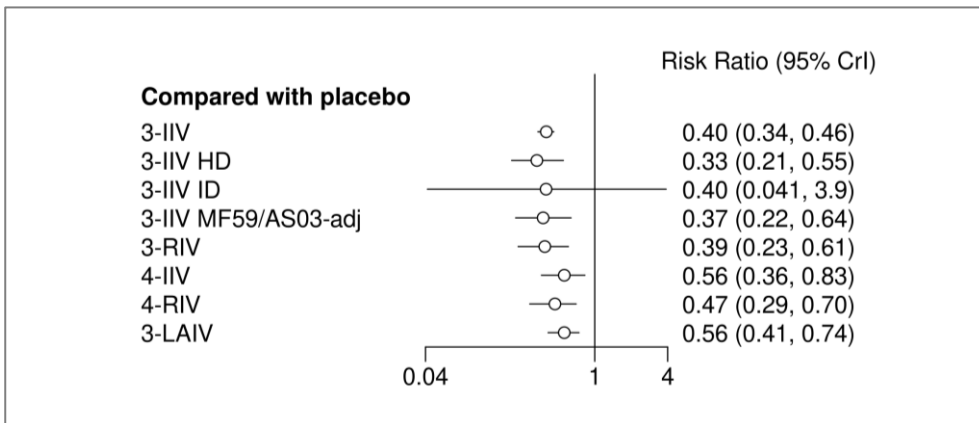
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**Adults and the elderly: Forest plots of laboratory- confirmed influenza, comparison with placebo/no vaccine and with 3-IIV\***



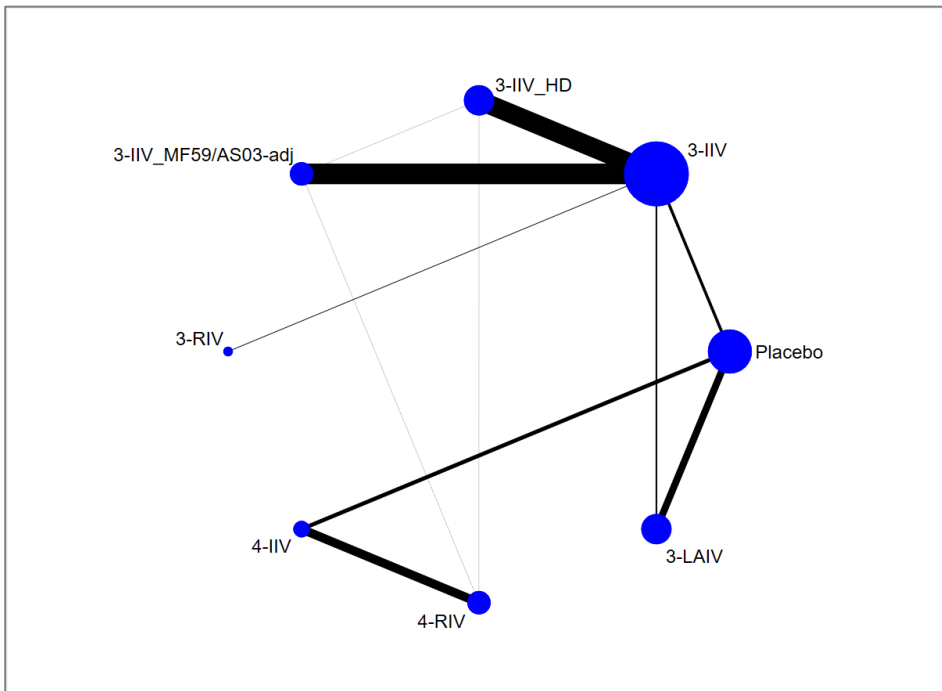
OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

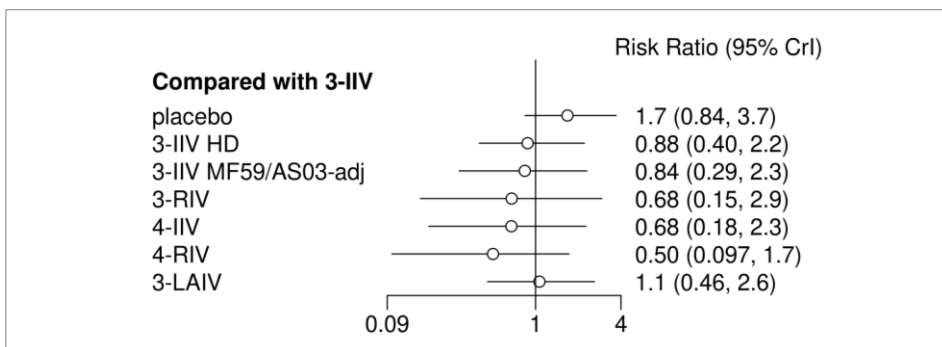
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**The elderly (≥61 years): Network geometry of laboratory -confirmed influenza\***

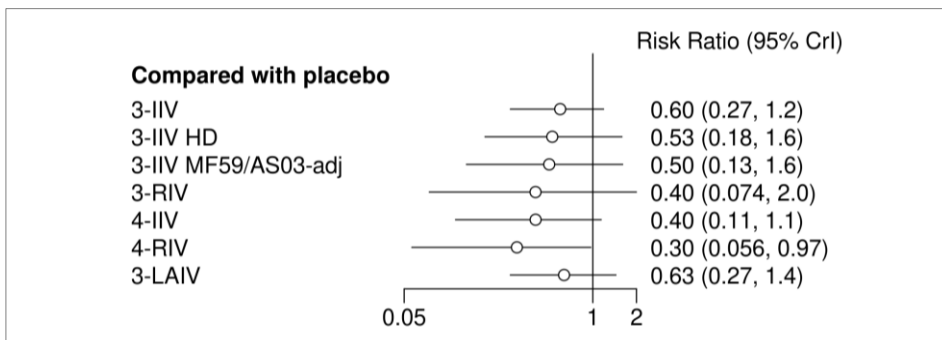


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**The elderly (≥61 years): Forest plots of laboratory-confirmed influenza, comparison with placebo-no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.



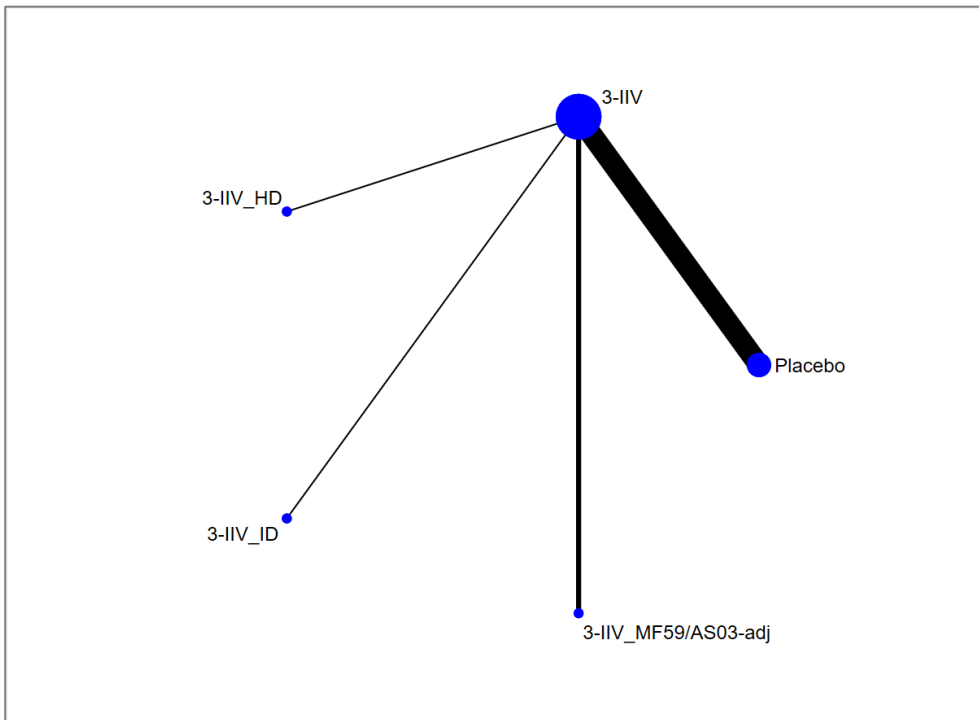
**The elderly (≥61 years): Netleague analysis of laboratory- confirmed influenza\***

<b>placebo</b>	0.6 (0.27, 1.19)	0.53 (0.18, 1.59)	0.5 (0.13, 1.61)	0.4 (0.07, 2)	0.4 (0.11, 1.14)	<b>0.3 (0.06, 0.97)</b>	0.63 (0.27, 1.44)
1.68 (0.84, 3.7)	<b>3-IIV</b>	0.88 (0.4, 2.21)	0.84 (0.29, 2.3)	0.68 (0.15, 2.93)	0.68 (0.18, 2.27)	0.5 (0.1, 1.72)	1.06 (0.46, 2.6)
1.9 (0.63, 5.54)	1.14 (0.45, 2.49)	<b>3-IIV HD</b>	0.95 (0.27, 2.79)	0.76 (0.13, 3.95)	0.76 (0.16, 2.83)	0.56 (0.1, 2.03)	1.21 (0.35, 3.84)
2 (0.62, 7.44)	1.19 (0.43, 3.45)	1.05 (0.36, 3.72)	<b>3-IIV MF59/AS03-adj</b>	0.81 (0.14, 4.99)	0.81 (0.17, 3.5)	0.6 (0.1, 2.45)	1.27 (0.36, 5.06)
2.48 (0.5, 13.43)	1.47 (0.34, 6.48)	1.31 (0.25, 7.67)	1.23 (0.2, 7.36)	<b>3-RIV</b>	0.99 (0.13, 6.62)	0.73 (0.08, 4.88)	1.57 (0.29, 8.96)
2.48 (0.88, 8.85)	1.48 (0.44, 5.66)	1.31 (0.35, 6.31)	1.24 (0.29, 5.96)	1.01 (0.15, 7.45)	<b>4-IIV</b>	0.75 (0.21, 2.02)	1.57 (0.43, 6.95)
<b>3.34 (1.03, 17.71)</b>	2 (0.58, 10.29)	1.77 (0.49, 10.42)	1.67 (0.41, 9.63)	1.37 (0.21, 12.53)	1.33 (0.49, 4.79)	<b>4-RIV</b>	2.12 (0.55, 12.69)
1.58 (0.69, 3.71)	0.94 (0.38, 2.18)	0.83 (0.26, 2.86)	0.79 (0.2, 2.8)	0.64 (0.11, 3.4)	0.64 (0.14, 2.3)	0.47 (0.08, 1.81)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

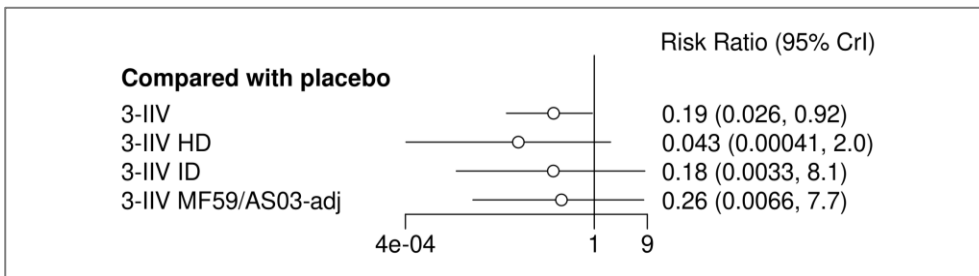
\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Immunocompromised/cancer patients: Network geometry of laboratory -confirmed influenza\***

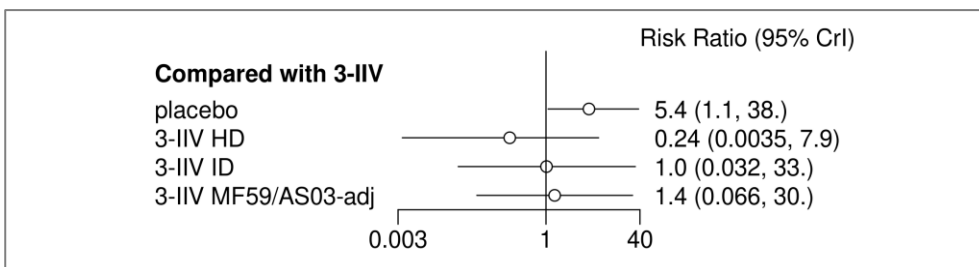


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**Immunocompromised/cancer patients: Forest plots of laboratory-confirmed influenza, comparison with placebo-no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

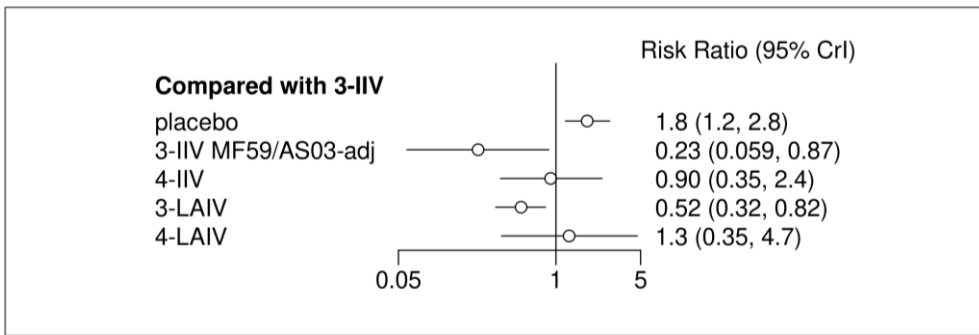
**Immunocompromised/cancer patients: Netleague analysis of laboratory- confirmed influenza\***

<b>placebo</b>	<b>0.19 (0.03, 0.92)</b>	0.04 (0, 1.96)	0.18 (0, 8.1)	0.26 (0.01, 7.74)
<b>5.4 (1.09, 37.91)</b>	<b>3-IIV</b>	0.24 (0, 7.89)	1.02 (0.03, 33.37)	1.4 (0.07, 29.93)
23.25 (0.51, 2439.31)	4.15 (0.13, 281.79)	<b>3-IIV HD</b>	4.45 (0.03, 938.25)	6 (0.06, 1022.82)
5.46 (0.12, 302.8)	0.98 (0.03, 31.37)	0.22 (0, 32.15)	<b>3-IIV ID</b>	1.38 (0.01, 137.12)
3.9 (0.13, 152.34)	0.71 (0.03, 15.1)	0.17 (0, 17.36)	0.73 (0.01, 70.38)	<b>3-IIV MF59/AS03-adj</b>

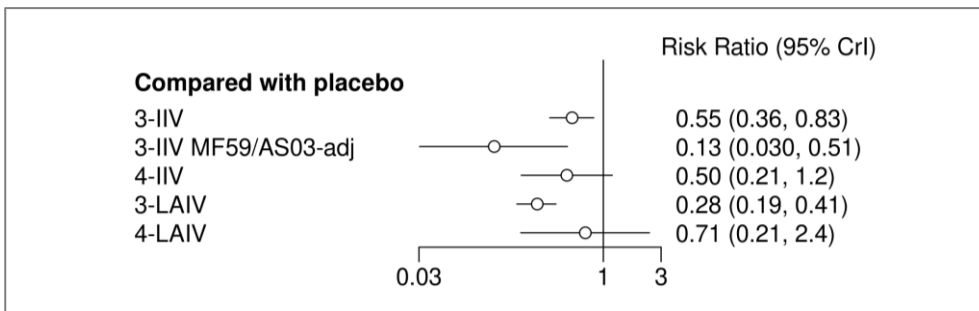
The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**All children: Forest plots of laboratory confirmed influenza, comparison with placebo/no vaccine and with 3-IIV\***



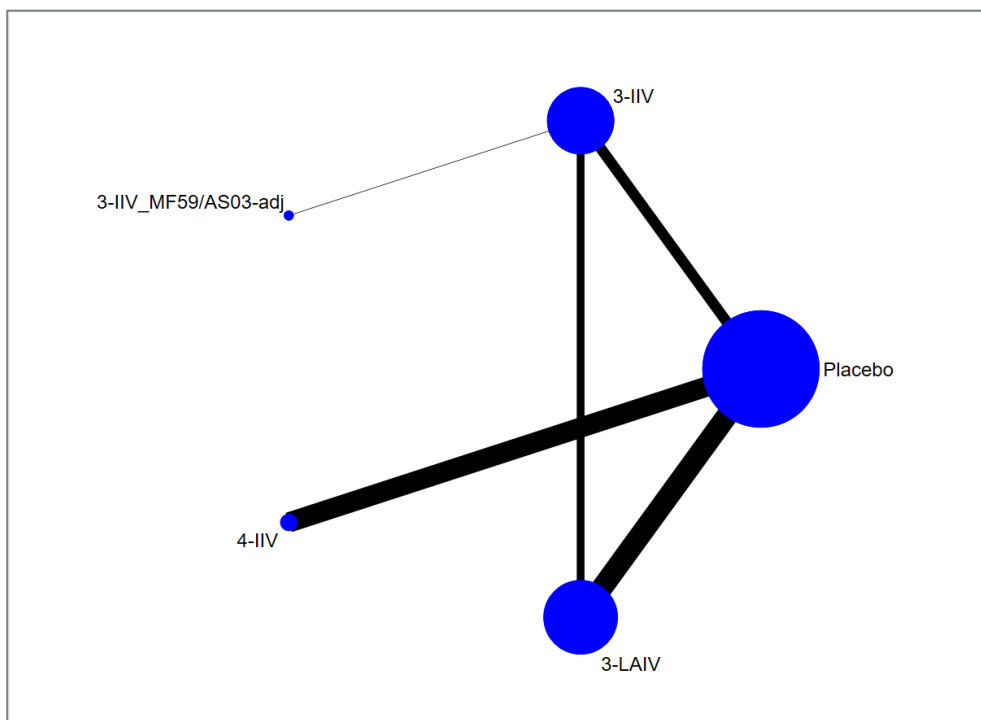
OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

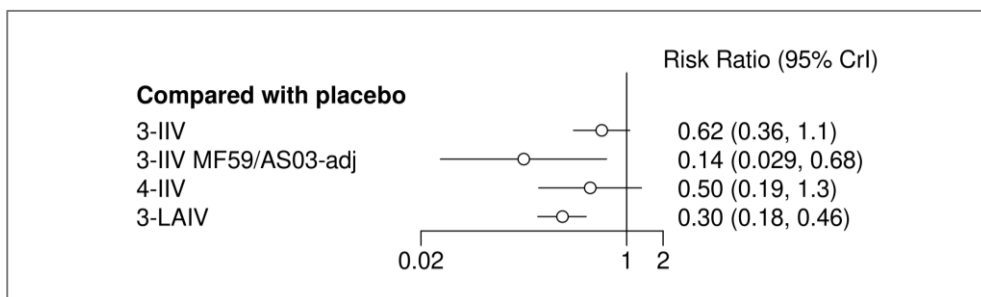
\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

### Children, aged ≤ 5 years: Network geometry of laboratory confirmed influenza\*

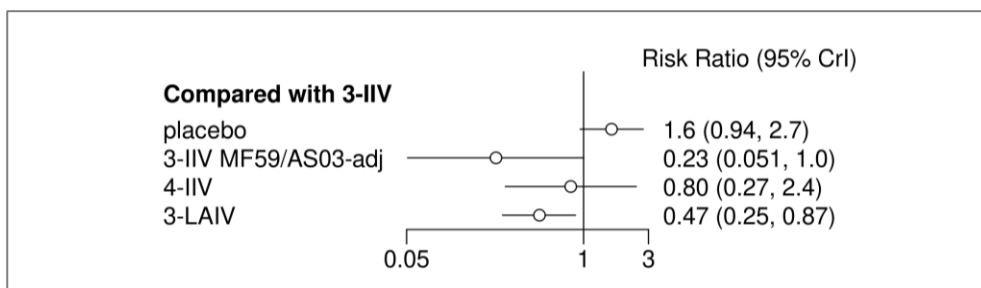


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

### Children, aged ≤ 5 years: Forest plots of laboratory confirmed influenza, comparison with placebo/no vaccine and with 3-IIV\*



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

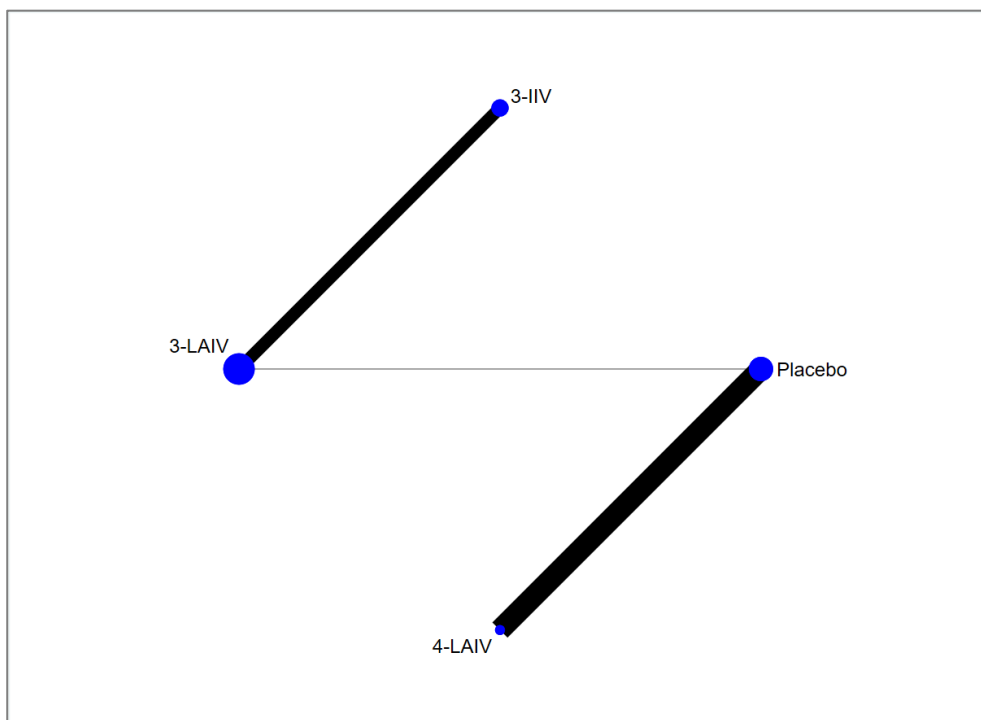
Children, aged ≤ 5 years: Netleague analysis of laboratory confirmed influenza \*

<b>placebo</b>	0.62 (0.36, 1.06)	<b>0.14 (0.03, 0.68)</b>	0.5 (0.19, 1.32)	<b>0.3 (0.18, 0.46)</b>
1.61 (0.94, 2.74)	<b>3-IIV</b>	0.23 (0.05, 1)	0.8 (0.27, 2.44)	<b>0.47 (0.25, 0.87)</b>
<b>7.07 (1.47, 34.5)</b>	4.41 (1, 19.67)	<b>3-IIV MF59/AS03-adj</b>	3.55 (0.56, 22.93)	2.09 (0.42, 10.45)
2 (0.76, 5.31)	1.24 (0.41, 3.76)	0.28 (0.04, 1.79)	<b>4-IIV</b>	0.59 (0.2, 1.71)
<b>3.39 (2.16, 5.41)</b>	<b>2.11 (1.15, 3.94)</b>	0.48 (0.1, 2.41)	1.7 (0.58, 5.01)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

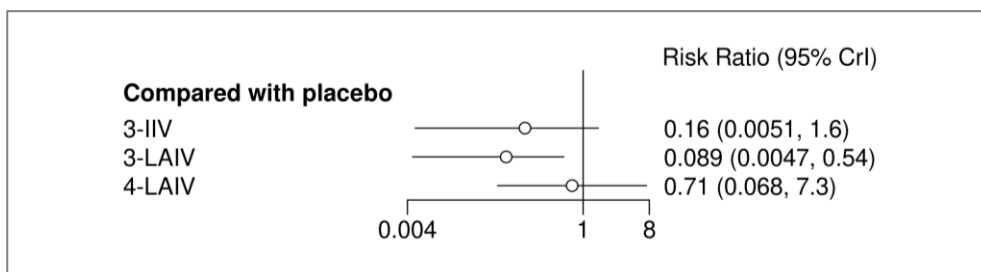
\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

## Children with pre-existing respiratory diseases: Network geometry of laboratory- confirmed influenza\*

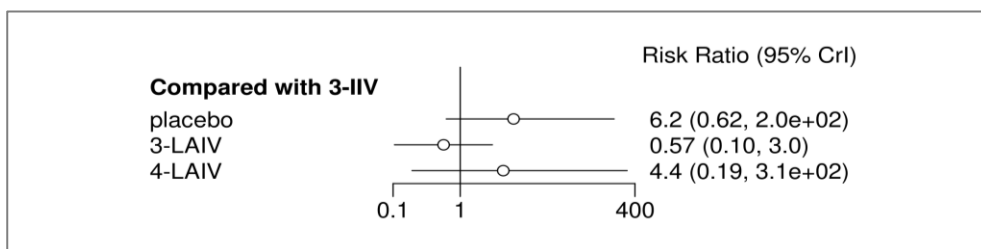


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

## Children with pre-existing respiratory diseases: Forest plots of laboratory confirmed influenza, comparison with placebo-no vaccine and with 3-IIV\*



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/ASO3-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/ASO3-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Children with pre-existing respiratory diseases: Netleague analysis of laboratory- confirmed influenza\***

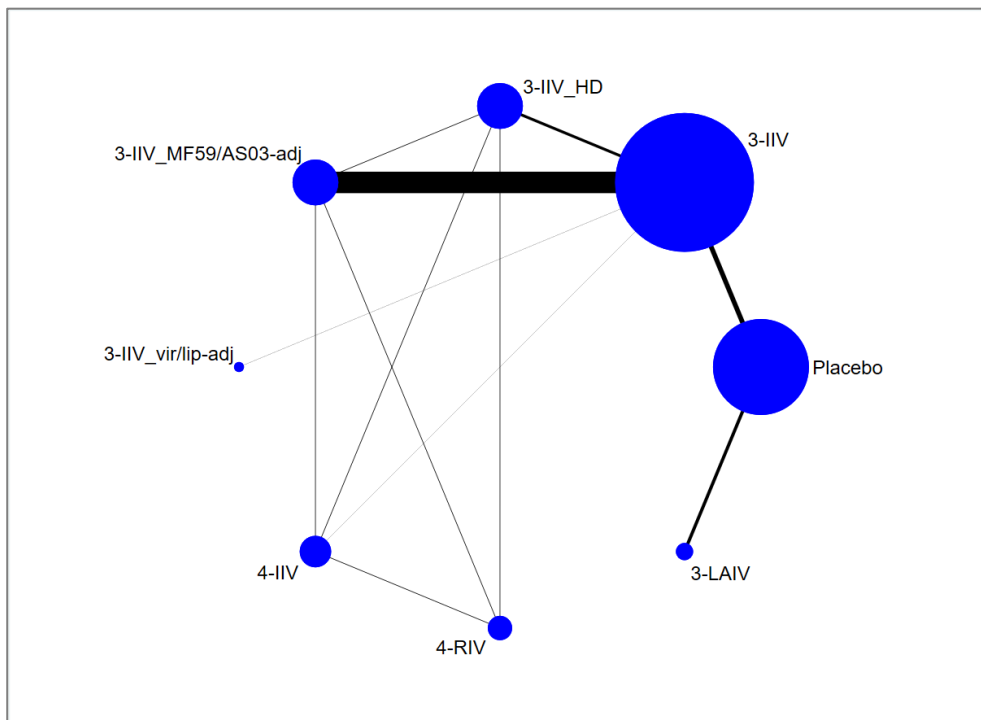
<b>placebo</b>	0.16 (0.01, 1.61)	<b>0.09 (0, 0.54)</b>	0.71 (0.07, 7.32)
6.23 (0.62, 195.63)	<b>3-IIV</b>	0.57 (0.1, 3.01)	4.37 (0.19, 305.6)
<b>11.23 (1.84, 213.35)</b>	1.77 (0.33, 9.54)	<b>3-LAIV</b>	7.82 (0.51, 372.38)
1.41 (0.14, 14.74)	0.23 (0, 5.22)	0.13 (0, 1.98)	<b>4-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

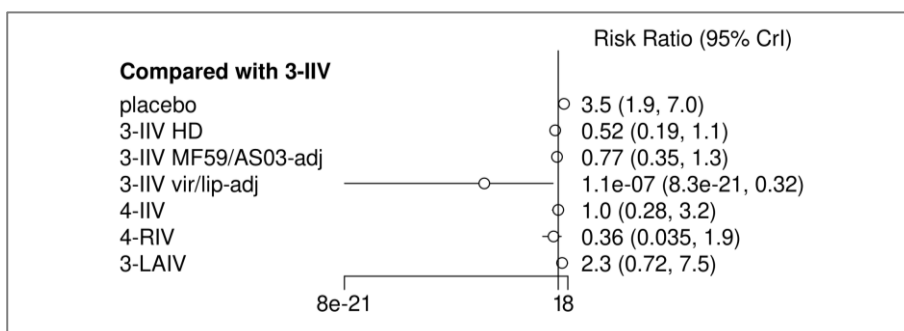


### Adults and the elderly: Network geometry of hospitalization rate\*

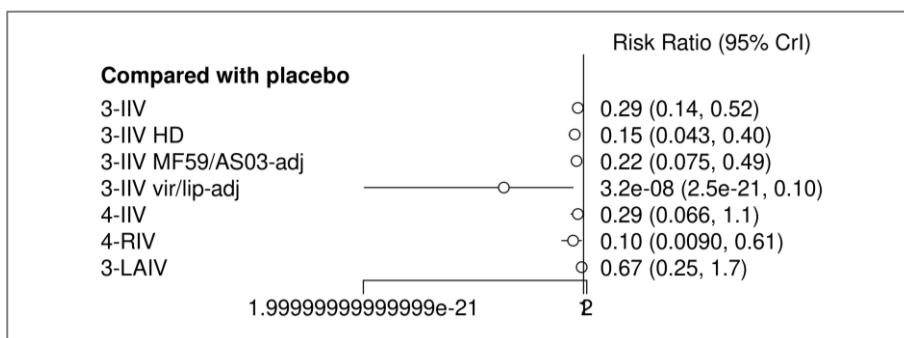


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

### Adults and the elderly: Forest plots of hospitalization rate, comparison with placebo-no vaccine and with 3-IIV\*



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

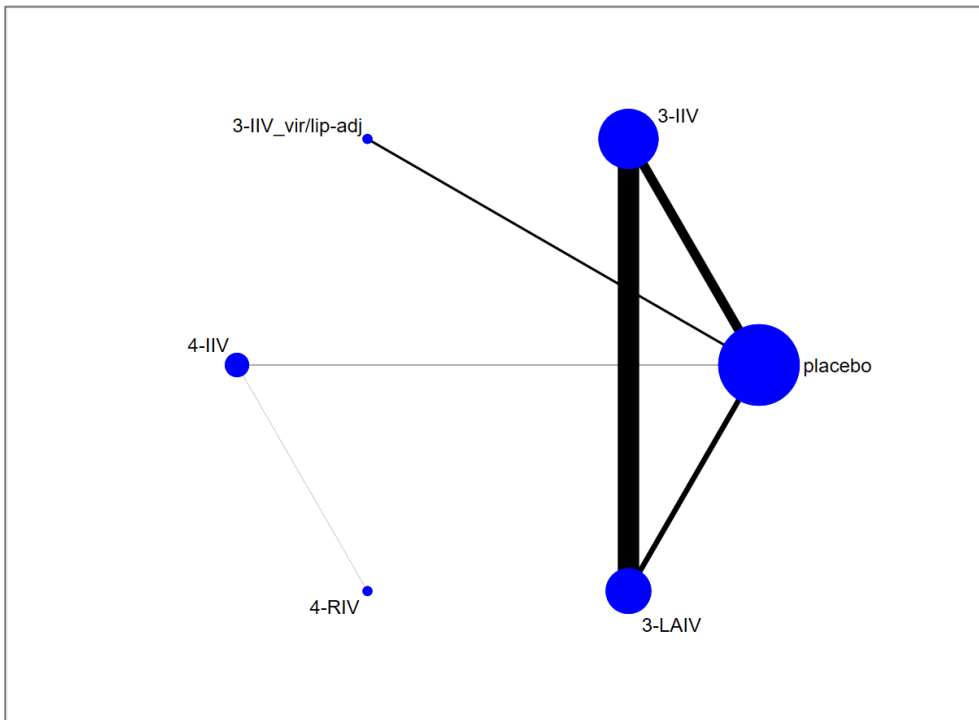
**Adults and the elderly: Netleague analysis of hospitalization rate\***

<b>placebo</b>	<b>0.29 (0.14, 0.52)</b>	<b>0.15 (0.04, 0.4)</b>	<b>0.22 (0.08, 0.49)</b>	<b>0 (0, 0.1)</b>	0.29 (0.07, 1.06)	<b>0.1 (0.01, 0.61)</b>	0.67 (0.25, 1.66)
<b>3.47 (1.91, 7.02)</b>	<b>3-IIV</b>	0.52 (0.19, 1.14)	0.77 (0.35, 1.27)	<b>0 (0, 0.32)</b>	1 (0.28, 3.23)	0.36 (0.04, 1.88)	2.31 (0.72, 7.54)
<b>6.76 (2.52, 23.05)</b>	1.93 (0.88, 5.18)	<b>3-IIV HD</b>	1.48 (0.56, 3.83)	<b>0 (0, 0.63)</b>	1.96 (0.57, 6.84)	0.71 (0.07, 3.87)	<b>4.51 (1.13, 20.77)</b>
<b>4.58 (2.04, 13.33)</b>	1.3 (0.79, 2.83)	0.68 (0.26, 1.79)	<b>3-IIV MF59/AS03-adj</b>	<b>0 (0, 0.43)</b>	1.34 (0.41, 4.55)	0.48 (0.05, 2.61)	3.06 (0.83, 12.62)
<b>30972861.93 (9.94, 4.04665306984859e+20)</b>	<b>8944012.79 (3.11, 1.19969832201764e+20)</b>	<b>4505391.98 (1.59, 66663854240978468864)</b>	<b>6471391.46 (2.35, 91274048805280546816)</b>	<b>3-IIV vir/lip-adj</b>	<b>9063508.09 (2.86, 1.25859629335449e+20)</b>	3210895.96 (0.91, 46301058464736493568)	<b>21054113.46 (5.47, 2.87605336845292e+20)</b>
3.46 (0.94, 15.13)	1 (0.31, 3.53)	0.51 (0.15, 1.74)	0.75 (0.22, 2.46)	<b>0 (0, 0.35)</b>	<b>4-IIV</b>	0.36 (0.04, 2.06)	2.29 (0.45, 12.93)
<b>9.72 (1.64, 110.92)</b>	2.76 (0.53, 28.46)	1.41 (0.26, 13.75)	2.07 (0.38, 20.33)	<b>0 (0, 1.1)</b>	2.75 (0.48, 27.71)	<b>4-RIV</b>	6.45 (0.86, 91.74)
1.5 (0.6, 4.07)	0.43 (0.13, 1.39)	<b>0.22 (0.05, 0.89)</b>	0.33 (0.08, 1.2)	<b>0 (0, 0.18)</b>	0.44 (0.08, 2.23)	0.16 (0.01, 1.16)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

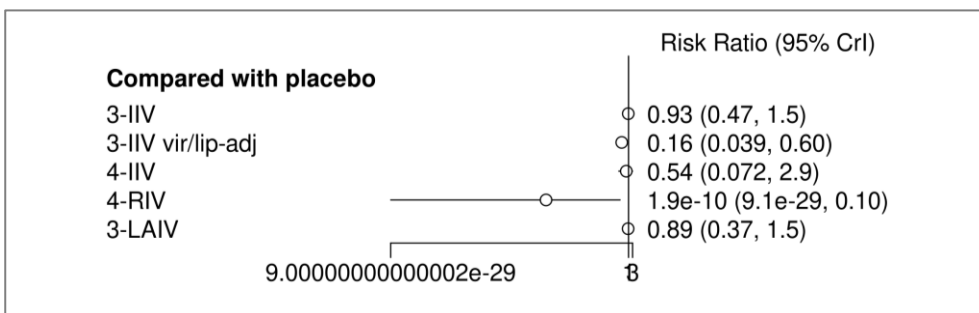
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**All children: Network geometry of hospitalization rate\***

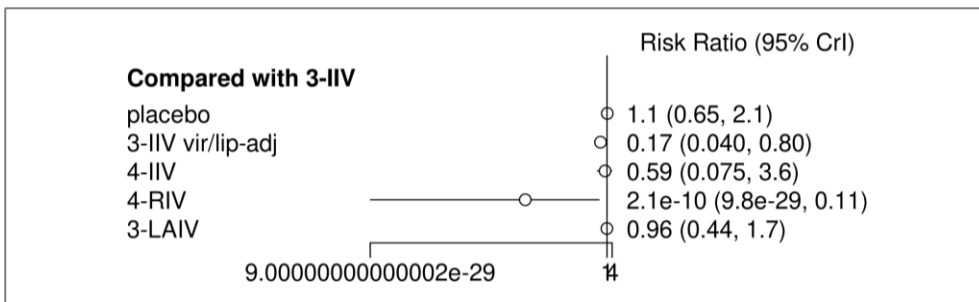


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**All children: Forest plots of hospitalization rate, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



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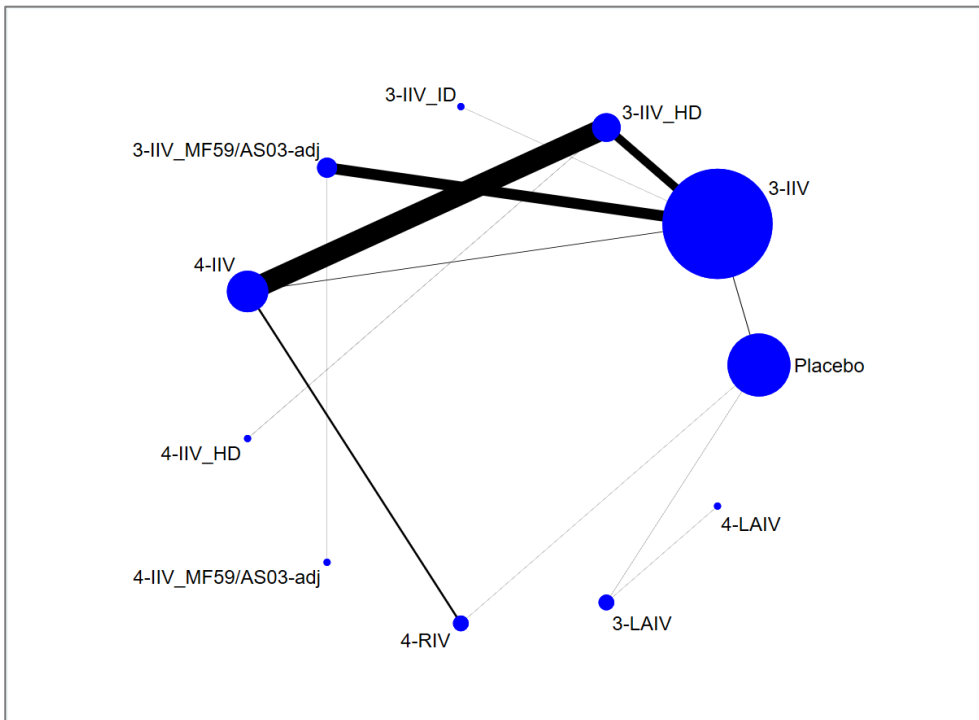
All children. Netleague analysis of hospitalization rate\*

<b>placebo</b>	0.93 (0.47, 1.55)	<b>0.16 (0.04, 0.6)</b>	0.54 (0.07, 2.94)	<b>0 (0, 0.1)</b>	0.89 (0.37, 1.53)
1.08 (0.65, 2.11)	<b>3-IIIV</b>	<b>0.17 (0.04, 0.8)</b>	0.59 (0.08, 3.57)	<b>0 (0, 0.11)</b>	0.96 (0.44, 1.72)
<b>6.33 (1.66, 25.63)</b>	<b>5.9 (1.25, 24.81)</b>	<b>3-IIIV vir/lip-adj</b>	3.46 (0.29, 29.68)	<b>0 (0, 0.69)</b>	<b>5.65 (1.04, 22.7)</b>
1.84 (0.34, 13.92)	1.7 (0.28, 13.29)	0.29 (0.03, 3.46)	<b>4-IIIV</b>	<b>0 (0, 0.17)</b>	1.61 (0.24, 12.28)
<b>5340664028.94 (9.96, 1.096985824046e+28)</b>	<b>4814636394.71 (8.84, 1.01619959257508e+28)</b>	<b>807035612.15 (1.45, 1.63374882187751e+27)</b>	<b>2736904700.67 (5.74, 5.91394639740442e+27)</b>	<b>4-RIV</b>	<b>4404777933.57 (8.32, 8.91148853023516e+27)</b>
1.12 (0.65, 2.73)	1.04 (0.58, 2.3)	<b>0.18 (0.04, 0.97)</b>	0.62 (0.08, 4.11)	<b>0 (0, 0.12)</b>	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo**: placebo/no vaccine; **3-IIIV**: trivalent inactivated intramuscular; **3-IIIV HD**: trivalent inactivated high dose intramuscular; **3-IIIV ID**: trivalent inactivated intradermal; **3-IIIV MF59/ASO3-adj**: trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIIV**: quadrivalent inactivated intramuscular; **4-IIIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIIV ID**: quadrivalent inactivated intradermal; **4-IIIV MF59/ASO3-adj**: quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

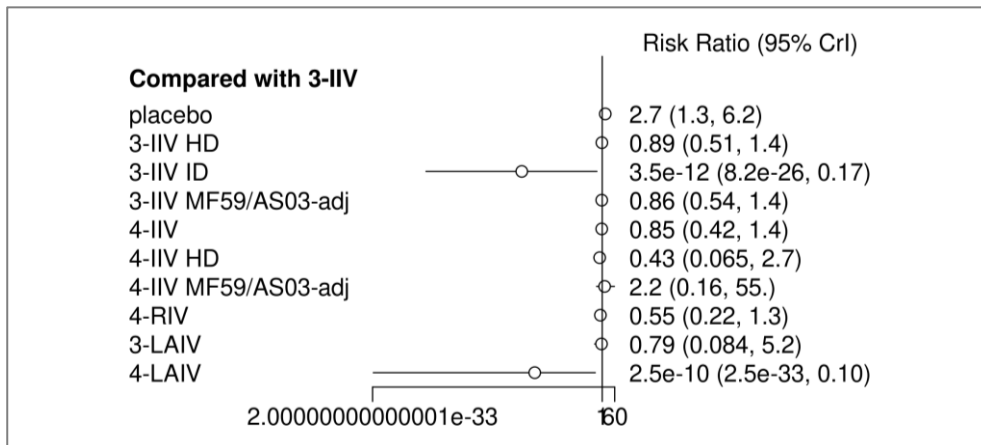
**Adults and the elderly: Network geometry of mortality of any cause\***



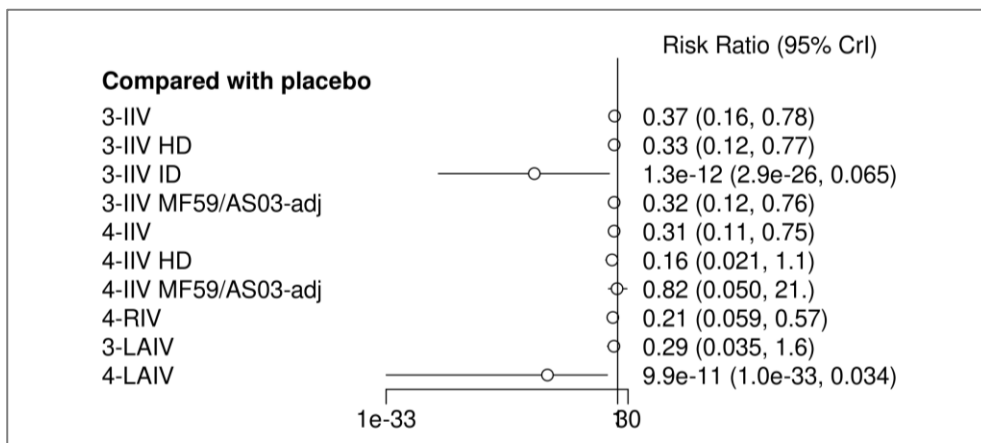
The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

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**Adults and the elderly: Forest plots of mortality of any cause, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

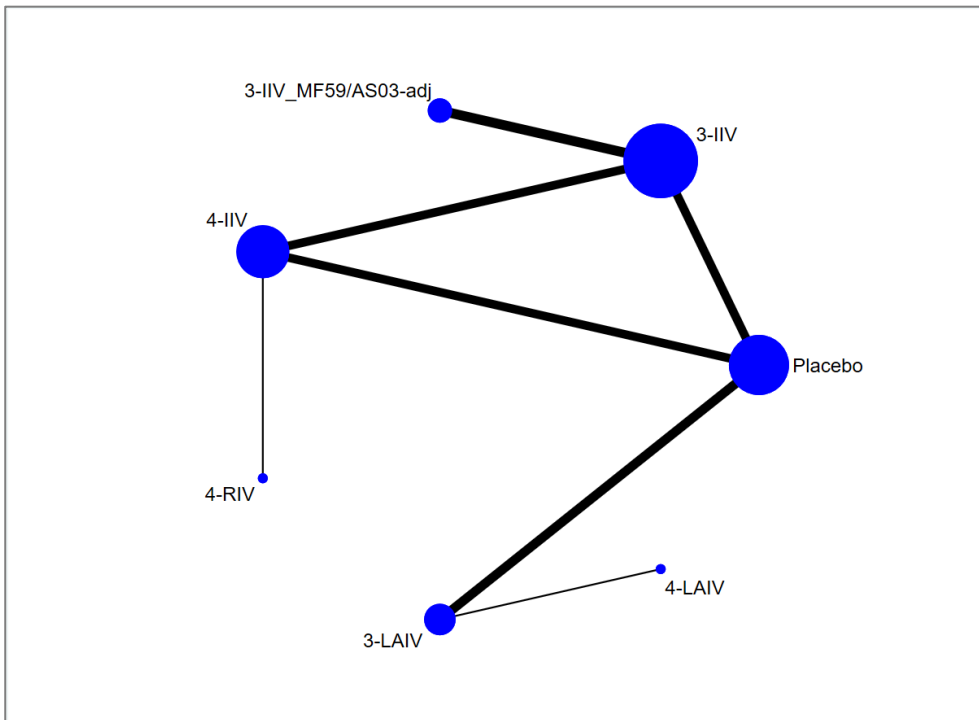
Adults and the elderly: Netleague analysis of mortality of any cause\*

<b>placebo</b>	<b>0.37 (0.16, 0.78)</b>	<b>0.33 (0.12, 0.77)</b>	<b>0 (0, 0.06)</b>	<b>0.32 (0.12, 0.76)</b>	<b>0.31 (0.11, 0.75)</b>	0.16 (0.02, 1.08)	0.82 (0.05, 20.72)	<b>0.21 (0.06, 0.57)</b>	0.29 (0.04, 1.56)	<b>0 (0, 0.03)</b>
<b>2.71 (1.28, 6.22)</b>	<b>3-IIIV</b>	0.89 (0.51, 1.37)	<b>0 (0, 0.17)</b>	0.86 (0.54, 1.43)	0.85 (0.42, 1.43)	0.43 (0.07, 2.69)	2.19 (0.16, 54.78)	0.55 (0.22, 1.26)	0.79 (0.08, 5.2)	<b>0 (0, 0.1)</b>
<b>3.07 (1.3, 8.25)</b>	1.12 (0.73, 1.95)	<b>3-IIIV HD</b>	<b>0 (0, 0.2)</b>	0.95 (0.53, 2.1)	0.96 (0.53, 1.52)	0.49 (0.08, 2.91)	2.51 (0.17, 64.74)	0.62 (0.26, 1.4)	0.9 (0.09, 6.36)	<b>0 (0, 0.12)</b>
<b>757095718859.98 (15.39, 3.4977133063661 6e+25)</b>	<b>286187249246.17 (5.75, 1.2259799445561 8e+25)</b>	<b>245802862233.05 (4.94, 1.1925140100424 6e+25)</b>	<b>3-IIIV IDI</b>	<b>251621058355.28 (5.08, 1.0878170368198 e+25)</b>	<b>227098867929.96 (4.81, 1.1084348584561 5e+25)</b>	<b>107043896605.87 (2.76, 9.9675391695237 7e+24)</b>	<b>1019261265498.1 4 (9.64, 4.7501169914977 3e+25)</b>	<b>148531142519.75 (3.17, 7.8568984830688 9e+24)</b>	<b>286361211425.39 (4.15, 1.5165521766662 3e+25)</b>	3.29 (0, 56397557097022 73024)
<b>3.16 (1.32, 8.12)</b>	1.17 (0.7, 1.85)	1.05 (0.48, 1.9)	<b>0 (0, 0.2)</b>	<b>3-IIIV MF59/AS03-adj</b>	0.99 (0.4, 1.91)	0.5 (0.07, 3.29)	2.53 (0.19, 60.55)	0.64 (0.22, 1.62)	0.92 (0.09, 6.38)	<b>0 (0, 0.12)</b>
<b>3.2 (1.34, 9.33)</b>	1.18 (0.7, 2.38)	1.05 (0.66, 1.89)	<b>0 (0, 0.21)</b>	1.01 (0.52, 2.52)	<b>4-IIIV</b>	0.52 (0.08, 3.38)	2.65 (0.18, 71.89)	0.66 (0.33, 1.3)	0.95 (0.1, 7.05)	<b>0 (0, 0.13)</b>
6.36 (0.93, 48.16)	2.31 (0.37, 15.35)	2.04 (0.34, 12.32)	<b>0 (0, 0.36)</b>	1.99 (0.3, 14.2)	1.93 (0.3, 12.39)	<b>4-IIIV-HD</b>	5.19 (0.21, 217.7)	1.28 (0.18, 9.28)	1.78 (0.1, 26.11)	<b>0 (0, 0.27)</b>
1.22 (0.05, 19.84)	0.46 (0.02, 6.32)	0.4 (0.02, 5.93)	<b>0 (0, 0.1)</b>	0.4 (0.02, 5.18)	0.38 (0.01, 5.54)	0.19 (0, 4.78)	<b>4-IIIV MF59/AS03-adj</b>	0.25 (0.01, 4.04)	0.33 (0.01, 9.06)	<b>0 (0, 0.07)</b>
<b>4.86 (1.74, 16.81)</b>	1.81 (0.8, 4.62)	1.61 (0.72, 3.78)	<b>0 (0, 0.32)</b>	1.55 (0.62, 4.65)	1.52 (0.77, 3)	0.78 (0.11, 5.66)	4.07 (0.25, 116.16)	<b>4-RIV</b>	1.44 (0.14, 11.53)	<b>0 (0, 0.2)</b>
3.42 (0.64, 28.48)	1.27 (0.19, 11.86)	1.12 (0.16, 10.95)	<b>0 (0, 0.24)</b>	1.09 (0.16, 10.92)	1.06 (0.14, 10.5)	0.56 (0.04, 9.63)	3 (0.11, 132.65)	0.69 (0.09, 7.17)	<b>3-LAIV</b>	<b>0 (0, 0.12)</b>
<b>10107830726.22 (29.6, 9.5580916052585 4e+32)</b>	<b>4076335867.09 (9.74, 3.9244379676983 4e+32)</b>	<b>3601897655.47 (8.1, 3.8375142539474 e+32)</b>	0.3 (0, 5.2880740316551 7e+21)	<b>3562104292.46 (8.34, 3.2587760706471 9e+32)</b>	<b>3365344196.61 (7.45, 3.6440765384085 2e+32)</b>	<b>1795204173.83 (3.73, 1.8667492740111 8e+32)</b>	<b>15586288987.02 (14.99, 1.3674335239756 7e+33)</b>	<b>2241877333.4 (5.11, 2.4142977531005 5e+32)</b>	<b>2707506275.43 (8.65, 1.9352925184977 2e+32)</b>	<b>4-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

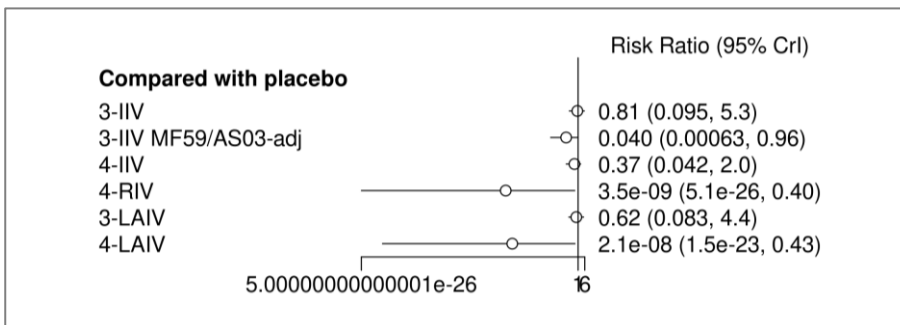
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**All children: Network geometry of mortality of any cause\***

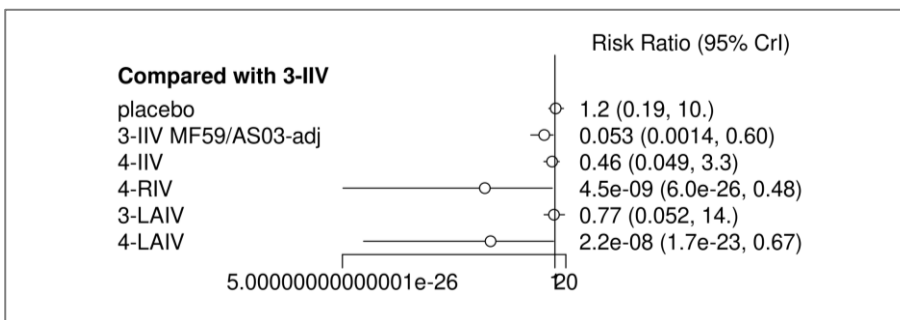


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**All children: Forest plots of mortality of any cause, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



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\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.



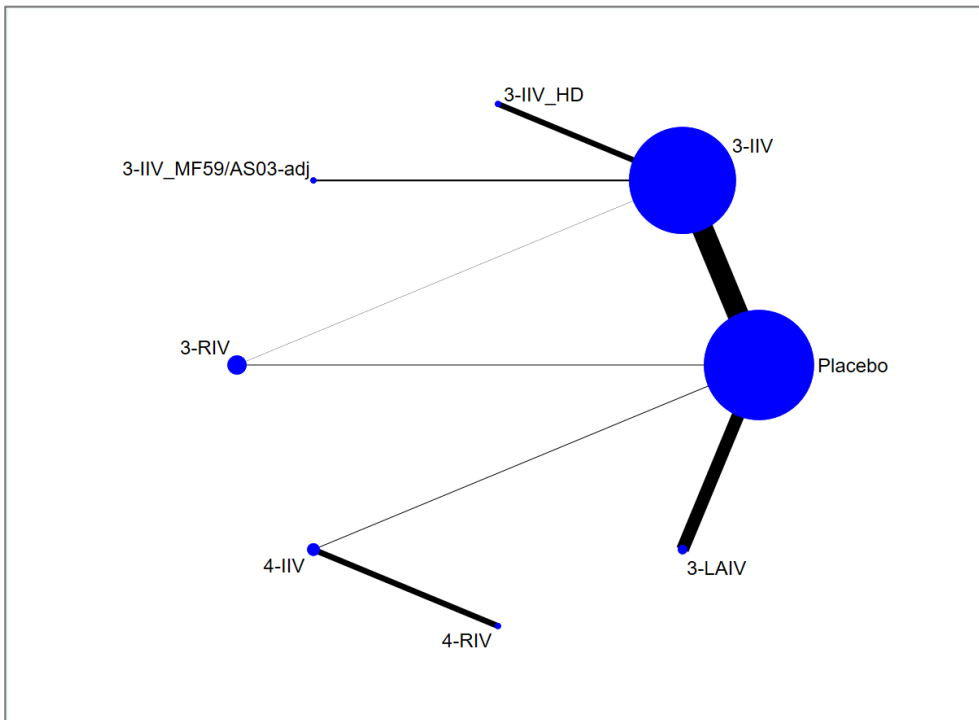
All children: Netleague analysis of mortality of any cause\*

<b>placebo</b>	0.81 (0.1, 5.29)	<b>0.04 (0, 0.96)</b>	0.37 (0.04, 1.99)	<b>0 (0, 0.4)</b>	0.62 (0.08, 4.4)	<b>0 (0, 0.43)</b>
1.23 (0.19, 10.48)	<b>3-IIV</b>	<b>0.05 (0, 0.6)</b>	0.46 (0.05, 3.31)	<b>0 (0, 0.48)</b>	0.77 (0.05, 13.81)	<b>0 (0, 0.67)</b>
<b>24.98 (1.04, 1590.74)</b>	<b>18.73 (1.67, 733.69)</b>	<b>3-IIV MF59/AS03-adj</b>	9.16 (0.32, 495.19)	0 (0, 15.98)	15.68 (0.38, 1503.99)	0 (0, 23.08)
2.67 (0.5, 24.07)	2.17 (0.3, 20.38)	0.11 (0, 3.17)	<b>4-IIV</b>	<b>0 (0, 0.85)</b>	1.66 (0.13, 33.67)	0 (0, 1.52)
<b>282779832.13 (2.48, 1.94616517443502e+25)</b>	<b>221298718.92 (2.09, 1.67813234994266e+25)</b>	10423201.26 (0.06, 8.60967118893389e+23)	<b>95951450.43 (1.18, 5.93571191264789e+24)</b>	<b>4-RIV</b>	<b>178659206.29 (1.36, 1.14939258421012e+25)</b>	7.51 (0, 4489974184834196992)
1.61 (0.23, 11.99)	1.3 (0.07, 19.33)	0.06 (0, 2.66)	0.6 (0.03, 7.46)	<b>0 (0, 0.74)</b>	<b>3 LAIV</b>	<b>0 (0, 0.55)</b>
<b>48385226.43 (2.31, 6.76804260880723e+22)</b>	<b>46155629.06 (1.49, 5.95182453746959e+22)</b>	1897383.53 (0.04, 4.9873964888541e+21)	21705948.16 (0.66, 2.73166229700137e+22)	0.13 (0, 19521316104692516)	<b>32696951.53 (1.83, 3.64266067903709e+22)</b>	<b>4 LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

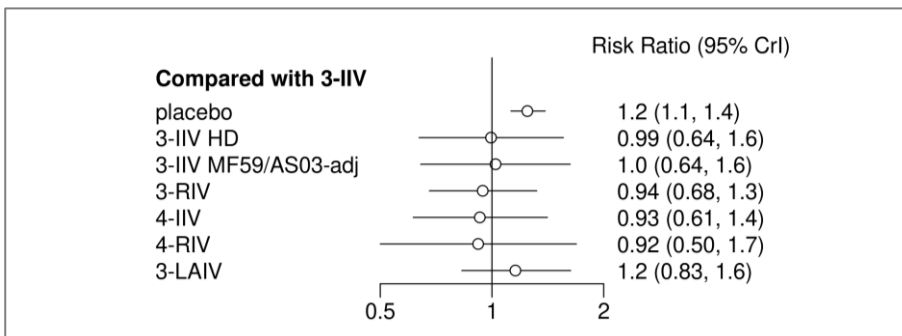
\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

**Adults and the elderly: Network geometry of Influenza like Illness (ILI) \***

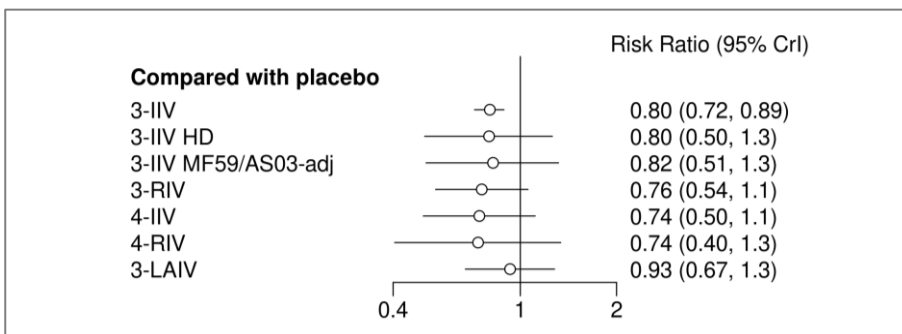


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**Adults and the elderly: Forest plot of ILI, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

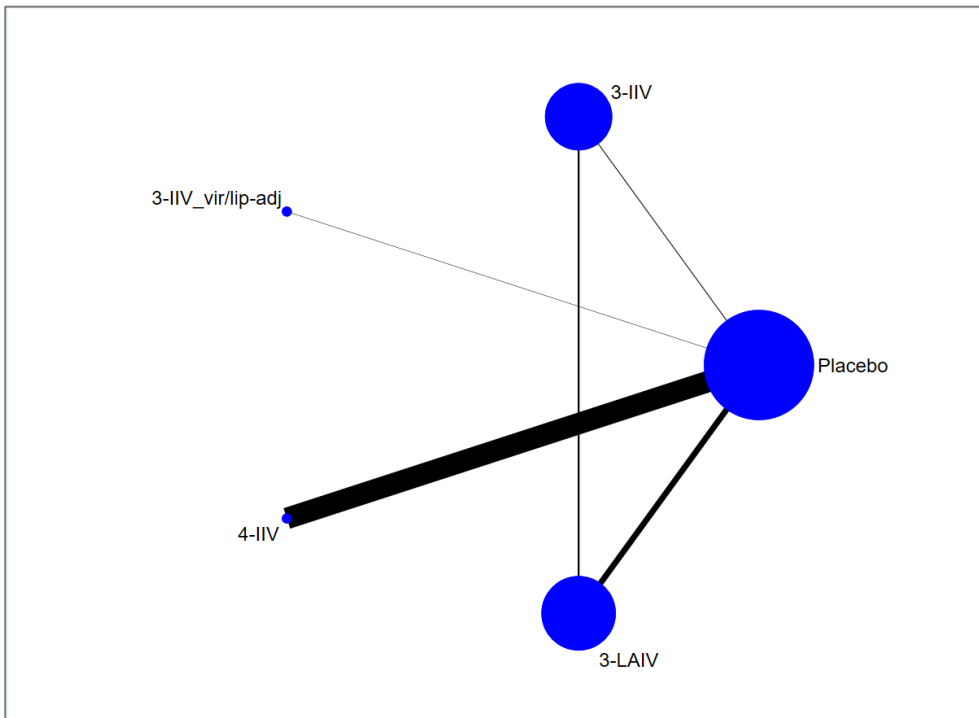
**Adults and the elderly: Netleague analysis of ILI\***

<b>placebo</b>	<b>0.8 (0.72, 0.89)</b>	0.8 (0.5, 1.26)	0.82 (0.51, 1.32)	0.76 (0.54, 1.06)	0.74 (0.5, 1.11)	0.74 (0.4, 1.34)	0.93 (0.67, 1.28)
<b>1.25 (1.13, 1.39)</b>	<b>3-IIV</b>	0.99 (0.64, 1.56)	1.02 (0.64, 1.62)	0.94 (0.68, 1.32)	0.93 (0.61, 1.41)	0.92 (0.5, 1.69)	1.16 (0.83, 1.63)
1.25 (0.79, 1.99)	1.01 (0.64, 1.57)	<b>3-IIV HD</b>	1.03 (0.54, 1.95)	0.95 (0.54, 1.66)	0.93 (0.51, 1.72)	0.92 (0.43, 1.97)	1.16 (0.67, 2.04)
1.22 (0.76, 1.97)	0.98 (0.62, 1.56)	0.97 (0.51, 1.85)	<b>3-IIV MF59/AS03-adj</b>	0.92 (0.52, 1.64)	0.91 (0.48, 1.7)	0.9 (0.42, 1.94)	1.13 (0.64, 2.01)
1.32 (0.95, 1.84)	1.06 (0.76, 1.47)	1.05 (0.6, 1.84)	1.08 (0.61, 1.92)	<b>3-RIV</b>	0.98 (0.58, 1.65)	0.97 (0.49, 1.93)	1.23 (0.77, 1.94)
1.34 (0.9, 2.01)	1.08 (0.71, 1.63)	1.07 (0.58, 1.97)	1.1 (0.59, 2.06)	1.02 (0.6, 1.72)	<b>4-IIV</b>	0.99 (0.64, 1.55)	1.25 (0.75, 2.09)
1.36 (0.75, 2.47)	1.09 (0.59, 2)	1.08 (0.51, 2.31)	1.11 (0.51, 2.4)	1.03 (0.52, 2.05)	1.01 (0.65, 1.57)	<b>4-RIV</b>	1.26 (0.64, 2.5)
1.08 (0.78, 1.49)	0.86 (0.61, 1.21)	0.86 (0.49, 1.5)	0.88 (0.5, 1.56)	0.82 (0.51, 1.29)	0.8 (0.48, 1.34)	0.79 (0.4, 1.56)	<b>3 LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

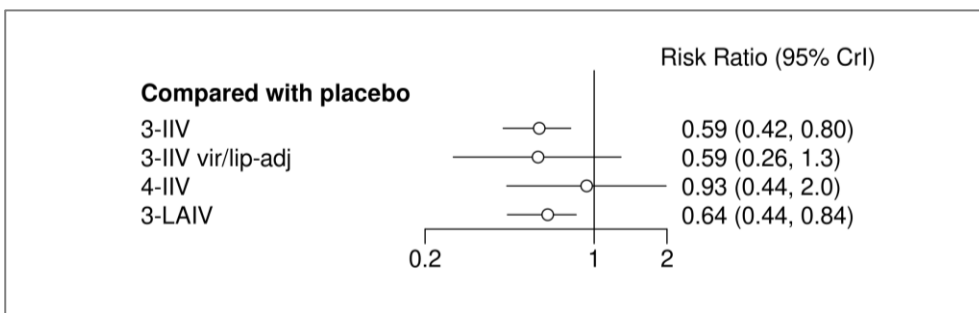
\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

### All children: Network geometry of ILI\*

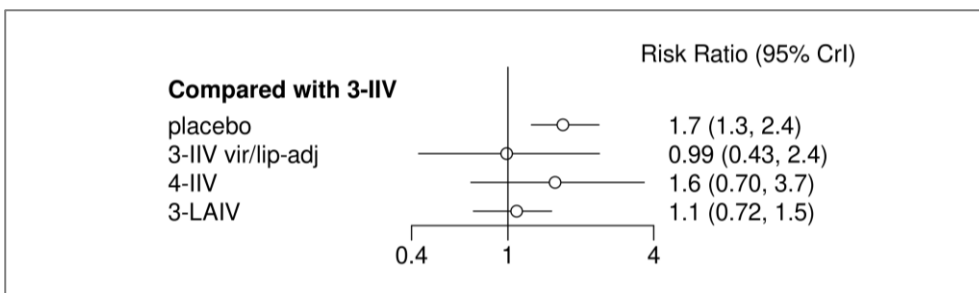


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

### All children: Forest plots of ILI. Comparison with placebo/no vaccine and with 3-IIV\*



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

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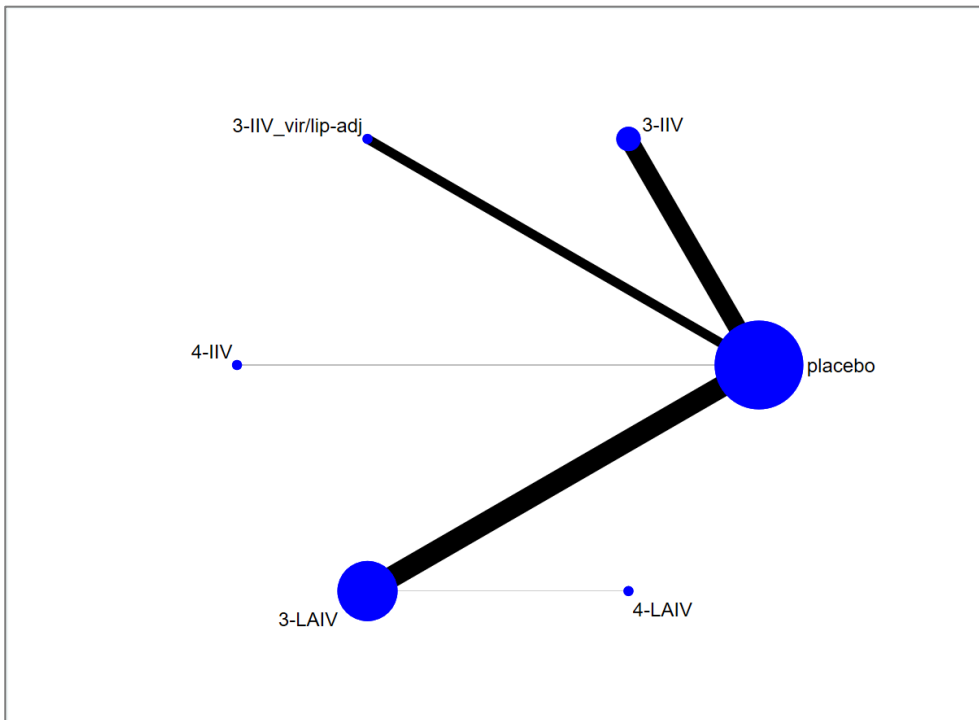
All children: Netleague analysis of ILI\*

<b>placebo</b>	<b>0.59 (0.42, 0.8)</b>	0.59 (0.26, 1.29)	0.93 (0.44, 1.98)	<b>0.64 (0.44, 0.84)</b>
<b>1.69 (1.25, 2.38)</b>	<b>3-IIV</b>	0.99 (0.43, 2.39)	1.57 (0.7, 3.66)	1.09 (0.72, 1.51)
1.71 (0.78, 3.82)	1.01 (0.42, 2.34)	<b>3-IIV vir/lip-adj</b>	1.59 (0.53, 4.79)	1.1 (0.44, 2.45)
1.07 (0.5, 2.3)	0.64 (0.27, 1.42)	0.63 (0.21, 1.88)	<b>4-IIV</b>	0.69 (0.29, 1.47)
<b>1.56 (1.19, 2.28)</b>	0.92 (0.66, 1.39)	0.91 (0.41, 2.28)	1.44 (0.68, 3.5)	<b>3 LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

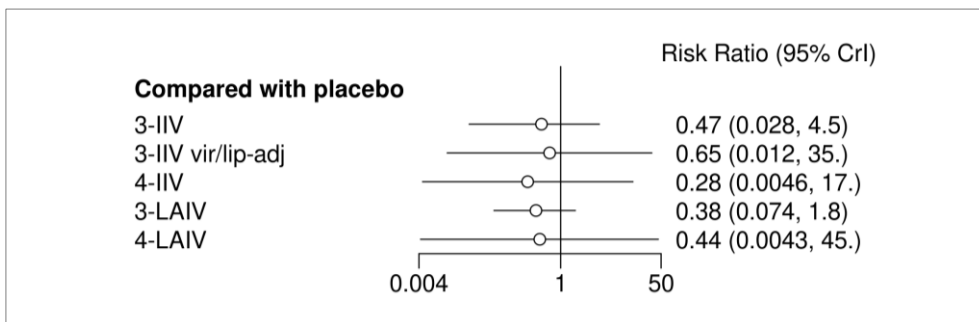
\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

**All children: Network geometry of acute otitis media\***

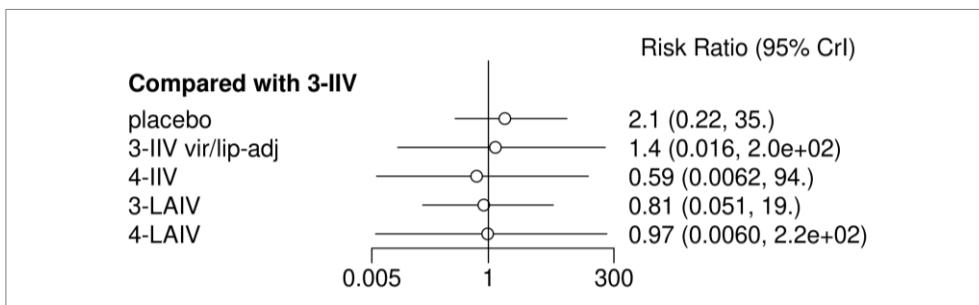


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**All children: Forest plot of acute otitis media, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**All children: Netleague analysis of acute otitis media\***

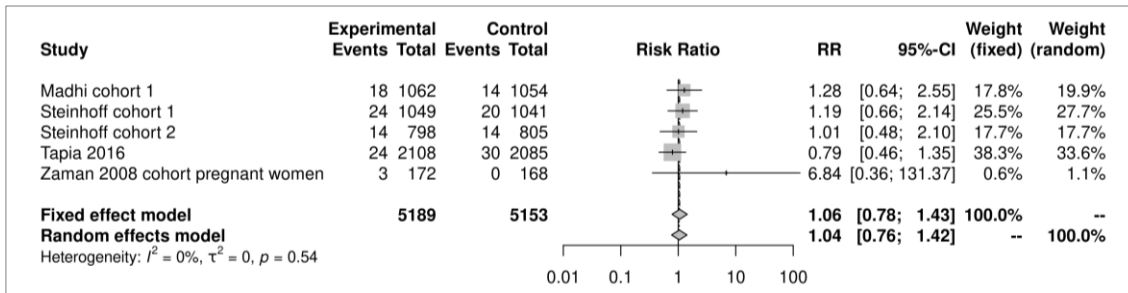
<b>placebo</b>	0.47 (0.03, 4.51)	0.65 (0.01, 34.87)	0.28 (0, 16.7)	0.38 (0.07, 1.77)	0.44 (0, 44.83)
2.11 (0.22, 35.3)	<b>3-IIV</b>	1.37 (0.02, 201.44)	0.59 (0.01, 93.54)	0.81 (0.05, 19.04)	0.97 (0.01, 216.91)
1.54 (0.03, 83.13)	0.73 (0, 61.45)	<b>3-IIV vir/lip-adj</b>	0.43 (0, 130.05)	0.59 (0.01, 40.8)	0.69 (0, 288.72)
3.62 (0.06, 217.29)	1.71 (0.01, 161.07)	2.34 (0.01, 745.27)	<b>4-IIV</b>	1.38 (0.02, 105.68)	1.63 (0, 746.01)
2.62 (0.56, 13.44)	1.24 (0.05, 19.75)	1.7 (0.02, 131.34)	0.72 (0.01, 61.6)	<b>3 LAIV</b>	1.16 (0.02, 93.17)
2.26 (0.02, 234.81)	1.04 (0, 167.64)	1.46 (0, 698.03)	0.61 (0, 314.4)	0.86 (0.01, 63.6)	<b>4 LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

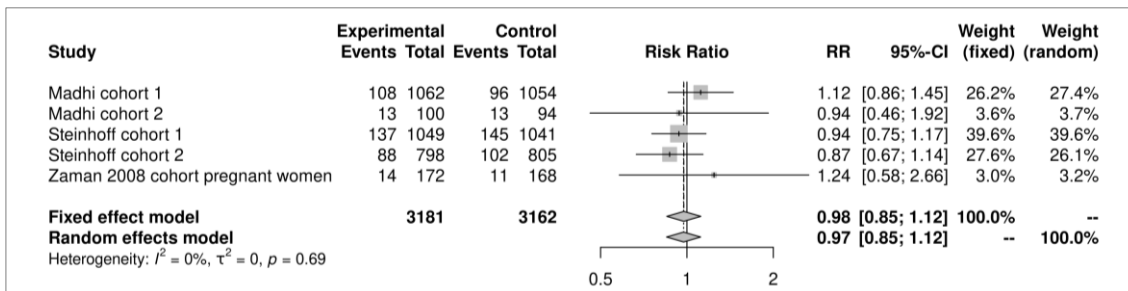
\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

## Pregnancy outcomes: 3-IIV vs placebo/no vaccine, pairwise meta-analyses\*

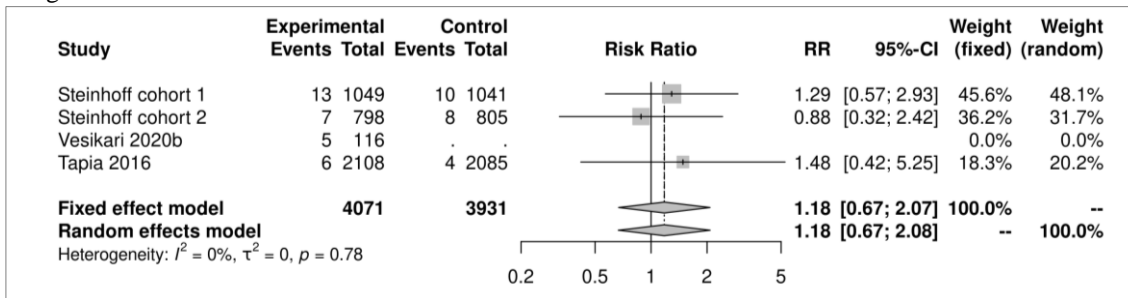
### Abortion



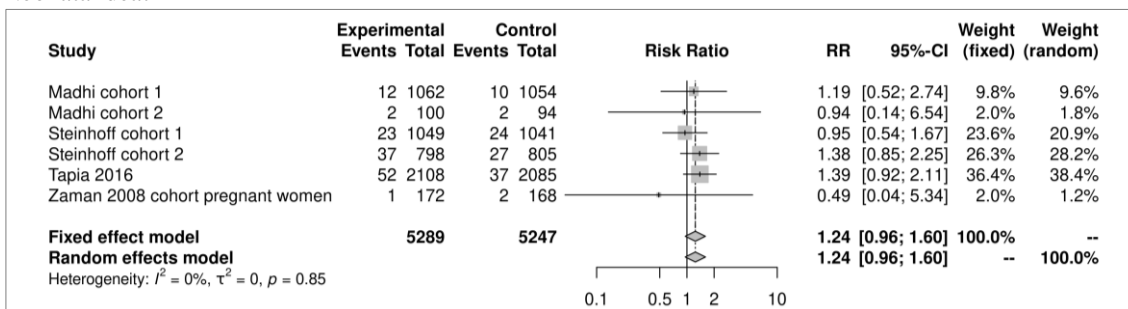
### Preterm birth



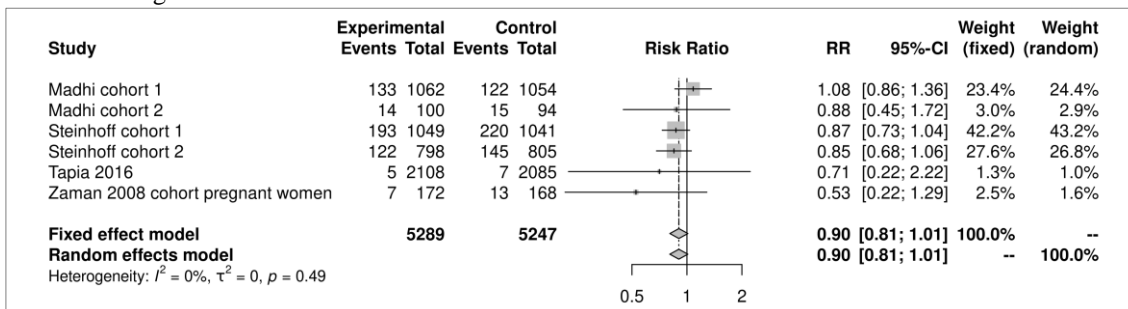
### Congenital malformation



### Neonatal death



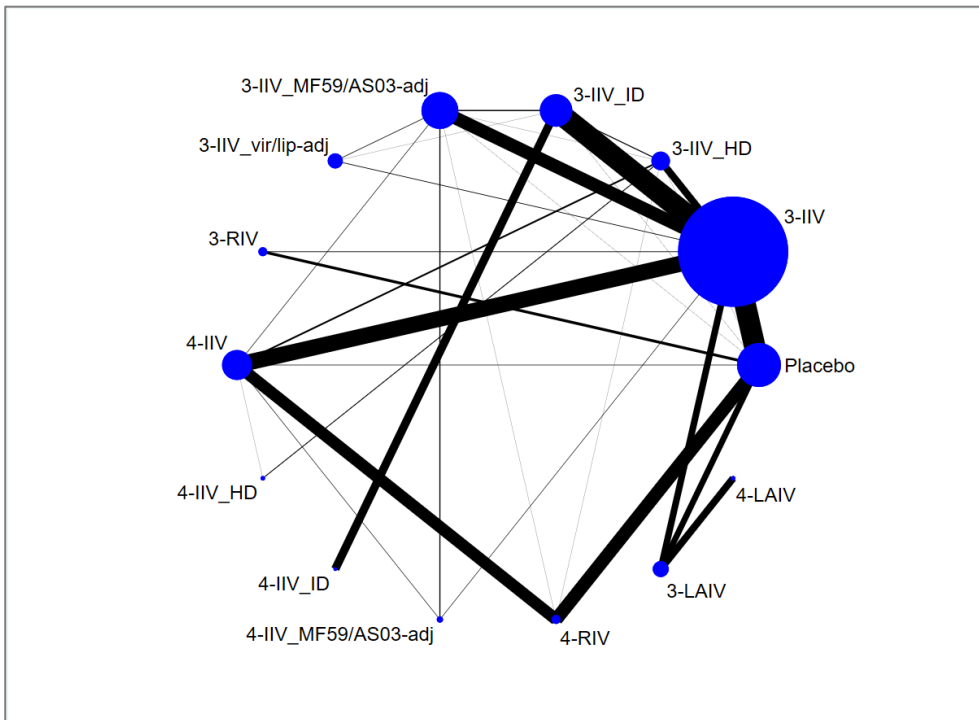
### Low birth weight



\* RR < 1 favors 3-IIV compared to placebo or no vaccine



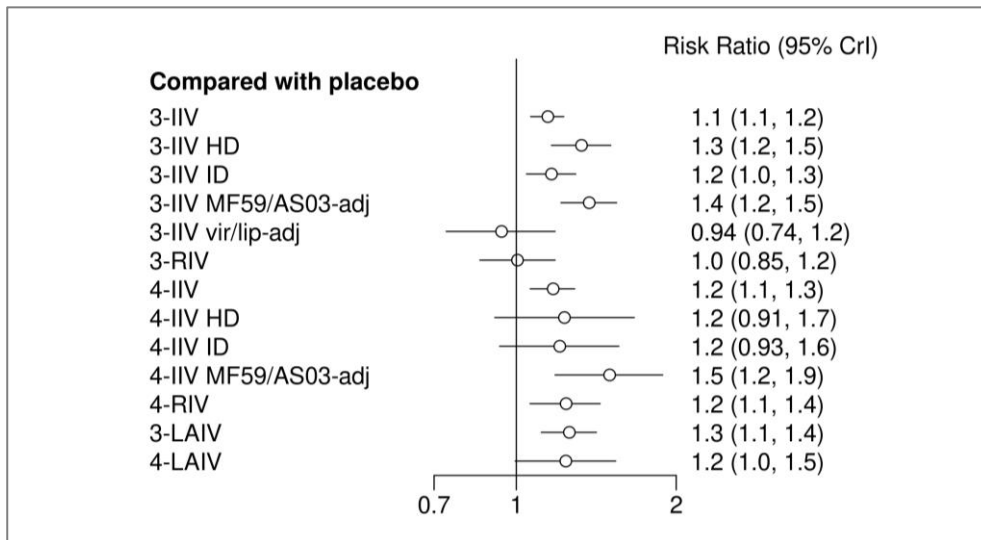
**Adults and the elderly: Network geometry of any systemic adverse event\***



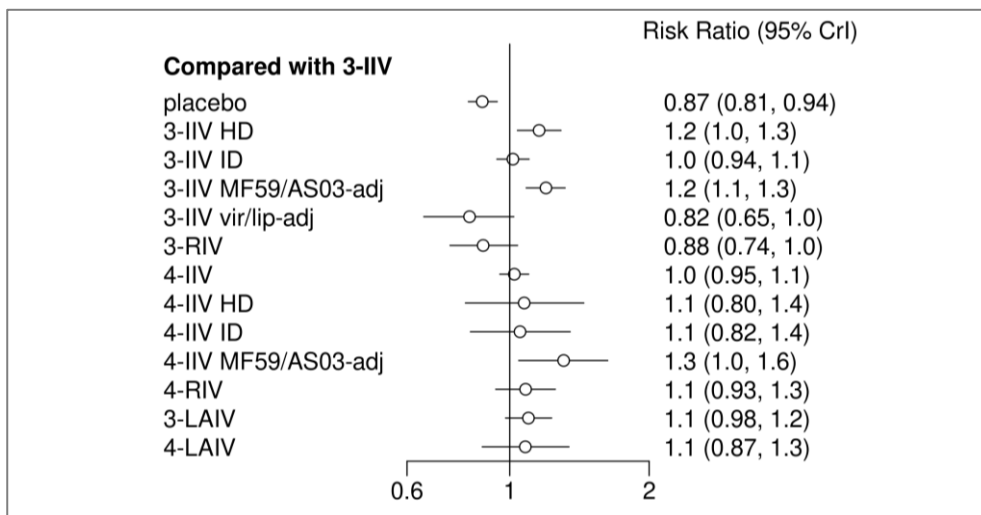
The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Adults and the elderly: Forest plots of any systemic adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

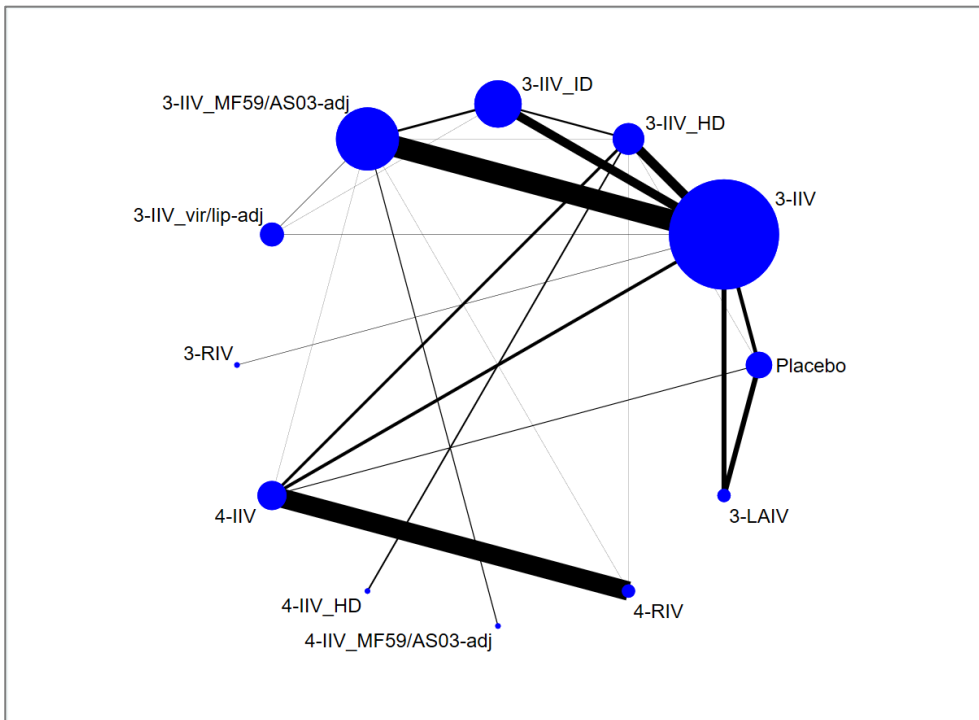
Adults and the elderly: Netleague analysis of any systemic adverse event\*

placebo	<b>1.15 (1.06, 1.23)</b>	<b>1.33 (1.16, 1.51)</b>	<b>1.16 (1.05, 1.29)</b>	<b>1.37 (1.21, 1.54)</b>	0.94 (0.74, 1.18)	1 (0.85, 1.18)	<b>1.17 (1.06, 1.29)</b>	1.23 (0.91, 1.67)	1.21 (0.93, 1.56)	<b>1.5 (1.18, 1.89)</b>	<b>1.24 (1.06, 1.44)</b>	<b>1.26 (1.11, 1.42)</b>	1.24 (1, 1.54)
<b>0.87 (0.81, 0.94)</b>	<b>3-IIV</b>	<b>1.16 (1.04, 1.29)</b>	1.02 (0.94, 1.1)	<b>1.2 (1.09, 1.32)</b>	0.82 (0.65, 1.02)	0.88 (0.74, 1.04)	1.02 (0.95, 1.1)	1.07 (0.8, 1.45)	1.05 (0.82, 1.35)	<b>1.31 (1.05, 1.63)</b>	1.08 (0.93, 1.25)	1.1 (0.98, 1.23)	1.08 (0.87, 1.34)
<b>0.75 (0.66, 0.86)</b>	<b>0.86 (0.78, 0.96)</b>	<b>3-IIV HD</b>	0.88 (0.77, 1)	1.03 (0.89, 1.19)	<b>0.71 (0.55, 0.9)</b>	<b>0.76 (0.62, 0.93)</b>	0.88 (0.78, 1)	0.93 (0.7, 1.23)	0.91 (0.7, 1.19)	1.13 (0.88, 1.44)	0.93 (0.78, 1.12)	0.95 (0.81, 1.11)	0.93 (0.74, 1.19)
<b>0.86 (0.77, 0.96)</b>	0.98 (0.91, 1.07)	1.14 (1, 1.3)	<b>3-IIV ID</b>	<b>1.18 (1.04, 1.32)</b>	0.81 (0.64, 1.01)	0.86 (0.72, 1.04)	1.01 (0.9, 1.12)	1.06 (0.78, 1.43)	1.04 (0.82, 1.31)	<b>1.29 (1.02, 1.62)</b>	1.06 (0.9, 1.26)	1.08 (0.94, 1.24)	1.06 (0.85, 1.34)
<b>0.73 (0.65, 0.82)</b>	<b>0.84 (0.76, 0.92)</b>	0.97 (0.84, 1.12)	<b>0.85 (0.75, 0.96)</b>	<b>3-IIV MF59/AS03-adj</b>	<b>0.68 (0.54, 0.86)</b>	<b>0.73 (0.61, 0.89)</b>	<b>0.85 (0.76, 0.96)</b>	0.9 (0.66, 1.22)	0.88 (0.68, 1.15)	1.09 (0.88, 1.35)	0.9 (0.76, 1.08)	0.92 (0.79, 1.07)	0.9 (0.72, 1.15)
1.07 (0.85, 1.36)	1.22 (0.98, 1.53)	<b>1.41 (1.11, 1.81)</b>	1.24 (0.99, 1.57)	<b>1.46 (1.17, 1.84)</b>	<b>3-IIV vir/lip-adj</b>	1.07 (0.81, 1.43)	1.25 (0.99, 1.58)	1.31 (0.91, 1.91)	1.29 (0.93, 1.79)	<b>1.6 (1.17, 2.17)</b>	<b>1.32 (1.01, 1.73)</b>	<b>1.34 (1.04, 1.73)</b>	1.32 (0.97, 1.8)
1 (0.85, 1.17)	1.14 (0.96, 1.35)	<b>1.32 (1.08, 1.61)</b>	1.16 (0.96, 1.39)	<b>1.37 (1.12, 1.65)</b>	0.93 (0.7, 1.23)	<b>3-RIV</b>	1.17 (0.97, 1.39)	1.23 (0.87, 1.72)	1.2 (0.89, 1.62)	<b>1.49 (1.12, 1.97)</b>	1.24 (0.99, 1.53)	<b>1.25 (1.03, 1.52)</b>	1.23 (0.94, 1.61)
<b>0.85 (0.78, 0.94)</b>	0.98 (0.91, 1.05)	1.13 (1, 1.28)	0.99 (0.89, 1.11)	<b>1.17 (1.04, 1.32)</b>	0.8 (0.63, 1.01)	0.86 (0.72, 1.03)	<b>4-IIV</b>	1.05 (0.78, 1.42)	1.03 (0.8, 1.33)	<b>1.28 (1.02, 1.6)</b>	1.06 (0.92, 1.22)	1.07 (0.94, 1.23)	1.06 (0.85, 1.33)
0.81 (0.6, 1.1)	0.93 (0.69, 1.25)	1.08 (0.81, 1.42)	0.95 (0.7, 1.28)	1.11 (0.82, 1.52)	0.76 (0.52, 1.1)	0.82 (0.58, 1.15)	0.95 (0.71, 1.28)	<b>4-IIV-HD</b>	0.98 (0.67, 1.44)	1.22 (0.84, 1.75)	1.01 (0.73, 1.39)	1.02 (0.74, 1.4)	1.01 (0.7, 1.45)
0.83 (0.64, 1.08)	0.95 (0.74, 1.22)	1.1 (0.84, 1.43)	0.97 (0.76, 1.22)	1.14 (0.87, 1.48)	0.78 (0.56, 1.08)	0.83 (0.62, 1.13)	0.97 (0.75, 1.25)	1.02 (0.69, 1.5)	<b>4-IIV-ID</b>	1.24 (0.89, 1.73)	1.03 (0.77, 1.37)	1.04 (0.79, 1.37)	1.03 (0.74, 1.43)
<b>0.67 (0.53, 0.85)</b>	<b>0.76 (0.61, 0.96)</b>	0.89 (0.69, 1.13)	<b>0.78 (0.62, 0.98)</b>	0.92 (0.74, 1.14)	<b>0.63 (0.46, 0.85)</b>	<b>0.67 (0.51, 0.89)</b>	<b>0.78 (0.62, 0.98)</b>	0.82 (0.57, 1.19)	0.81 (0.58, 1.12)	<b>4-IIV MF59/AS03-adj</b>	0.83 (0.64, 1.08)	0.84 (0.66, 1.08)	0.83 (0.61, 1.13)
<b>0.81 (0.7, 0.94)</b>	0.92 (0.8, 1.07)	1.07 (0.89, 1.28)	0.94 (0.79, 1.11)	1.11 (0.93, 1.32)	<b>0.76 (0.58, 0.99)</b>	0.81 (0.65, 1.01)	0.95 (0.82, 1.09)	0.99 (0.72, 1.38)	0.97 (0.73, 1.3)	1.21 (0.93, 1.57)	<b>4-RIV</b>	1.01 (0.85, 1.22)	1 (0.77, 1.3)
<b>0.79 (0.71, 0.9)</b>	0.91 (0.81, 1.02)	1.05 (0.9, 1.23)	0.93 (0.8, 1.06)	1.09 (0.94, 1.26)	<b>0.75 (0.58, 0.96)</b>	<b>0.8 (0.66, 0.97)</b>	0.93 (0.81, 1.06)	0.98 (0.72, 1.34)	0.96 (0.73, 1.26)	1.19 (0.93, 1.53)	0.99 (0.82, 1.18)	<b>3-LAIV</b>	0.98 (0.82, 1.18)
0.81 (0.65, 1)	0.93 (0.75, 1.15)	1.07 (0.84, 1.36)	0.94 (0.75, 1.18)	1.11 (0.87, 1.4)	0.76 (0.55, 1.03)	0.81 (0.62, 1.06)	0.95 (0.75, 1.18)	0.99 (0.69, 1.43)	0.97 (0.7, 1.35)	1.21 (0.89, 1.64)	1 (0.77, 1.29)	1.02 (0.85, 1.22)	<b>4-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

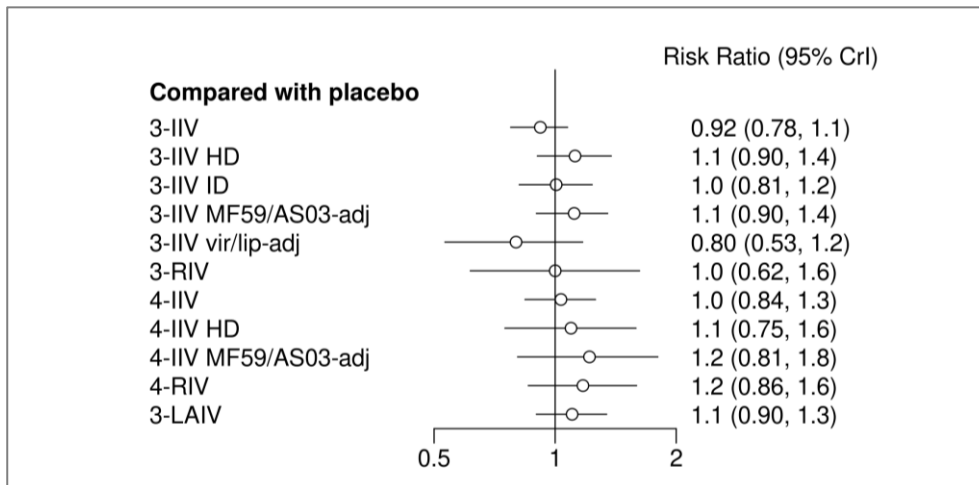
**The elderly,  $\geq 61$  years: Network geometry of any systemic adverse event \***



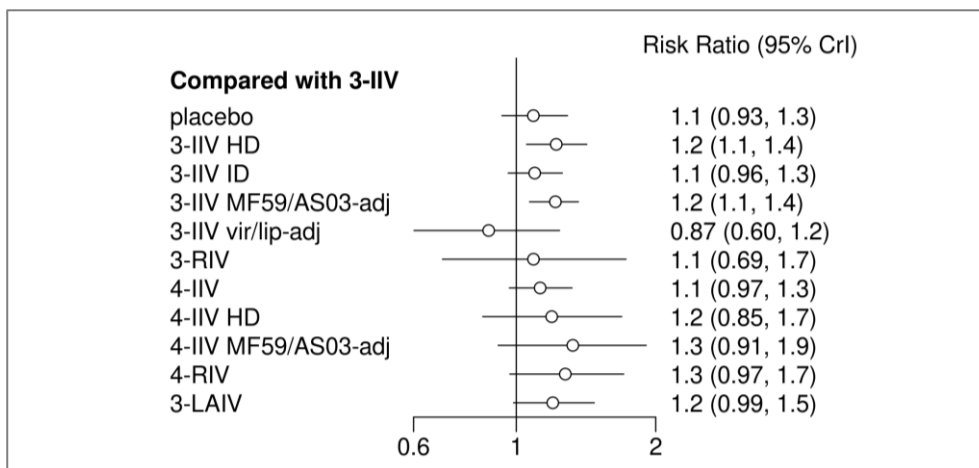
The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**The elderly,  $\geq 61$  years: Forest plot of any systemic adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

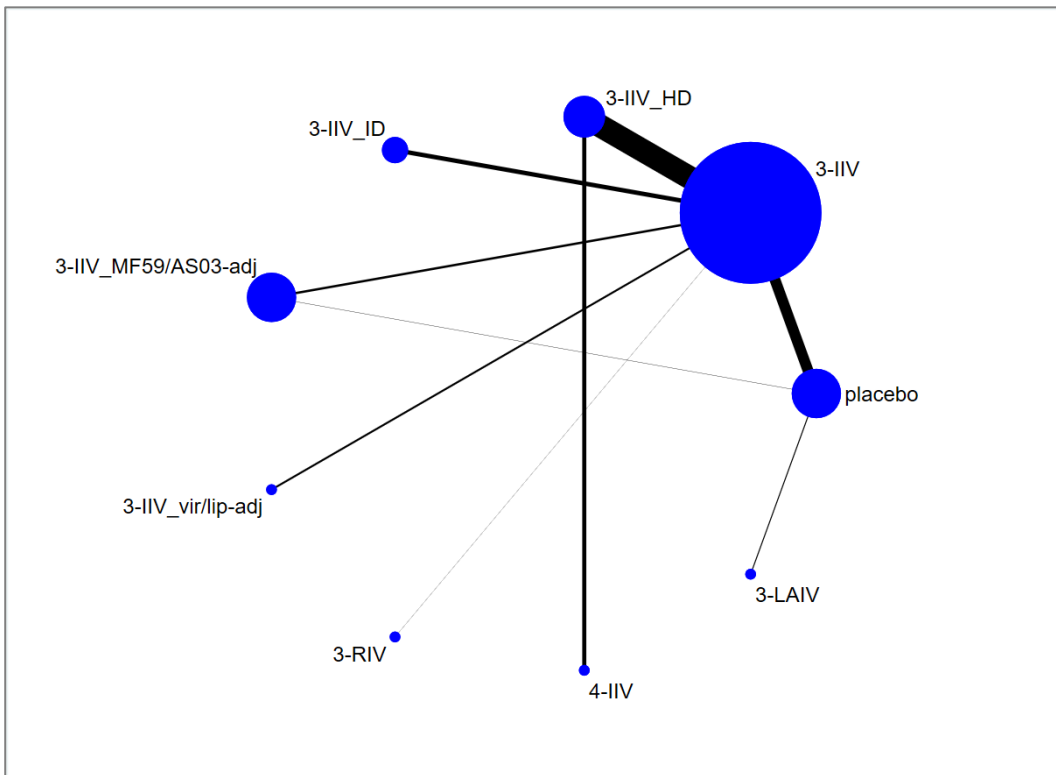
**The elderly, ≥61 years: Netleague analysis of any systemic adverse event\***

<b>placebo</b>	0.92 (0.78, 1.07)	1.12 (0.9, 1.38)	1.01 (0.81, 1.24)	1.12 (0.9, 1.35)	0.8 (0.53, 1.17)	1 (0.62, 1.62)	1.03 (0.84, 1.26)	1.1 (0.75, 1.59)	1.22 (0.81, 1.8)	1.17 (0.86, 1.59)	1.1 (0.9, 1.34)
1.09 (0.93, 1.29)	<b>3-IIV</b>	<b>1.22 (1.05, 1.42)</b>	1.1 (0.96, 1.26)	<b>1.21 (1.07, 1.36)</b>	0.87 (0.6, 1.24)	1.09 (0.69, 1.73)	1.13 (0.97, 1.32)	1.19 (0.85, 1.69)	1.32 (0.91, 1.91)	1.28 (0.97, 1.71)	1.2 (0.99, 1.47)
0.89 (0.73, 1.11)	<b>0.82 (0.7, 0.95)</b>	<b>3-IIV HD</b>	0.9 (0.75, 1.08)	1 (0.82, 1.19)	0.71 (0.48, 1.04)	0.89 (0.55, 1.45)	0.92 (0.77, 1.11)	0.98 (0.72, 1.33)	1.09 (0.73, 1.6)	1.05 (0.78, 1.42)	0.98 (0.77, 1.26)
0.99 (0.81, 1.23)	0.91 (0.8, 1.04)	1.11 (0.92, 1.34)	<b>3-IIV ID</b>	1.11 (0.93, 1.29)	0.8 (0.54, 1.14)	0.99 (0.62, 1.6)	1.03 (0.84, 1.25)	1.09 (0.76, 1.56)	1.21 (0.82, 1.76)	1.17 (0.86, 1.59)	1.09 (0.86, 1.4)
0.9 (0.74, 1.11)	<b>0.82 (0.73, 0.94)</b>	1 (0.84, 1.23)	0.9 (0.77, 1.07)	<b>3-IIV MF59/AS03-adj</b>	0.72 (0.5, 1.03)	0.9 (0.56, 1.45)	0.93 (0.77, 1.14)	0.98 (0.69, 1.43)	1.09 (0.77, 1.55)	1.05 (0.79, 1.45)	0.99 (0.79, 1.27)
1.25 (0.85, 1.88)	1.15 (0.81, 1.66)	1.4 (0.96, 2.09)	1.26 (0.88, 1.84)	1.39 (0.98, 2.01)	<b>3-IIV vir/lip-adj</b>	1.26 (0.7, 2.26)	1.29 (0.88, 1.93)	1.37 (0.84, 2.26)	1.53 (0.92, 2.53)	1.47 (0.94, 2.33)	1.38 (0.92, 2.1)
1 (0.62, 1.63)	0.92 (0.58, 1.44)	1.12 (0.69, 1.8)	1.01 (0.62, 1.61)	1.11 (0.69, 1.77)	0.8 (0.44, 1.42)	<b>3-RIV</b>	1.03 (0.64, 1.67)	1.09 (0.62, 1.92)	1.22 (0.67, 2.16)	1.17 (0.68, 2.01)	1.1 (0.67, 1.81)
0.97 (0.79, 1.19)	0.89 (0.76, 1.04)	1.08 (0.9, 1.3)	0.97 (0.8, 1.19)	1.08 (0.88, 1.3)	0.77 (0.52, 1.13)	0.97 (0.6, 1.57)	<b>4-IIV</b>	1.06 (0.74, 1.52)	1.18 (0.79, 1.74)	1.13 (0.9, 1.45)	1.07 (0.84, 1.36)
0.91 (0.63, 1.33)	0.84 (0.59, 1.18)	1.02 (0.75, 1.39)	0.92 (0.64, 1.32)	1.02 (0.7, 1.45)	0.73 (0.44, 1.19)	0.91 (0.52, 1.62)	0.94 (0.66, 1.35)	<b>4-IIV-HD</b>	1.11 (0.67, 1.82)	1.07 (0.7, 1.65)	1.01 (0.68, 1.5)
0.82 (0.56, 1.24)	0.76 (0.52, 1.09)	0.92 (0.62, 1.38)	0.83 (0.57, 1.22)	0.92 (0.65, 1.29)	0.66 (0.4, 1.09)	0.82 (0.46, 1.49)	0.85 (0.57, 1.27)	0.9 (0.55, 1.5)	<b>4-IIV MF59/AS03-adj</b>	0.96 (0.61, 1.54)	0.91 (0.6, 1.38)
0.85 (0.63, 1.17)	0.78 (0.59, 1.03)	0.96 (0.71, 1.28)	0.86 (0.63, 1.17)	0.95 (0.69, 1.27)	0.68 (0.43, 1.07)	0.85 (0.5, 1.46)	0.88 (0.69, 1.12)	0.93 (0.61, 1.43)	1.04 (0.65, 1.63)	<b>4-RIV</b>	0.94 (0.67, 1.32)
0.91 (0.74, 1.11)	0.83 (0.68, 1.01)	1.02 (0.79, 1.3)	0.91 (0.72, 1.16)	1.01 (0.79, 1.27)	0.73 (0.48, 1.09)	0.91 (0.55, 1.5)	0.94 (0.73, 1.19)	0.99 (0.67, 1.47)	1.1 (0.72, 1.66)	1.06 (0.76, 1.5)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

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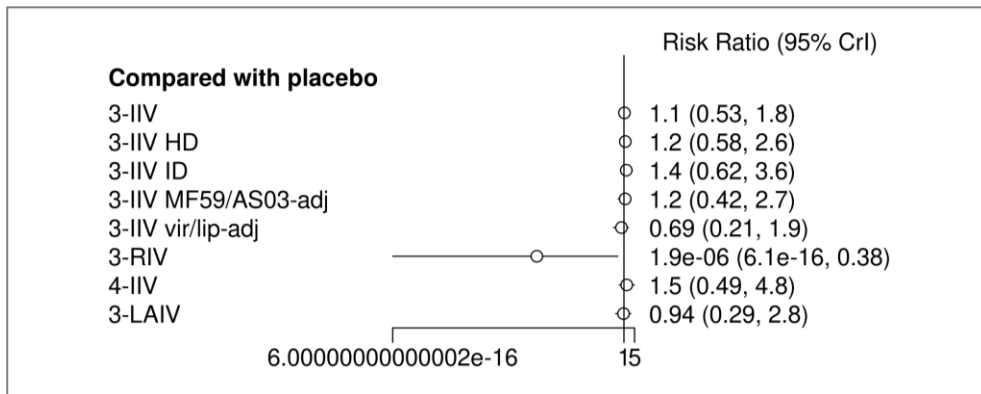
**Adult and the elderly, immunocompromised-cancer participants: Network geometry of any systemic adverse event\***



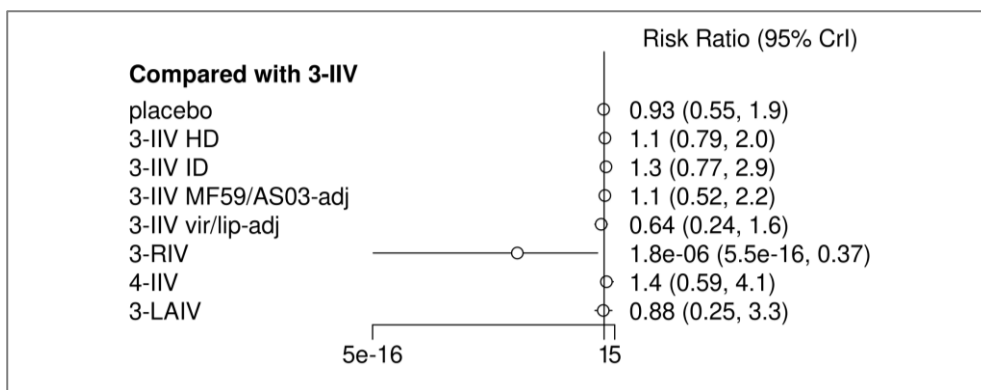
The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

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**Adult and the elderly, immunocompromised-cancer participants: Forest plots of any systemic adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



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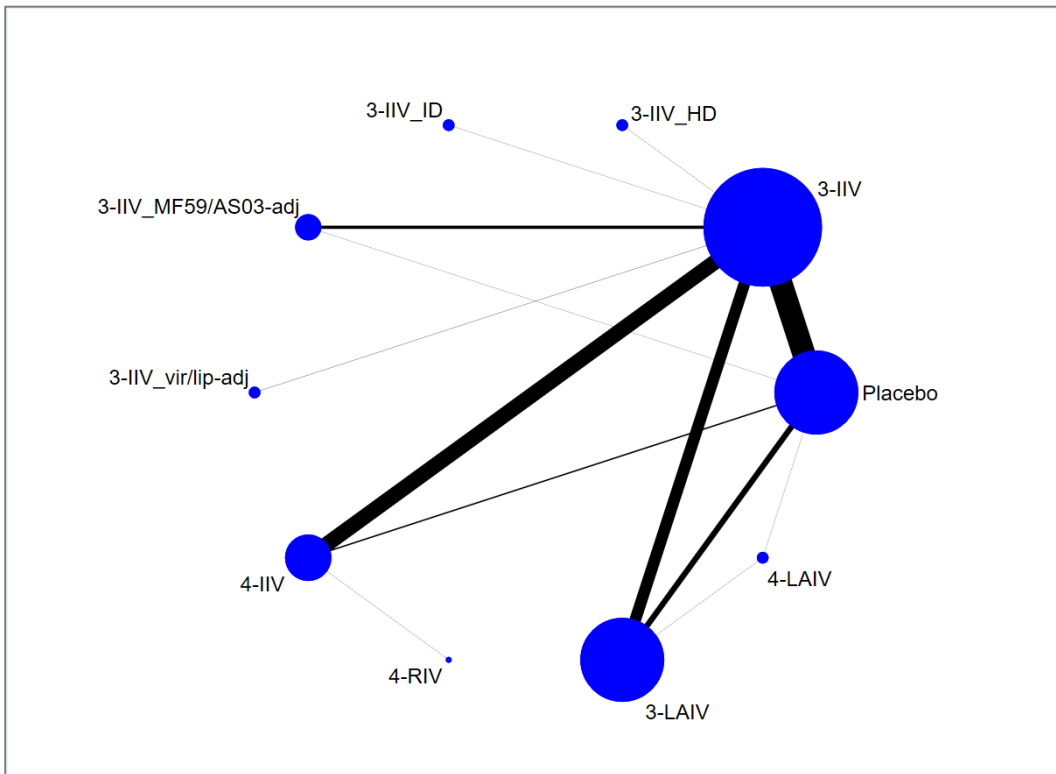
**Adult and the elderly, immunocompromised-cancer participants: Netleague analysis of any systemic adverse event\***

<b>placebo</b>	1.08 (0.53, 1.83)	1.22 (0.58, 2.63)	1.42 (0.62, 3.62)	1.2 (0.42, 2.72)	0.69 (0.21, 1.95)	<b>0 (0, 0.38)</b>	1.52 (0.49, 4.76)	0.94 (0.29, 2.83)
0.93 (0.55, 1.89)	<b>3-IIV</b>	1.13 (0.79, 1.98)	1.33 (0.77, 2.91)	1.12 (0.52, 2.24)	0.64 (0.24, 1.65)	<b>0 (0, 0.37)</b>	1.42 (0.59, 4.07)	0.88 (0.25, 3.29)
0.82 (0.38, 1.74)	0.88 (0.51, 1.26)	<b>3-IIV-HD</b>	1.16 (0.56, 2.68)	0.98 (0.36, 2.12)	0.56 (0.18, 1.47)	<b>0 (0, 0.31)</b>	1.24 (0.53, 2.9)	0.77 (0.19, 2.88)
0.7 (0.28, 1.61)	0.75 (0.34, 1.3)	0.86 (0.37, 1.8)	<b>3-IIV-ID</b>	0.84 (0.27, 2.03)	0.48 (0.13, 1.36)	<b>0 (0, 0.27)</b>	1.07 (0.33, 3.21)	0.66 (0.15, 2.58)
0.83 (0.37, 2.4)	0.89 (0.45, 1.92)	1.02 (0.47, 2.75)	1.19 (0.49, 3.77)	<b>3-IIV MF59/AS03-adj</b>	0.57 (0.18, 1.97)	<b>0 (0, 0.35)</b>	1.26 (0.43, 4.9)	0.78 (0.2, 3.65)
1.46 (0.51, 4.86)	1.56 (0.61, 4.09)	1.79 (0.68, 5.52)	2.09 (0.74, 7.5)	1.77 (0.51, 5.59)	<b>3-IIV vir/lip-adj</b>	<b>0 (0, 0.62)</b>	2.22 (0.63, 9.28)	1.37 (0.29, 7.08)
<b>540422.99 (2.6, 1641730164398524)</b>	<b>543516.4 (2.7, 1808085701935791)</b>	<b>640275.63 (3.2, 2125998396124094)</b>	<b>734852.91 (3.7, 2394122047876191)</b>	<b>657357.39 (2.88, 2209682118404833)</b>	<b>335286.59 (1.62, 1150286171477600)</b>	<b>3-RIV</b>	<b>808442.48 (3.79, 2574872698940468)</b>	<b>483429.27 (2.2, 1466279156913650)</b>
0.66 (0.21, 2.03)	0.71 (0.25, 1.7)	0.8 (0.35, 1.88)	0.93 (0.31, 3.07)	0.79 (0.2, 2.33)	0.45 (0.11, 1.58)	<b>0 (0, 0.26)</b>	<b>4-IIV</b>	0.62 (0.12, 2.92)
1.07 (0.35, 3.45)	1.14 (0.3, 4.02)	1.3 (0.35, 5.18)	1.52 (0.39, 6.73)	1.28 (0.27, 5.04)	0.73 (0.14, 3.44)	<b>0 (0, 0.46)</b>	1.62 (0.34, 8.21)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

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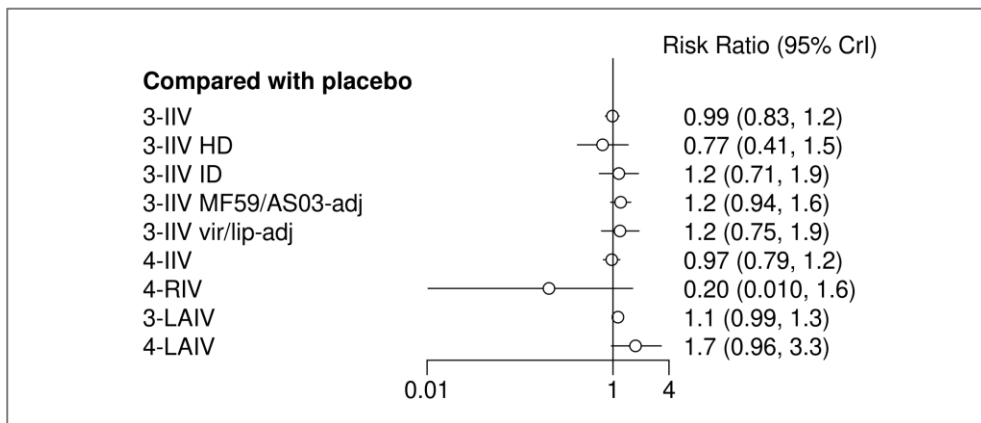
**All children: Network geometry of any systemic adverse event\***



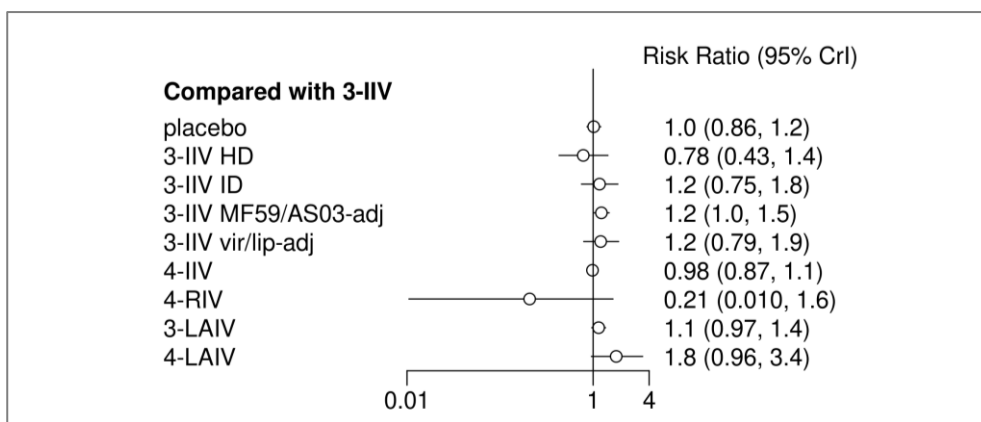
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**All children: Forest plots of any systemic adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



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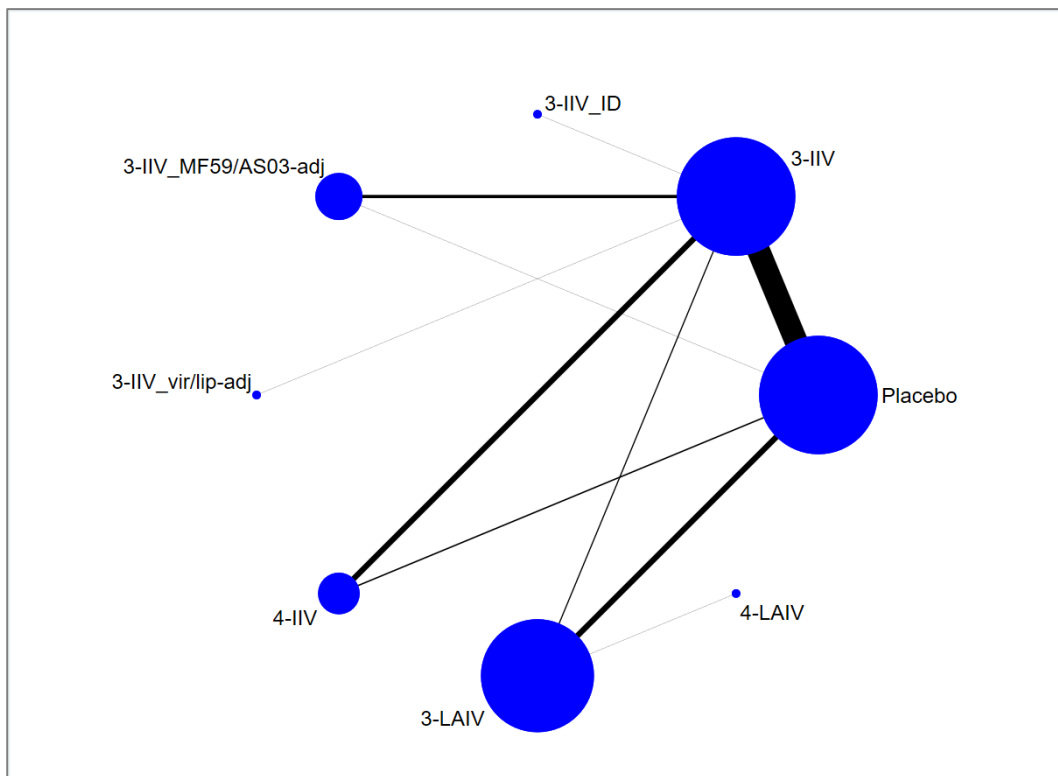
All children: Netleague analysis of any systemic adverse event\*

<b>placebo</b>	0.99 (0.83, 1.16)	0.77 (0.41, 1.45)	1.15 (0.71, 1.87)	1.21 (0.94, 1.55)	1.19 (0.75, 1.9)	0.97 (0.79, 1.18)	0.2 (0.01, 1.63)	1.13 (0.99, 1.28)	1.75 (0.96, 3.3)
1.01 (0.86, 1.21)	<b>3-IIV</b>	0.78 (0.43, 1.44)	1.17 (0.75, 1.85)	<b>1.23 (1.02, 1.49)</b>	1.21 (0.79, 1.88)	0.98 (0.87, 1.12)	0.21 (0.01, 1.64)	1.15 (0.97, 1.36)	1.77 (0.96, 3.41)
1.3 (0.69, 2.41)	1.28 (0.69, 2.32)	<b>3-IIV HD</b>	1.5 (0.7, 3.19)	1.57 (0.83, 2.94)	1.54 (0.73, 3.24)	1.26 (0.67, 2.31)	0.26 (0.01, 2.28)	1.46 (0.77, 2.72)	2.27 (0.95, 5.45)
0.87 (0.53, 1.4)	0.85 (0.54, 1.33)	0.67 (0.31, 1.42)	<b>3-IIV ID</b>	1.05 (0.64, 1.71)	1.03 (0.55, 1.94)	0.84 (0.52, 1.34)	0.18 (0.01, 1.48)	0.98 (0.6, 1.58)	1.51 (0.7, 3.35)
0.83 (0.64, 1.06)	<b>0.82 (0.67, 0.98)</b>	0.64 (0.34, 1.2)	0.95 (0.59, 1.56)	<b>3-IIV MF59/AS03-adj</b>	0.98 (0.62, 1.58)	0.8 (0.64, 1)	0.17 (0.01, 1.34)	0.93 (0.72, 1.2)	1.44 (0.76, 2.84)
0.84 (0.53, 1.33)	0.83 (0.53, 1.26)	0.65 (0.31, 1.37)	0.97 (0.52, 1.81)	1.02 (0.63, 1.62)	<b>3-IIV vir/lip-adj</b>	0.82 (0.52, 1.26)	0.17 (0.01, 1.41)	0.95 (0.59, 1.5)	1.47 (0.69, 3.2)
1.03 (0.84, 1.27)	1.02 (0.9, 1.15)	0.8 (0.43, 1.49)	1.19 (0.75, 1.91)	1.25 (1, 1.57)	1.22 (0.79, 1.94)	<b>4-IIV</b>	0.21 (0.01, 1.66)	1.17 (0.95, 1.43)	1.8 (0.96, 3.5)
4.89 (0.61, 97.48)	4.81 (0.61, 95.31)	3.8 (0.44, 76.63)	5.66 (0.68, 114.54)	5.91 (0.75, 116.85)	5.82 (0.71, 114.47)	4.73 (0.6, 93.43)	<b>4-RIV</b>	5.52 (0.7, 109.88)	<b>8.6 (1.01, 184.89)</b>
0.88 (0.78, 1.01)	0.87 (0.74, 1.03)	0.68 (0.37, 1.29)	1.02 (0.63, 1.67)	1.07 (0.84, 1.38)	1.05 (0.67, 1.69)	0.86 (0.7, 1.05)	0.18 (0.01, 1.44)	<b>3-LAIV</b>	1.55 (0.85, 2.93)
0.57 (0.3, 1.04)	0.56 (0.29, 1.04)	0.44 (0.18, 1.05)	0.66 (0.3, 1.42)	0.69 (0.35, 1.32)	0.68 (0.31, 1.45)	0.56 (0.29, 1.04)	<b>0.12 (0.01, 0.99)</b>	0.65 (0.34, 1.18)	<b>4-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

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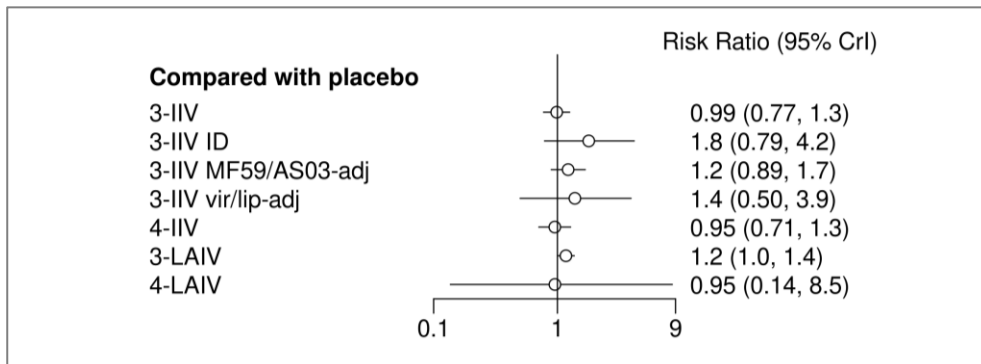
**Children, aged  $\leq 5$  years: Network geometry of any systemic adverse event\***



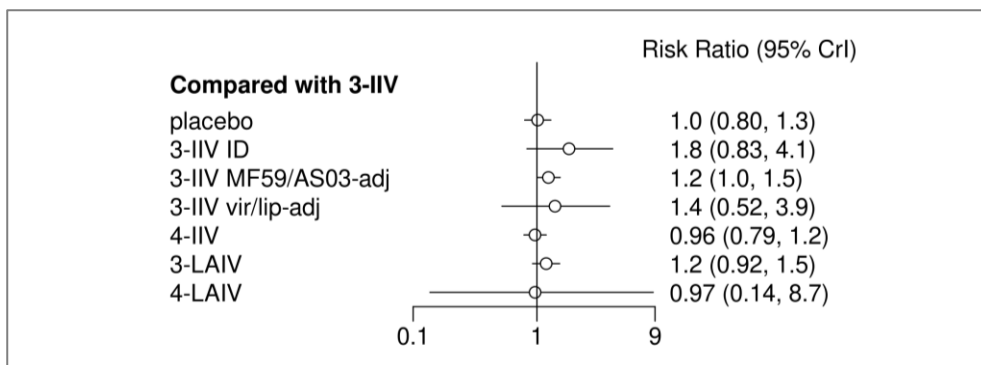
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**Children, aged ≤5 years: Forest plots of any systemic adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



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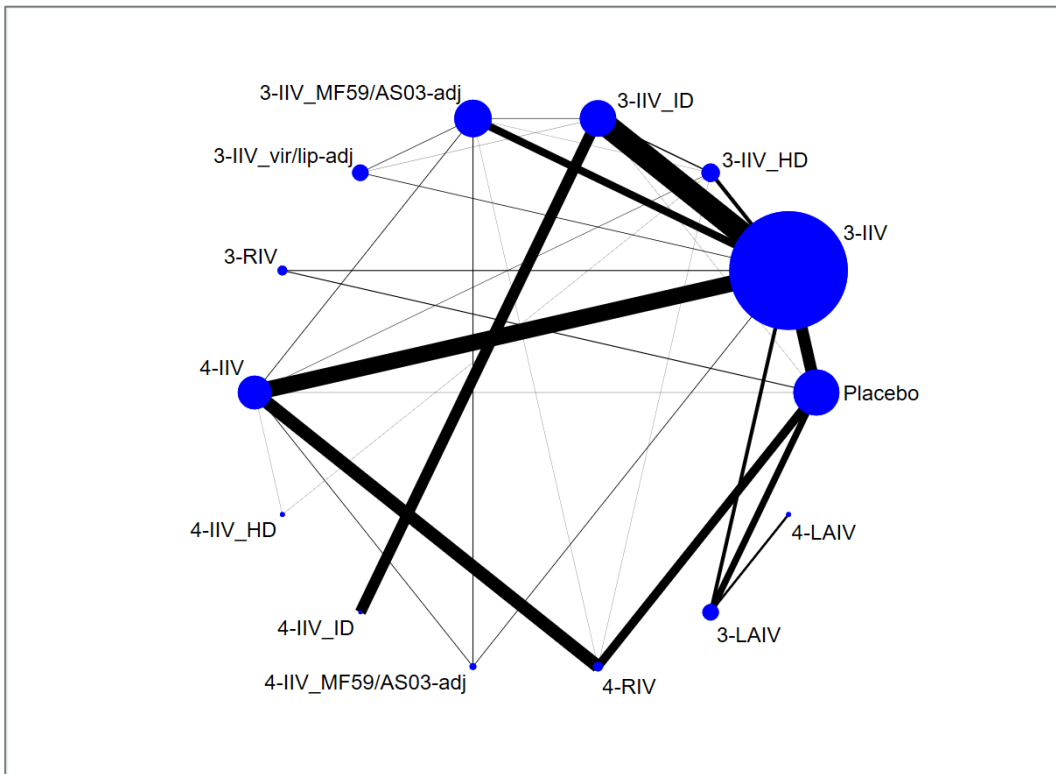
**Children, aged ≤5 years: Netleague analysis of any systemic adverse event\***

<b>placebo</b>	0.99 (0.77, 1.26)	1.79 (0.79, 4.18)	1.22 (0.89, 1.68)	1.38 (0.5, 3.94)	0.95 (0.71, 1.28)	1.17 (1, 1.37)	0.95 (0.14, 8.48)
1.01 (0.8, 1.29)	<b>3-IIV</b>	1.82 (0.83, 4.09)	1.24 (1, 1.54)	1.4 (0.52, 3.87)	0.96 (0.79, 1.19)	1.19 (0.92, 1.53)	0.97 (0.14, 8.7)
0.56 (0.24, 1.27)	0.55 (0.24, 1.2)	<b>3-IIV ID</b>	0.68 (0.29, 1.54)	0.77 (0.22, 2.76)	0.53 (0.23, 1.19)	0.65 (0.28, 1.49)	0.53 (0.07, 5.47)
0.82 (0.6, 1.12)	0.81 (0.65, 1)	1.47 (0.65, 3.4)	<b>3-IIV MF59/AS03-adj</b>	1.13 (0.41, 3.21)	0.78 (0.58, 1.05)	0.96 (0.69, 1.32)	0.78 (0.11, 7.05)
0.72 (0.25, 2)	0.71 (0.26, 1.92)	1.29 (0.36, 4.63)	0.88 (0.31, 2.43)	<b>3-IIV vir/lip-adj</b>	0.69 (0.24, 1.89)	0.85 (0.3, 2.35)	0.69 (0.08, 7.53)
1.05 (0.78, 1.41)	1.04 (0.84, 1.27)	1.88 (0.84, 4.35)	1.28 (0.96, 1.73)	1.45 (0.53, 4.1)	<b>4-IIV</b>	1.23 (0.9, 1.67)	1 (0.14, 9.13)
0.85 (0.73, 1)	0.84 (0.66, 1.08)	1.53 (0.67, 3.58)	1.04 (0.76, 1.45)	1.18 (0.43, 3.36)	0.81 (0.6, 1.11)	<b>3 LAIV</b>	0.81 (0.12, 7.16)
1.05 (0.12, 7.33)	1.03 (0.11, 7.32)	1.88 (0.18, 15.32)	1.28 (0.14, 9.15)	1.44 (0.13, 12.84)	1 (0.11, 7.11)	1.23 (0.14, 8.55)	<b>4 LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Adults and the elderly: Network geometry of any local adverse event\***

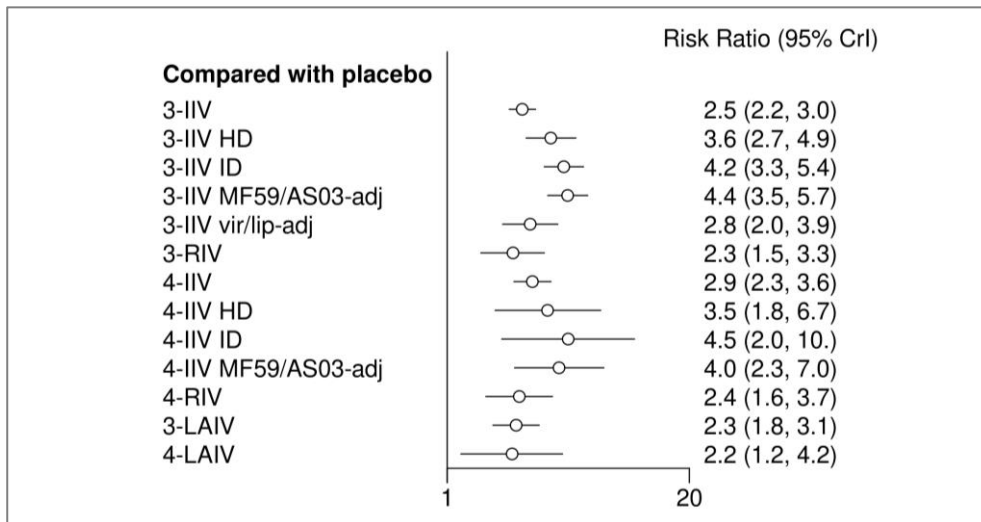


The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

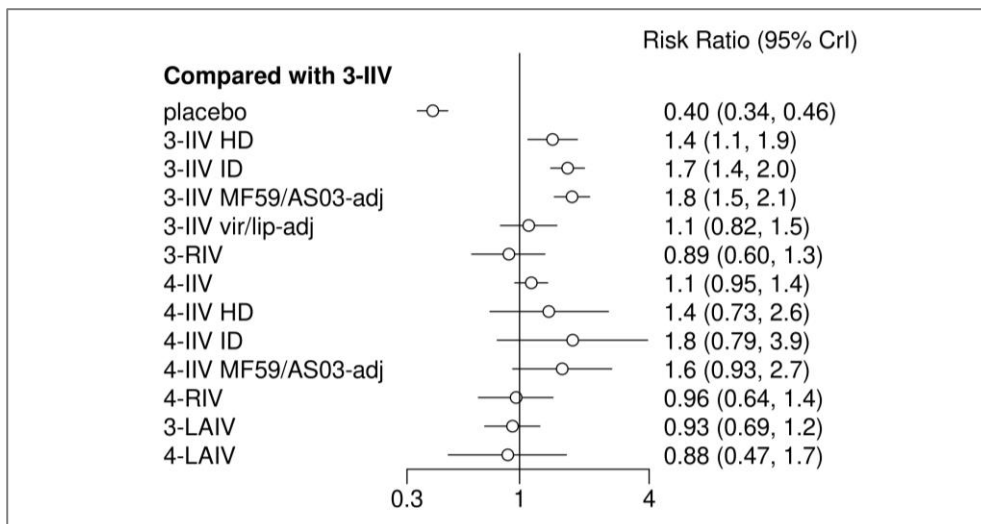
\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.



**Adults and the elderly: Forest plots of any local adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

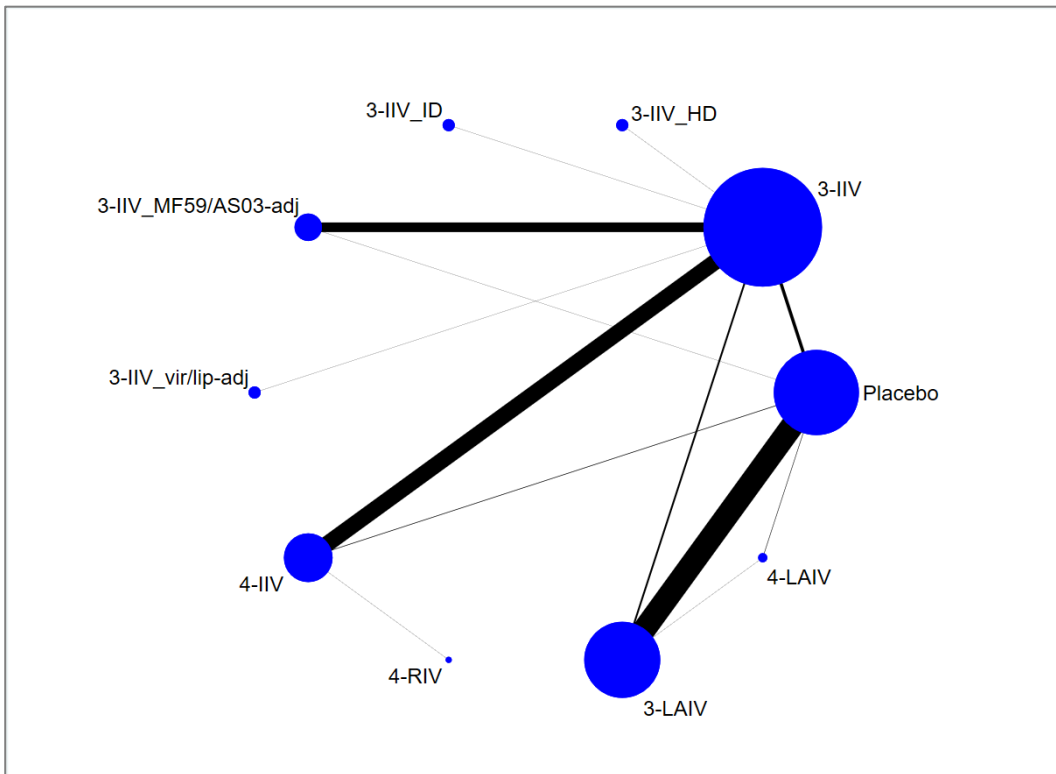
Adults and the elderly: Netleague analysis of any local adverse event\*

placebo	2.53 (2.16, 2.98)	3.6 (2.66, 4.91)	4.23 (3.32, 5.4)	4.44 (3.47, 5.69)	2.79 (1.99, 3.93)	2.26 (1.52, 3.33)	2.87 (2.29, 3.61)	3.46 (1.81, 6.68)	4.47 (1.96, 10.15)	3.99 (2.3, 6.95)	2.44 (1.61, 3.68)	2.35 (1.76, 3.12)	2.23 (1.18, 4.17)
0.4 (0.34, 0.46)	3-IIV	1.42 (1.09, 1.86)	1.67 (1.4, 2)	1.75 (1.45, 2.12)	1.1 (0.82, 1.49)	0.89 (0.6, 1.31)	1.13 (0.95, 1.35)	1.37 (0.73, 2.59)	1.77 (0.79, 3.93)	1.58 (0.93, 2.68)	0.96 (0.64, 1.43)	0.93 (0.69, 1.24)	0.88 (0.47, 1.65)
0.28 (0.2, 0.38)	0.7 (0.54, 0.91)	3-IIV HD	1.18 (0.86, 1.6)	1.23 (0.89, 1.69)	0.77 (0.52, 1.15)	0.63 (0.39, 1)	0.8 (0.6, 1.07)	0.96 (0.52, 1.8)	1.24 (0.53, 2.87)	1.11 (0.61, 1.99)	0.68 (0.43, 1.07)	0.65 (0.44, 0.96)	0.62 (0.31, 1.22)
0.24 (0.19, 0.3)	0.6 (0.5, 0.72)	0.85 (0.62, 1.17)	3-IIV ID	1.05 (0.82, 1.34)	0.66 (0.47, 0.92)	0.53 (0.35, 0.82)	0.68 (0.53, 0.87)	0.82 (0.43, 1.59)	1.06 (0.48, 2.31)	0.94 (0.54, 1.64)	0.58 (0.37, 0.89)	0.55 (0.39, 0.78)	0.53 (0.27, 1.01)
0.23 (0.18, 0.29)	0.57 (0.47, 0.69)	0.81 (0.59, 1.12)	0.95 (0.75, 1.22)	3-IIV MF59/AS03-adj	0.63 (0.46, 0.86)	0.51 (0.33, 0.78)	0.65 (0.5, 0.83)	0.78 (0.41, 1.52)	1.01 (0.44, 2.29)	0.9 (0.53, 1.52)	0.55 (0.35, 0.85)	0.53 (0.37, 0.75)	0.5 (0.26, 0.97)
0.36 (0.25, 0.5)	0.91 (0.67, 1.23)	1.29 (0.87, 1.92)	1.52 (1.09, 2.11)	1.59 (1.16, 2.18)	3-IIV vir/lip-adj	0.81 (0.49, 1.32)	1.03 (0.73, 1.45)	1.24 (0.62, 2.51)	1.6 (0.68, 3.75)	1.43 (0.79, 2.6)	0.87 (0.53, 1.43)	0.84 (0.55, 1.28)	0.8 (0.4, 1.6)
0.44 (0.3, 0.66)	1.12 (0.76, 1.67)	1.6 (1, 2.57)	1.88 (1.23, 2.89)	1.97 (1.28, 3.05)	1.24 (0.76, 2.03)	3-RIV	1.27 (0.83, 1.95)	1.53 (0.73, 3.25)	1.98 (0.81, 4.86)	1.77 (0.92, 3.44)	1.08 (0.63, 1.87)	1.04 (0.65, 1.67)	0.99 (0.48, 2.07)
0.35 (0.28, 0.44)	0.88 (0.74, 1.05)	1.26 (0.94, 1.68)	1.48 (1.15, 1.89)	1.55 (1.2, 1.99)	0.97 (0.69, 1.37)	0.79 (0.51, 1.2)	4-IIV	1.21 (0.65, 2.28)	1.56 (0.68, 3.53)	1.39 (0.81, 2.4)	0.85 (0.58, 1.24)	0.82 (0.58, 1.15)	0.78 (0.4, 1.49)
0.29 (0.15, 0.55)	0.73 (0.39, 1.37)	1.04 (0.55, 1.94)	1.22 (0.63, 2.35)	1.28 (0.66, 2.46)	0.81 (0.4, 1.62)	0.65 (0.31, 1.37)	0.83 (0.44, 1.54)	4-IIV HD	1.29 (0.46, 3.58)	1.15 (0.51, 2.59)	0.7 (0.34, 1.45)	0.68 (0.33, 1.35)	0.64 (0.26, 1.57)
0.22 (0.1, 0.51)	0.57 (0.25, 1.27)	0.81 (0.35, 1.88)	0.95 (0.43, 2.08)	0.99 (0.44, 2.27)	0.62 (0.27, 1.46)	0.51 (0.21, 1.24)	0.64 (0.28, 1.47)	0.78 (0.28, 2.16)	4-IIV ID	0.89 (0.34, 2.34)	0.55 (0.22, 1.34)	0.53 (0.22, 1.24)	0.5 (0.18, 1.39)
0.25 (0.14, 0.43)	0.63 (0.37, 1.08)	0.9 (0.5, 1.63)	1.06 (0.61, 1.85)	1.11 (0.66, 1.87)	0.7 (0.39, 1.27)	0.57 (0.29, 1.09)	0.72 (0.42, 1.24)	0.87 (0.39, 1.97)	1.12 (0.43, 2.93)	4-IIV MF59/AS03-adj	0.61 (0.32, 1.17)	0.59 (0.32, 1.07)	0.56 (0.24, 1.27)
0.41 (0.27, 0.62)	1.04 (0.7, 1.55)	1.48 (0.93, 2.35)	1.73 (1.12, 2.7)	1.82 (1.18, 2.82)	1.14 (0.7, 1.89)	0.93 (0.53, 1.6)	1.18 (0.81, 1.73)	1.42 (0.69, 2.96)	1.83 (0.75, 4.5)	1.64 (0.85, 3.17)	4-RIV	0.96 (0.59, 1.57)	0.91 (0.44, 1.91)
0.43 (0.32, 0.57)	1.08 (0.8, 1.45)	1.53 (1.04, 2.29)	1.8 (1.28, 2.55)	1.89 (1.34, 2.69)	1.19 (0.78, 1.81)	0.96 (0.6, 1.54)	1.22 (0.87, 1.72)	1.48 (0.74, 2.99)	1.9 (0.81, 4.49)	1.7 (0.93, 3.14)	1.04 (0.64, 1.69)	3-LAIV	0.95 (0.54, 1.66)
0.45 (0.24, 0.84)	1.13 (0.61, 2.14)	1.61 (0.82, 3.23)	1.9 (0.99, 3.68)	1.99 (1.03, 3.85)	1.25 (0.62, 2.52)	1.01 (0.48, 2.1)	1.29 (0.67, 2.48)	1.55 (0.64, 3.82)	2 (0.72, 5.58)	1.79 (0.79, 4.1)	1.09 (0.52, 2.29)	1.05 (0.6, 1.84)	4-LAIV

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

\* **Placebo**: placebo/no vaccine; **3-IIV**: trivalent inactivated intramuscular; **3-IIV HD**: trivalent inactivated high dose intramuscular; **3-IIV ID**: trivalent inactivated intradermal; **3-IIV MF59/AS03-adj**: trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj**: trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV**: trivalent recombinant intramuscular; **4-IIV**: quadrivalent inactivated intramuscular; **4-IIV HD**: quadrivalent inactivated high dose intramuscular; **4-IIV ID**: quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj**: quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj**: quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV**: quadrivalent recombinant intramuscular; **3-LAIV**: trivalent live attenuated intranasal; **4-LAIV**: quadrivalent live attenuated intranasal.

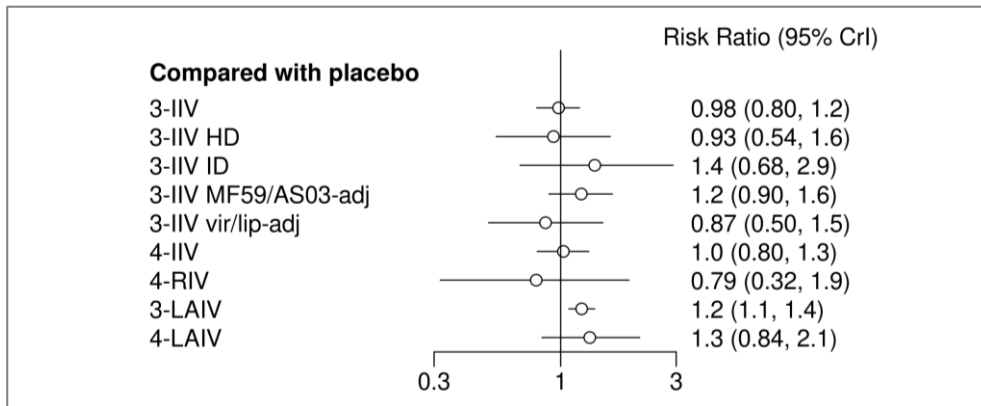
**All children: Network geometry of any local adverse event\***



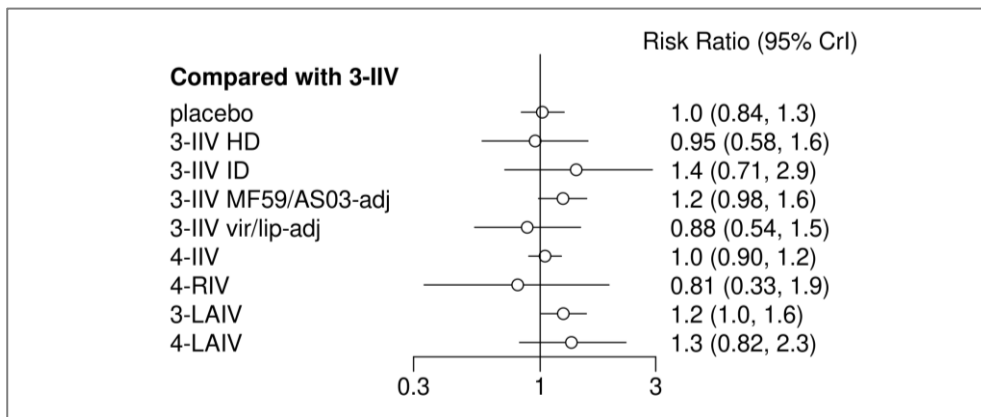
The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

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**All children: Forest plots of any local adverse event, comparison with placebo/no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV



OR <1 favors experimental vaccine compared to placebo or 3-IIV

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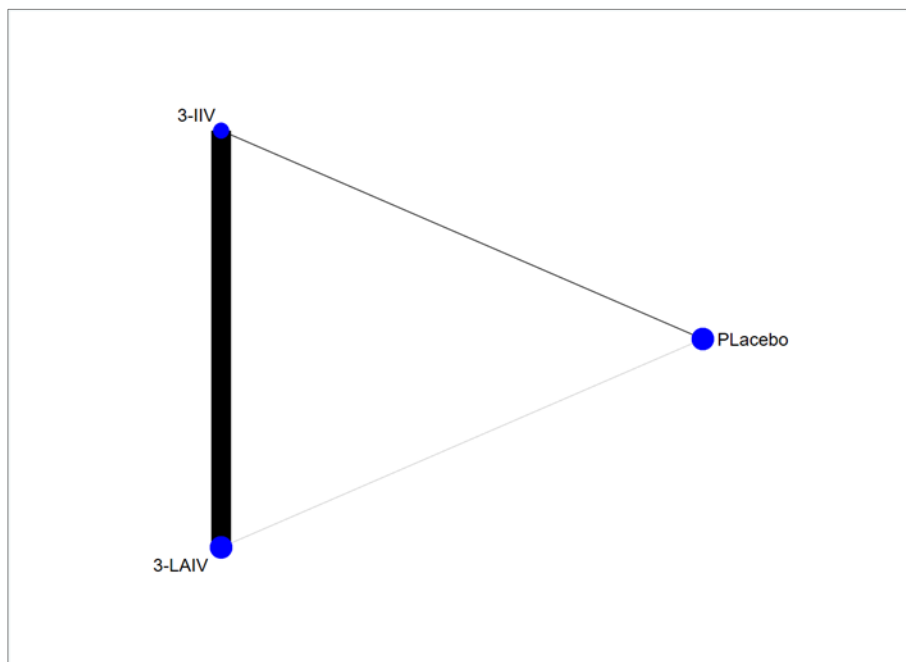
**All children: Netleague analysis of any local adverse event\***

<b>placebo</b>	0.98 (0.8, 1.2)	0.93 (0.54, 1.6)	1.38 (0.68, 2.91)	1.22 (0.9, 1.63)	0.87 (0.5, 1.49)	1.03 (0.8, 1.31)	0.79 (0.32, 1.91)	<b>1.22 (1.08, 1.38)</b>	1.32 (0.84, 2.12)
1.02 (0.84, 1.26)	<b>3-IIV</b>	0.95 (0.58, 1.57)	1.41 (0.71, 2.91)	1.24 (0.98, 1.56)	0.88 (0.54, 1.47)	1.05 (0.9, 1.22)	0.81 (0.33, 1.92)	<b>1.25 (1.01, 1.55)</b>	1.35 (0.82, 2.26)
1.07 (0.62, 1.85)	1.05 (0.64, 1.74)	<b>3-IIV HD</b>	1.48 (0.64, 3.6)	1.3 (0.75, 2.26)	0.93 (0.46, 1.91)	1.1 (0.65, 1.86)	0.85 (0.31, 2.3)	1.31 (0.76, 2.27)	1.41 (0.7, 2.92)
0.72 (0.34, 1.47)	0.71 (0.34, 1.4)	0.68 (0.28, 1.57)	<b>3-IIV ID</b>	0.88 (0.41, 1.8)	0.63 (0.26, 1.47)	0.74 (0.36, 1.49)	0.57 (0.18, 1.72)	0.88 (0.42, 1.8)	0.95 (0.4, 2.27)
0.82 (0.61, 1.12)	0.81 (0.64, 1.02)	0.77 (0.44, 1.34)	1.14 (0.56, 2.44)	<b>3-IIV MF59/AS03-adj</b>	0.71 (0.41, 1.25)	0.84 (0.64, 1.12)	0.65 (0.26, 1.6)	1 (0.74, 1.38)	1.09 (0.63, 1.92)
1.15 (0.67, 1.98)	1.13 (0.68, 1.86)	1.08 (0.52, 2.18)	1.6 (0.68, 3.85)	1.4 (0.8, 2.43)	<b>3-IIV vir/lip-adj</b>	1.18 (0.7, 2)	0.91 (0.33, 2.5)	1.41 (0.81, 2.43)	1.52 (0.75, 3.14)
0.97 (0.77, 1.25)	0.95 (0.82, 1.11)	0.91 (0.54, 1.54)	1.35 (0.67, 2.82)	1.19 (0.9, 1.56)	0.84 (0.5, 1.44)	<b>4-IIV</b>	0.77 (0.32, 1.81)	1.19 (0.93, 1.54)	1.29 (0.77, 2.2)
1.26 (0.52, 3.14)	1.24 (0.52, 3.01)	1.18 (0.43, 3.26)	1.76 (0.58, 5.44)	1.54 (0.62, 3.84)	1.09 (0.4, 3.06)	1.3 (0.55, 3.12)	<b>4-RIV</b>	1.54 (0.64, 3.84)	1.67 (0.62, 4.68)
<b>0.82 (0.72, 0.92)</b>	<b>0.8 (0.64, 0.99)</b>	0.76 (0.44, 1.32)	1.13 (0.55, 2.39)	1 (0.73, 1.35)	0.71 (0.41, 1.23)	0.84 (0.65, 1.08)	0.65 (0.26, 1.57)	<b>3-LAIV</b>	1.08 (0.68, 1.75)
0.76 (0.47, 1.19)	0.74 (0.44, 1.22)	0.71 (0.34, 1.43)	1.05 (0.44, 2.51)	0.92 (0.52, 1.58)	0.66 (0.32, 1.33)	0.78 (0.45, 1.3)	0.6 (0.21, 1.62)	0.93 (0.57, 1.47)	<b>4-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

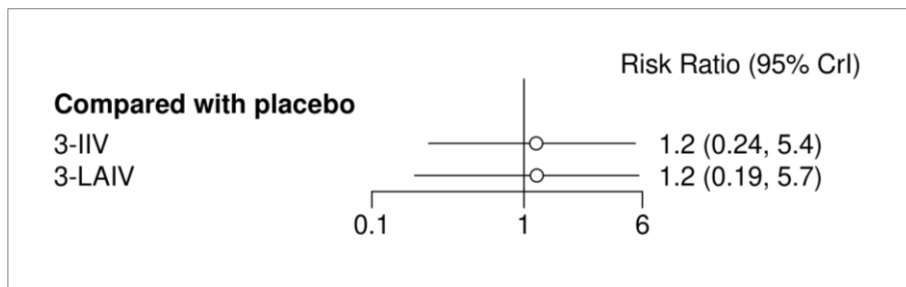
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**Children with pre-existing respiratory diseases: Network geometry of exacerbation chronic respiratory disease\***



The thickness of the line is proportional to the precision of each direct estimate, and the width of each circle is proportional to the number of studies included in the treatment.

**Children with pre-existing respiratory diseases: Forest plots of exacerbation chronic respiratory disease, comparison with placebo-no vaccine and with 3-IIV\***



OR <1 favors experimental vaccine compared to placebo or 3-IIV

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/AS03 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/AS03 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.

**Children with pre-existing respiratory diseases: Netleague analysis of exacerbation chronic respiratory disease\***

<b>placebo</b>	1.2 (0.24, 5.39)	1.21 (0.19, 5.68)
0.83 (0.19, 4.22)	<b>3-IIV</b>	1.02 (0.2, 4.26)
0.82 (0.18, 5.22)	0.98 (0.23, 5.05)	<b>3-LAIV</b>

The estimate is located at the intersection of the column-defining vaccine and the row-defining vaccine. Data are RRs (95% CrI). Significant results are in bold. In the upper triangle, comparisons of treatments should be read from right to left. An RR below 1 favors the medication on the bottom right vs. the medication on the top left in the diagonal.

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### SUCRA Adults and the elderly\*

vaccine	laboratory confirmed influenza	any systemic adverse events
3-IIV HD	0.80	0.22
3-IIV MF59/AS03-adj	0.69	0.15
3-RIV	0.67	0.87
3-IIV	0.66	0.64
3-IIV ID	0.56	0.58
4-RIV	0.49	0.40
4-IIV	0.30	0.56
3-LAIV	0.29	0.35
placebo	0.02	0.89
3-IIV vir/lip-adj		0.93
4-IIV HD		0.44
4-IIV ID		0.48
4-IIV MF59/AS03-adj		0.07
4-LAIV		0.41

### SUCRA probability any Children\*

vaccine	laboratory confirmed influenza	any systemic adverse events
3-IIV MF59/AS03-adj	0.95	
3-LAIV	0.79	0.34
4-IIV	0.47	0.66
3-IIV	0.42	0.63
4-LAIV	0.29	0.07
placebo	0.07	0.60
3-IIV HD		0.77
3-IIV ID		0.37
3-IIV vir/lip-adj		0.34
4-IIV vir/lip-adj		0.25
4-RIV		0.94

\* **Placebo:** placebo/no vaccine; **3-IIV:** trivalent inactivated intramuscular; **3-IIV HD:** trivalent inactivated high dose intramuscular; **3-IIV ID:** trivalent inactivated intradermal; **3-IIV MF59/AS03-adj:** trivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **3-IIV vir/lip-adj:** trivalent inactivated adjuvanted with Virosome/liposome intramuscular; **3-RIV:** trivalent recombinant intramuscular; **4-IIV:** quadrivalent inactivated intramuscular; **4-IIV HD:** quadrivalent inactivated high dose intramuscular; **4-IIV ID:** quadrivalent inactivated intradermal; **4-IIV MF59/AS03-adj:** quadrivalent inactivated adjuvanted with MF59/ASO3 intramuscular; **4-IIV vir/lip-adj:** quadrivalent inactivated adjuvanted with virosome/liposome intramuscular; **4-RIV:** quadrivalent recombinant intramuscular; **3-LAIV:** trivalent live attenuated intranasal; **4-LAIV:** quadrivalent live attenuated intranasal.



**Analyses of outcomes and subgroups not performed because of paucity of data**

**The elderly >61 years:** hospitalization, mortality, ILI, any local AE

**Children < 5 years:** hospitalization, mortality, ILI, any local AE, acute otitis media

**Adult immunocompromised/cancer:** hospitalization, mortality, ILI, any local AE

**Adult with pre-existing chronic respiratory disease:** laboratory confirmed influenza, hospitalization, mortality, ILI, any systemic AE, any local AE, exacerbation pre-existing chronic respiratory disease

**Children immunocompromised/cancer:** laboratory confirmed influenza, hospitalization, mortality, ILI, any systemic AE, any local AE

**Children with pre-existing chronic respiratory disease:** hospitalization, mortality, ILI, any systemic AE, any local AE