Online supplemental Table 1. List of the randomized clinical trials included in the meta-analyses on the efficacy of influenza vaccine for healthy children. The studies for which there may be some discrepancy between meta-analysis inclusion criteria and extracted data (or data exclusion) are underlined.

	Negri et al. [1]	**Manzoli et al.** [2]	**Jefferson et al.** [3]	**Rhorer et al. *** [4]	**Osterholm et al.** [5]
End date of the search (mm/yy)	12/2003	05/2005	09/2007	Not reported	02/2011
Participant's age-range (years)	≤18	≤18	<16	≤17	All ages §
Study inclusion criteria for RCTs (all meta-analyses only included studies assessing wild-strain naturally-occurring infections)	- Published in English - Published after 1990 - More than 80% of healthy individuals in the sample - At least 30 subjects per treatment group	- More than 70% of healthy individuals in the sample	- Healthy children (unless otherwise stated)	- FluMist ® LAV - Culture-confirmed symptomatic influenza cases as outcome	- Vaccines licensed in USA after 1966 for LAV and 1975 for PIV - RT-PCR or culture-confirmed influenza cases as outcome - Indexed in Medline
Study exclusion criteria	- Control group receiving another influenza vaccine		- Control group receiving another influenza vaccine	- Control group receiving no intervention	- Control group receiving another influenza vaccine or no intervention
Laboratory-confirmed cases					
Individual datasets on PIV *					
Wesselius, 1972 [6] (n=353)	Not included: date	Included – LCC-S	Not included: outcome only based on serology	Not included: vaccine type	Not included: vaccine type
Hoskins, 1973 [7] (n=724)	Not included: date	Included – LCC-S	Not included: influenza B vaccine as control	Not included: vaccine type	Not included: vaccine type
Beutner, 1979 [8] (n=875)	Not included: date	Included – LCC-S	Included – LCC-S (n=525) γ	Not included: only serological confirmation	Not included: only serological confirmation
Feldman (b), 1985 [9] (n=39)	Not included: date	Included – LCC-S	Not included: outcome only based on serology	Not included: outcome only based on serology	Not included: outcome only based on serology
Gruber (a), 1990 [10] (n=131)	Included – LCC-C α	Included – LCC-S	Included – LCC-S	Not included: mixed cultural and serological confirmation	Not included: mixed cultural and serological confirmation
Clover (b), 1991 [11] (n=136)	Included – LCC-C α	Included – LCC-S (n=95) Ω	Included – LCC-S	Not included: mixed cultural and serological confirmation	Not included: vaccine not used as licensed in USA
Piedra (b), 1991 [12] (n=131)	Not included: probably missed in the search	Included – LCC-S (n=96) Ω	Not included: unclear motivation γ	Not included: mixed cultural and serological confirmation	Not included: mixed cultural and serological confirmation
Slepushkin (b), 1993 [13] (n=140)	Included – LCC-S	Not included: incorrect randomization	Not included: incorrect randomization	Not included: vaccine type	Not included: vaccine type

Slepushkin (d), 1993 [13] (n=77)	Included – LCC-S	Not included: incorrect randomization	Not included: incorrect randomization	Not included: vaccine type	Not included: vaccine type
Khan (a), 1996 [14] (n=310)	Included – LCC-S	Included – LCC-S (n=228) Ω	Not included: outcome only based on serology	Not included: vaccine type	Not included: vaccine type
Hurwitz, 2000 [15] (n=97)	Included – LCC-S	Not included: children admitted in day care	Not included: hepatitis A vaccine as control	Not included: only serological confirmation	Not included: only serological confirmation
Neuzil (b), 2001 [16] (n=621)	Included – LCC-C, LCC-S	Included – LCC-S (n=922) Ω	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)
Neuzil (d), 2001 [16] (n=588)	Included – LCC-C, LCC-S	Included – LCC-S (joined with d)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)
Hoberman (a), 2003 [17] (n=411)	Included – LCC-C	Included – LCC-S	Included – LCC-S	Not included: vaccine type	Included – LCC-C
Hoberman (b), 2003 [17] (n=375)	Included – LCC-C	Included – LCC-S	Included – LCC-S	Not included: vaccine type	Included – LCC-C
Individual datasets on LAV *					
Feldman (a), 1985 [9] (n=43)	Not included: date	Included – LCC-S	Not included: outcome only based on serology	Not included: outcome only based on serology	Not included: outcome only based on serology
Gruber (b), 1990 [10] (n=135)	Included – LCC-C α	Not included: outcome complex to identify α	Not included: unclear motivation γ	Not included: mixed cultural and serological confirmation	Not included: mixed cultural and serological confirmation
Clover (a), 1991 [11] (n=138)	Included – LCC-C α	Included – LCC-S (n=97) Ω	Included – LCC-S	Not included: mixed cultural and serological confirmation	Not included: vaccine not used as licensed in USA
Piedra (a), 1991 [12] (n=130)	Not included: probably missed in the search	Included – LCC-S (n=95) Ω	Not included: unclear motivation γ	Not included: mixed cultural and serological confirmation	Not included: mixed cultural and serological confirmation
Slepushkin (a), 1993 [13] (n=168)	Included – LCC-S	Not included: incorrect randomization	Not included: incorrect randomization	Not included: only serological confirmation	Not included: only serological confirmation
Slepushkin (c), 1993 [13] (n=83)	Included – LCC-S	Not included: incorrect randomization	Not included: incorrect randomization	Not included: only serological confirmation	Not included: only serological confirmation
Khan (b), 1996 [14] (n=323)	Included – LCC-S	Included – LCC-S (n=242) Ω	Not included: outcome only based on serology	Not included: only serological confirmation	Not included: only serological confirmation
Belshe (a), 1998 [18] (n=1602)	Included – LCC-C	Included – LCC-S	Included – LCC-S	Included – LCC-C (n=1259) ε	Included – LCC-C
Belshe (b), 1998 [18] (n=1358)	Included – LCC-C	Included – LCC-S	Included – LCC-S	Included into a separate analysis for year two	Included – LCC-C

Neuzil (a), 2001 [16] (n=605)	Included – LCC-C, LCC-S	Included – LCC-S (n=887) Ω	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)
Neuzil (c), 2001 [16] (n=569)	Included – LCC-C, LCC-S	Included – LCC-S (joined with a)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)	Not included: influenza B vaccine as control in years 2 and 5 (data not split)
Vesikari (a), 2006 [19] (n=1784)	Not included: date	Not included: date	Included – LCC-S	Included – LCC-C	Included – LCC-C
Vesikari (b), 2006 [19] (n=1119)	Not included: date	Not included: date	Included – LCC-S	Included into a separate analysis for year two	Included – LCC-C
Tam (a), 2007 [20] (n=2764)	Not included: date	Not included: date	Not included: unclear motivation γ	Included – LCC-C	Included – LCC-C
Tam (b), 2007 [20] (n=997)	Not included: date	Not included: date	Not included: unclear motivation γ	Included into a separate analysis for year two	Included – LCC-C
Forrest, 2008 [21] (n=1041)	Not included: date	Not included: date	Not included: date	Included – LCC-C	Not included: vaccine type
Bracco, 2009 [22] (n=1886)	Not included: date	Not included: date	Not included: date	Included – LCC-C	Not included: vaccine type
Lum, 2010 [23] (n=1232)	Not included: date	Not included: date	Not included: date	Included – LCC-C	Included – LCC-C
Clinically-confirmed cases					
Individual datasets on PIV *					
Maynard (a), 1968 [24] (n=250)	Not included: date	Included	Not included: influenza B vaccine as control	Not included: outcome not considered	Not included: outcome not considered
Maynard (b), 1968 [24] (n=238)	Not included: date	Included	Not included: influenza B vaccine as control	Not included: outcome not considered	Not included: outcome not considered
Hoskins, 1973 [7] (n=724)	Not included: date	Included	Not included: influenza B vaccine as control	Not included: outcome not considered	Not included: outcome not considered
Gruber, 1990 [10] (n=131)	Included	Included	Included	Not included: outcome not considered	Not included: outcome not considered
Clover (b), 1991 [11] (n=136)	Not included: outcome complex to identify α	Not included: outcome complex to identify α	Included: data extraction unclear γ	Not included: outcome not considered	Not included: outcome not considered
Piedra (b), 1991 [12] (n=131)	Not included: probably missed in the search	Included (n=96) Ω	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (b), 1993 [25] (n=8144)	Included	Included (n=6060) Ω	Included (n=8174)	Not included: outcome not considered	Not included: outcome not considered

Rudenko (d), 1993 [25] (n=10,603)	Included	Included (n=7503) Ω	Included	Not included: outcome not considered	Not included: outcome not considered
Slepushkin (b), 1993 [13] (n=140)	Included	Not included: incorrect randomization	Not included: incorrect randomization	Not included: outcome not considered	Not included: outcome not considered
Khan (a), 1996 [14] (n=354)	Included	Included (n=260) Ω	Not included: criteria for diagnosis heterogeneous γ	Not included: outcome not considered	Not included: outcome not considered
Colombo, 2001 [26] (n=344)	Included	Included	Included	Not included: outcome not considered	Not included: outcome not considered
Marchisio, 2002 [27] (n=133)	Included	Not included: children admitted in day care	Not included: children with recurrent otitis media	Not included: outcome not considered	Not included: outcome not considered
Individual datasets on LAV *					
Slepushkin, 1974 [28] (n=1000)	Not included: date	Included	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Alexandrova, 1986 [29] (n=31,141)	Not included: date	Included	Included	Not included: outcome not considered	Not included: outcome not considered
Rudenko, 1988 [30] (n=7802)	Not included: date	Not included: unclear randomization	Included	Not included: outcome not considered	Not included: outcome not considered
Clover (a), 1991 [11] (n=138)	Not included: outcome complex to identify α	Not included: outcome complex to identify α	Included: data extraction unclear γ	Not included: outcome not considered	Not included: outcome not considered
Piedra (a), 1991 [12] (n=130)	Not included: probably missed in the search	Included (96) Ω	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (a), 1993 [25] (n=8861)	Included	Included (n=6777) Ω	Included (n=8891)	Not included: outcome not considered	Not included: outcome not considered
Rudenko (c), 1993 [25] (n=11,071)	Included	Included (n=7970) Ω	Included (n=10,971)	Not included: outcome not considered	Not included: outcome not considered
Slepushkin (a), 1993 [13] (n=168)	Included	Not included: incorrect randomization	Not included: incorrect randomization	Not included: outcome not considered	Not included: outcome not considered
Khan (b), 1996 [14] (n=383)	Included	Included (n=290) Ω	Not included: criteria for diagnosis heterogeneous γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (a), 1996 [31] (n=53,820)	Included	Included	Not included: epidemic started too early γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko, (b), 1996 [31] (n=61,559)	Included	Included	Included	Not included: outcome not considered	Not included: outcome not considered
Rudenko (c), 1996 [31] (n=1445)	Included α	Not included: missed in data extraction	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered

Rudenko, (d), 1996 [31] (n=1418)	Included α	Not included: missed in data extraction	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (e), 1996 [31] (n=1383)	Included α	Not included: missed in data extraction	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (f), 1996 [31] (n=1424)	Included α	Not included: missed in data extraction	Not included: unclear motivation γ	Not included: outcome not considered	Not included: outcome not considered
Rudenko (g-rus), 1996 [32] (n=66,980)	Not included: Russian language	Included	Included	Not included: outcome not considered	Not included: outcome not considered
Grigorieva, 2002 [33] (n=2278)	Not included: Russian language	Included	Included (n=836) γ	Not included: outcome not considered	Not included: outcome not considered

PIV=Parenteral inactivated vaccine; LAV=Live attenuated vaccine. LCC-C=laboratory-confirmed cases, with culture confirmation only; LCC-S=laboratory-confirmed cases, with culture and/or serological confirmation.

*

Name of the first author, year of publication, sample included in the analysis. In all meta-analyses, when more than one treatment arm was included into the same study, the study was divided into sub-trials. When the meta-analysis included both LAV and PIV to derive an overall estimate, the placebo group should have been equally split between the sub-trials to avoid the inclusion of placebo data twice or more times. In single meta-analyses, it is thus possible that the total number of a study is different, depending upon the meta-analysis in which it has been included: the entire placebo arm is usually included if the meta-analysis is referred to only one type of vaccine (LAV or PIV), but the placebo arm could (and should) be split by the number of sub-trials if the meta-analysis is referred to both PIV and LAV (however, Negri et al. did not split placebo data and included such data twice or even four times: i.e. Rudenko 1996 c to f). We have reported here the total sample of each trial as the placebo arm was not split. The letters under brackets are referred to the sub-trial and have been assigned by the authors of the first meta-analysis including the study.

§

Only the results on healthy children are here considered.

α

Clover 1991: LCC – Negri et al. classified this study as reporting “culture-confirmed influenza”, however only a the outcome of study was defined as clinical symptoms with viral isolation or antibody rise. Thus, the outcome should have been classified as LCC-S. CCC – These data were reported in Table 7 and the outcome was not mentioned in the text: it was thus difficult to identify and probably missed by the authors.

Gruber 1990: Negri et al. classified this study as reporting “culture-confirmed influenza”, however the outcome of the study was defined as clinical symptoms with viral isolation or antibody rise. Thus, the outcome should have been classified as LCC-S. Manzoli et al. did not identify the outcome LCC for LAV: it was unclearly reported once in the text, with no raw numbers, and not mentioned anymore in the Results, Discussion, and tables.

Rudenko (c to f) 1996: Placebo data were included four times in the overall analysis by Negri et al.

Ω

Because the meta-analysis was referred to both LAV and PIV, authors correctly extracted the data splitting the placebo arm into two, avoiding data replication.

ε

Only data for children <72 months have been included.

γ

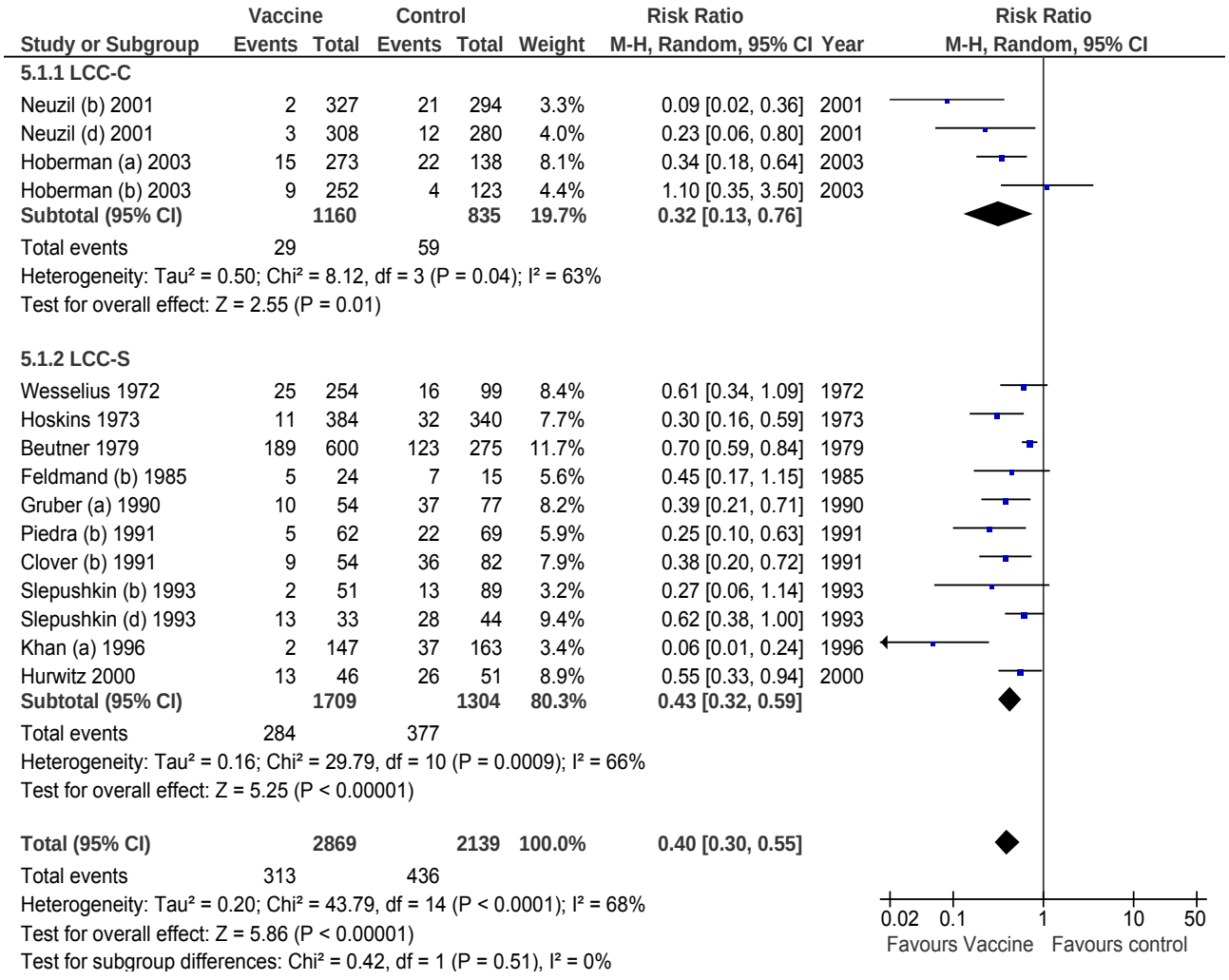
Gruber 1990: Authors stated that “No efficacy and effectiveness measure was determined for participants in the live vaccine arm”. However, data on the efficacy of LAV are available and have been extracted in other meta-analyses.

Piedra 1991: Authors wrote that this study was excluded because “Three studies in one. Two already included (Gruber 1990 and Clover 1991), the third is of uncertain provenience”. However, no details were provided in any part of the paper on what do authors exactly mean with “of uncertain provenience”.

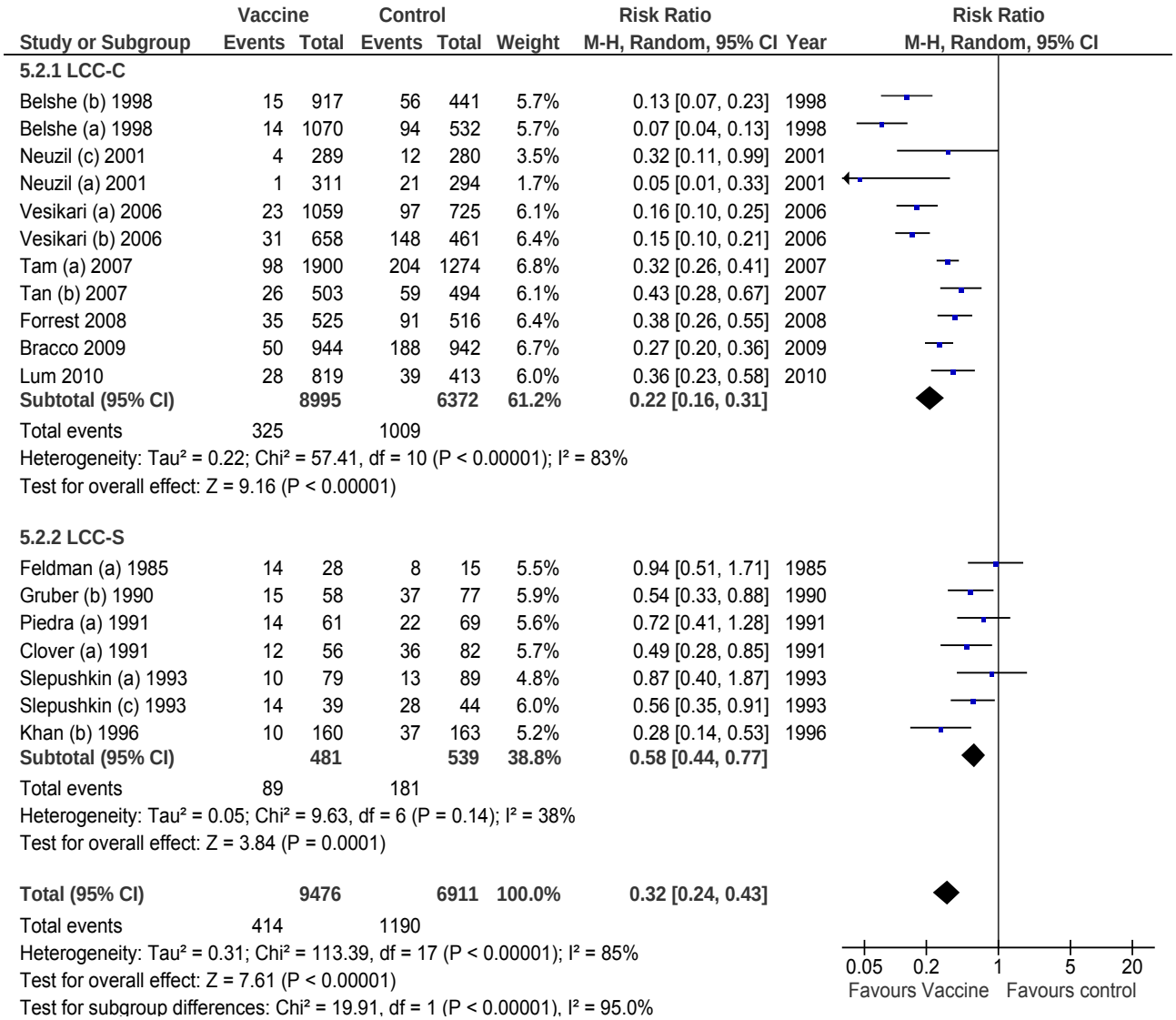
Tam 2007: Authors did not state that the study was excluded, but it was. Probably, the exclusion was due to what authors stated in the study description section: “Randomisation and allocation concealment are described very well but inconsistencies in the text (a vanished season), unclear denominators and a real possibility of biased follow up and

reporting bias of safety outcomes make this study at high risk of bias". In particular, authors reported that "Mean age at first vaccination is reported as 23.5 (SD7.4) months which is strange, as if the enrolees are always the same, most of them should have been out of age by the second season".
Beutner 1979: Authors only included one of the two groups of PIV vaccinated subjects (excluding the 300 subjects who received the inactivated influenza A vaccine containing the strain X-41 - A/Port Chalmers (H3N2) and a neuraminidase-specific recombinant vaccine of strain X-42, incorporating an equine derived hemagglutinin component – Heq1N2Ch). –
Grigorieva 2002: Only the group of subjects receiving two doses of LAV has been included, and the relative placebo arm.
Rudenko (a to f) 1996: LCC – Authors did not state that the first year of the study was excluded, but it was. Probably, the exclusion was due to what authors stated in the study description section: "The first epidemic season in Alma Ata was due to the strain A/Taiwan/1/86 (H1N1) and lasted between November 17th and December 21st . Considering that the epidemic began early than expected, it is possible that at this time not all study participants had received the second dose of vaccine or placebo, respectively". CCC – Authors reported that "All children in the Kazakhstan and Cuba studies were included in the trial of vaccine efficacy". However, only the data from Alma-Ata, 1989 (b – defined as "Rudenko 1996a" in the meta-analysis) were included in the analysis, and no reasons for the exclusion of the data from Cuba have been provided.
Slepushkin 1974: Authors describe the reasons why the second study reported in the paper was excluded, but did not state why the first study was also excluded from the analysis of efficacy.
Khan 1996: Authors excluded CCC data because "Specific diagnosis of influenza refers to an acute respiratory illness occurred during the official influenza season and is a clinical diagnosis, moreover the employed criteria were not uniform and these outcome not used)".
Clover 1991: Data were extracted from Table 7. However, the age-classes of the table are different from those used by the authors, and no explanations were provided on how the authors were able to derive the data used for the analysis.

Online supplemental Figure 1. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines (PIV) for preventing laboratory-confirmed cases of influenza (LCC-C if cultural confirmation only; LCC-S if cultural and/or serological confirmation) in healthy children. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.



Online supplemental Figure 2. Meta-analysis evaluating the efficacy of live attenuated vaccines (LAV) for preventing laboratory-confirmed cases of influenza (LCC-C if cultural confirmation only; LCC-S if cultural and/or serological confirmation) in healthy children. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

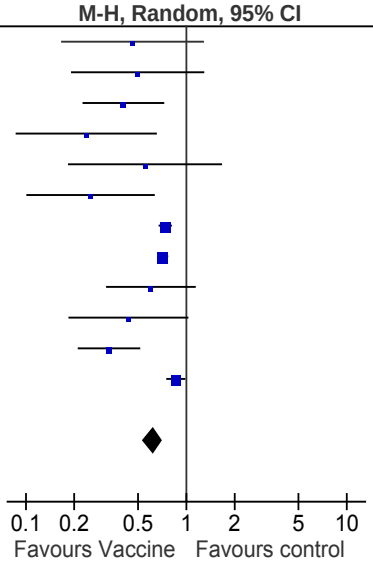


Online supplemental Figure 3. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines (PIV) for preventing clinically-confirmed cases of influenza (CCC) in healthy children. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

	Vaccine		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Maynard (a) 1968	7	171	7	79	2.1%	0.46 [0.17, 1.27]	
Maynard (b) 1968	8	159	8	79	2.4%	0.50 [0.19, 1.27]	
Hoskins 1973	16	384	35	340	5.6%	0.40 [0.23, 0.72]	
Gruber (a) 1990	4	54	24	77	2.2%	0.24 [0.09, 0.65]	
Clover (b) 1991	4	54	11	82	1.8%	0.55 [0.19, 1.64]	
Piedra (b) 1991	5	62	22	69	2.6%	0.25 [0.10, 0.63]	
Rudenko (b) 1993	743	3976	1062	4198	22.8%	0.74 [0.68, 0.80]	
Rudenko (d) 1993	1030	4402	2033	6201	23.5%	0.71 [0.67, 0.76]	
Slepushkin (b) 1993	10	51	29	89	4.8%	0.60 [0.32, 1.13]	
Khan (a) 1996	7	167	18	187	2.9%	0.44 [0.19, 1.02]	
Colombo 2001	22	177	63	167	8.2%	0.33 [0.21, 0.51]	
Marchisio 2002	55	67	63	66	21.1%	0.86 [0.76, 0.97]	
Total (95% CI)		**9724**		**11634**	**100.0%**	**0.62 [0.53, 0.72]**	
Total events	1911		3375				

Heterogeneity: Tau² = 0.03; Chi² = 39.20, df = 11 (P < 0.0001); I² = 72%

Test for overall effect: Z = 6.12 (P < 0.00001)

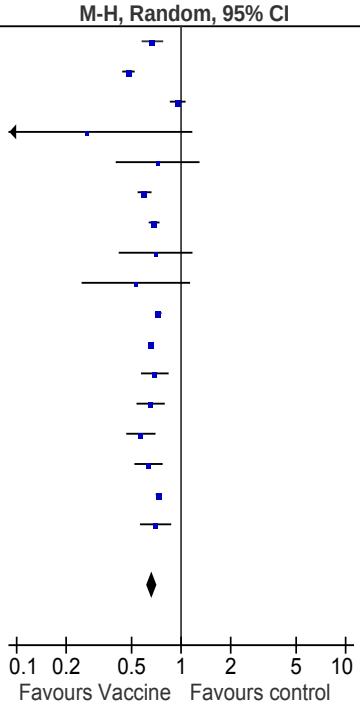


Online supplemental Figure 4. Meta-analysis evaluating the efficacy of live-attenuated vaccines (LAV) for preventing clinically-confirmed cases of influenza (CCC) in healthy children. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

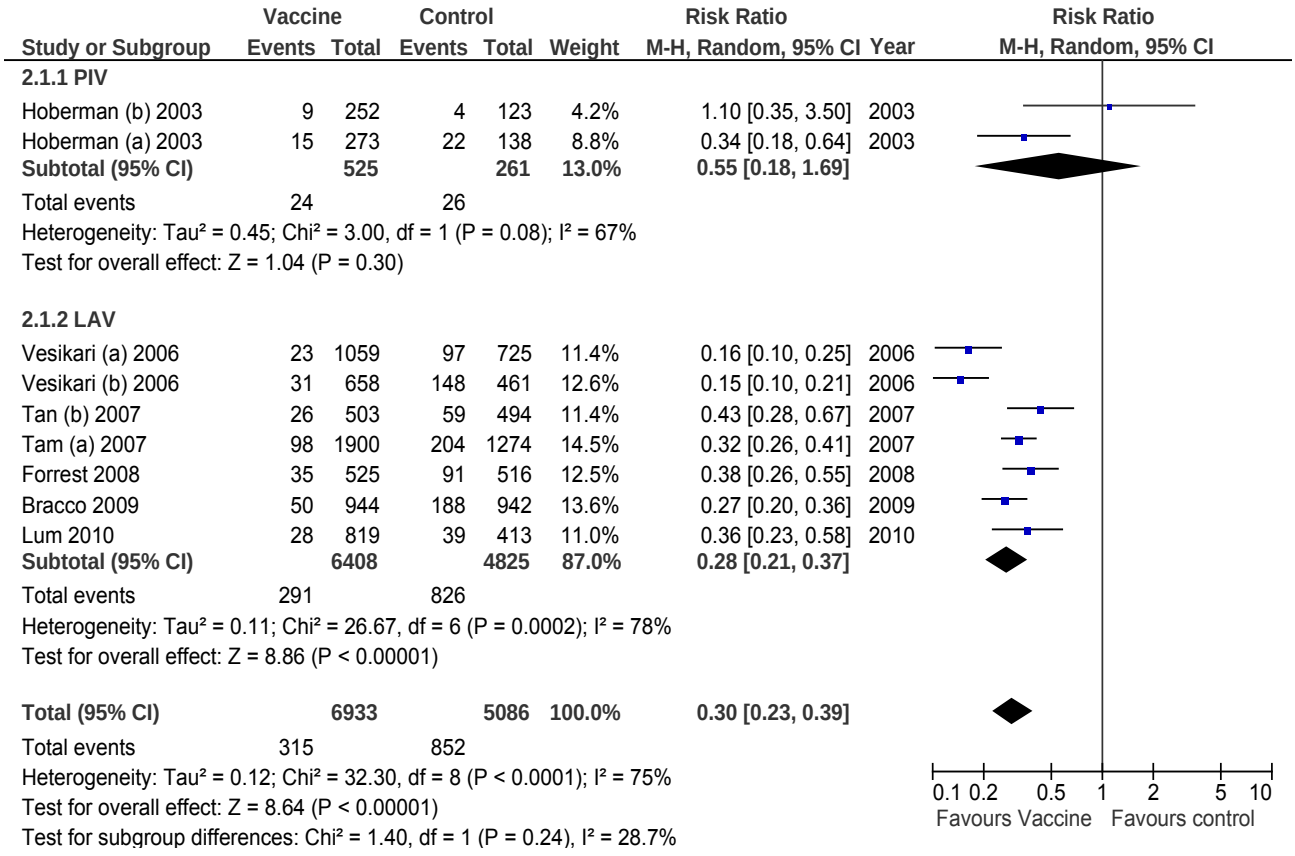
	Vaccine		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Slepushkin 1974	187	508	271	492	6.9%	0.67 [0.58, 0.77]	
Alexandrova 1986	963	16630	1755	14511	8.5%	0.48 [0.44, 0.52]	
Rudenko 1988	636	3823	695	3979	8.0%	0.95 [0.86, 1.05]	
Clover (a) 1991	2	56	11	82	0.2%	0.27 [0.06, 1.16]	
Piedra (a) 1991	14	61	22	69	1.3%	0.72 [0.41, 1.28]	
Rudenko (a) 1993	711	4693	1062	4198	8.3%	0.60 [0.55, 0.65]	
Rudenko (c) 1993	1093	4870	2033	6201	8.8%	0.68 [0.64, 0.73]	
Slepushkin (a) 1993	18	79	29	89	1.6%	0.70 [0.42, 1.16]	
Khan (b) 1996	10	196	18	187	0.8%	0.53 [0.25, 1.12]	
Rudenko (a) 1996	4466	25117	7049	28703	9.3%	0.72 [0.70, 0.75]	
Rudenko (b) 1996	6609	29690	10860	31869	9.3%	0.65 [0.64, 0.67]	
Rudenko (c-Cuba) 1996	265	776	83	168	5.8%	0.69 [0.58, 0.83]	
Rudenko (d-Cuba) 1996	240	749	82	167	5.6%	0.65 [0.54, 0.79]	
Rudenko (e-Cuba) 1996	202	714	83	167	5.5%	0.57 [0.47, 0.69]	
Rudenko (f-Cuba) 1996	238	755	83	167	5.7%	0.63 [0.53, 0.76]	
Rudenko (g-rus) 1996	5720	32095	8517	34885	9.3%	0.73 [0.71, 0.75]	
Grigorieva 2002	183	1510	133	768	5.2%	0.70 [0.57, 0.86]	
Total (95% CI)		**122322**		**126702**	**100.0%**	**0.67 [0.62, 0.71]**	
Total events	21557		32786				

Heterogeneity: Tau² = 0.01; Chi² = 187.04, df = 16 (P < 0.00001); I² = 91%

Test for overall effect: Z = 11.48 (P < 0.00001)



Online supplemental Figure 5. Meta-analysis evaluating the efficacy of live-attenuated vaccines (LAV) for preventing laboratory confirmed cases of influenza (LCC) in children aged 6-24 months (6-36 months in Vesikari 2006 and Bracco 2009 studies; 12-36 months in Tam 2007 study; 11-24 months in Lum 2010 study). All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.



Online Supplemental Table 2. Details on the differences between the two meta-analyses evaluating acute otitis media (AOM). Only randomized controlled trials (RCTs) have been considered.

First author (Ref.)	Manzoli et al. [2]	Jefferson et al. [3]	Reasons for exclusion / Notes
Clements 1995 [34]	One RCT included	Excluded	Hepatitis B vaccine as control.
Clover 1991 [11]	Two RCTs included (1 on LAV and 1 on PIV)	Two RCTs included (1 on LAV and 1 on PIV)	Authors extracted different results.
Colombo 2001 [26]	One RCT included	Included into a separate meta-analysis for studies with no intervention	Extracted data agreed.
Piedra 1991 [12]	Two RCTs included (1 on LAV and 1 on PIV)	Excluded	Authors only reported "3 studies in one. Two already included, the third is of uncertain provenance".
Belshe 1998 [18]	Two RCTs included	Included only the data from 1997 trial; data of 1996 trial have not been included	No explanation provided for the exclusion of Belshe 1996 trial. Extracted data from 1997 trial agreed.
Hoberman 2003 [17]	Two RCTs included	Two RCTs included	Extracted data agreed.
Alexandrova 1986 [29]	One RCT included	Not included	Authors reported that "The incidence of influenza-like illness; pneumonia; otitis media… were recorded for 6 months following the 2nd inoculation". However, study data on AOM were not included in the meta-analyses and no explanations were provided.
Vesikari 2006 [19]	Not included	One RCTs included	The study was published after the end of the search by Manzoli et al.

Online Supplemental Table 3. Serious adverse events (SAEs) and vaccine-related (VR) SAEs extracted from the meta-analysis by Jefferson et al. [3] on healthy children. Randomized controlled trials (RCTs) and observational studies.

First author (Ref.)	Adverse event	n-Vac	N-Vac	n-Ctrl	N-Ctrl
RCTs on LAV					
Belshe 1998 [18]	VR-SAEs	0	1070	0	532
Rudenko 1996 II [32]	Heart disease	1	1224	0	1191
Rudenko 1996 II (2nd year) [32]	Kidney disease	2	220	0	195
RCTs on PIV					
Vasilyeva 1998a [35]	Stomach, kidney or Nervous system illnesses	10	11,771	4	3493
Cohort studies					
Valilyeva 1998b * [36]	Hospitalization	5	5074	0	2135
Elshina 2000 [37]	Cardiovascular illnesses	5	930	3	905
Total	SAEs	23	20,289	7	8451

LAV = Live attenuated vaccines; PIV = Parenteral inactivated vaccines. Vac = Vaccinated; Ctrl = Controls. n=cases; N=total sample. * 5 hospitalization in the intervention group were recorded after the first dose; 1 after the second dose. Because no data were available on both doses, we extracted only the largest value.

Online supplemental Table 4. Main criticisms to USSR studies included in the meta-analysis on the efficacy and safety of influenza vaccine for healthy children by Jefferson et al. [3].

First Author (Ref.)	Main criticisms by Jefferson et al. [3]
Aksenov 1971[38]	The trial is reasonably reported but there probably is selection bias in serological testing.
Alexandrova 1986 [29]	There are three studies reported in this paper. The first is a phase 2, 5-day reactogenicity and safety trial carried out in 284 placebo recipients and 173 vaccine recipients. Although it claims randomisation it is unclear why the imbalance in numbers and because of the unclear text describing what went on I have classified it as C-RCT. As the denominators are different in all three studies and there is no way to understand what went on, it is very difficult to classify study design.
Bashliaeva 1986 [39]	Placebo-controlled cohort study (does not state whether children were randomly assigned to groups following division by age and school conditions) carried out in two regions of the then USSR during the 1983-1984 season among schoolchildren. Serology There are two apparently contradictory statements concerning serology and partly safety assessment. “The reactogenicity and antigenic activity of the vaccine were studied by observing the 305 vaccinated children and the 237 children who had received the placebo in 15 schools. They were assessed according to a series of well known indices, characterising the frequency and intensiveness of the local and general reactions to the vaccination” and “in order to study the antigenic activity of ‘Grippovac SE-AZH’, 320 samples of serum were taken from the inoculated children before vaccination, 280 samples were taken 21 days after the first injection and 170 samples were taken 21 days after the second injection”. The reasons for his apparent attrition are unclear. Notes This was a very difficult text to follow with many inconsistencies. Allocation and blinding are not described denominators are not clear.
Burtseva 1991 [40]	The authors conclude that BIV had better performance (they report protection indices), but the text has so many contradictions, lacks clarity and mentions exclusion of influenza B cases from the analysis that it is impossible to understand what went on. Children from ’internat’ roughly translates as state orphanage, could be ethical issues surrounding consent.
Chumakov 1987 [41]	Prospective cohort study, re-analysis of data from Bashliaeva 1986. Claim figures for numbers of children inoculated in Bashlyaeva 86 are wrong caused by error in calculation and designation of groups. Bashlyaeva 86 did not report that 411 inoculated children were eliminated from the observations for various reasons and should be excluded from the analysis.
Desheva 2002 [42]	The authors conclude that the vaccine is safe and effective. I do not think the data support this conclusion as for example the vaccine does not prevent against bronchitis. No viral circulation in community is described.
El’shina 2000 [37]	The authors conclude that Grippol is safe and effective and recommend immunisation of children. The extensive contradictions between text and figures, unexplained selective serological testing and vaccination make this a high risk of bias study. Figure for serologically confirmed is 60.4% of calculated per 1000 figure for number with influenza and ARI. Therefore serological confirmation is an estimate not an absolute figure and it may not be appropriate to include in meta-analysis of serologically confirmed influenza. Tables show period of seasonal rise from 07/97 to 04/98, likely to be mistake.
Grigor’eva 1994 [43]	Poor reporting (no description of blinding, placebo content and aspect, attrition etc.) and likely selection bias of safety and immunological samples.
Grigor’eva 2002 [33]	Possibly biased subset of influenza cases in follow-up. Means of selection of them and of children to assess antibody responses not described.

Khan 1996 [14]	Outcomes-Effectiveness: Specific diagnosis of influenza refers to an acute respiratory illness occurred during the official influenza season and is a clinical diagnosis, moreover the employed criteria were not uniform and these outcome not used. Outcomes-Safety: Some harms are reported with insufficient information for extraction (coryza and sore throat). The authors report ILI and assume it to be influenza because of the background rate. The text is also contradictory because half the participants are supposed to have had serology carried out on a non random basis but the middle line of Table 2 (reporting more than 4 fold titre rise) appears to indicate that school absentees had titres done and lumps absences with titre rises under “both” with a calculation of vaccine efficacy. The two placebos are not reported separately, so it is impossible to assess safety apart from what is in the text at page 173 right hand column. Denominators do not match between tables and text and the only mention of attrition is the statement that medical card for 5 of the 555 participants were not received.
Obrosova-Serova 1990 [44]	There was lot of unexplained attrition between the first and second inoculations.
Rudenko 1988 [30]	Serological: The basis for the sampling is not described. Safety: It is unclear on what basis the children in the samples were selected. The only outcome reported by arm was fever of various degrees but no definition is given. No description of the vaccine content and unclear randomisation and attrition/sampling make the interpretation of the results very difficult.
Rudenko 1993a [25]	Randomisation units were schools and results were presented both at cluster (which is right) and individual (which is wrong) levels. How this affects results is impossible to say as no cluster coefficients are reported. Second year study had no intramuscular placebo. This unblinding could have had some effect if different schools were in communication, and data have not been extracted. No separate reporting of spray and subcutaneous placebo for first year. Data from the pilot reactogenicity cohort (?) study not extracted as provenance and allocation of participants is not clear.
Rudenko 1996a [31]	Safety: Data about children, who were immunised for three successive years are reported but have not been extracted as it is unclear which year, which vaccine and most of all how to reconcile massive differences in denominators (for example for year 1, data for a total of 262 children only are reported). Febrile reactions and somatic and infectious diseases: To what group or groups belong the children? It is not possible to take back these data with the vaccination plan in table 1. Influenza and acute respiratory diseases in Havana: Arms in table 8 are not conform to the original randomised arms. Of how many arms consist the Havana trial? Were vaccination carried out in two years or were all subjects immunised in November 1990? Efficacy data consider a study population aged between 5 and 14. Individuals aged 3 or 4 were apparently not included. Number of children, who received placebo and polivaccine in table 8 coincide with those showed in the trial Havana 1991 in table 1 but the other are inconsistent. Influenza-like diseases in Alma Ata: Follow-up was probably carried out during the epidemics. Alma Ata 1986 - 87: From table 1 the number of placebo recipients aged 7-14 is 18164. From table 7 results that 22.963 recipients received vaccine. Could these two number be erroneously inverted? (and 4799 of the original 22963 vaccinated excluded). Any subject excluded from the safety analysis of 1988-89? What about effectiveness of influenza immunisation in Kalinigrad? Chaotic inconsistent reporting. No attempt at reconciling viral circulation and seroconversion rates with clinical symptoms so it is impossible to assess how many of the ILI episodes are in fact influenza.
Slepushkin 1974 [28]	Participants: Although the text states that ”Three equal groups of healthy children were formed at random“ the tables report 571 and 552 children in the vaccine and ”unvaccinated“ groups respectively. It could be that the 3 arm trial is different from the trial undertaken in January 1971, but the text is very confusing. There may even be a fourth study with again 3 arms. Outcomes: - Raised temperature up to 37.5 °C, number of days after vaccination not defined - Raised temperature > 37.5 °C, number of days after vaccination not defined - Emergency prevention of illness in first 15 days after vaccination (data not extracted, confounders, some children must have been sick over period of administration of 3 doses of vaccine, also no placebo arm carried out). The text is so confusing that only the data from the tables have been extracted. However, I am not sure of its relationship with the text.

Slepushkin 1988 [45]	Poorly conducted study: de facto unblinded, with unexplained attrition. Physical aspect of placebo and vaccine in coded vials was different making blinding inadequate. There is a strange sub-analysis of respiratory symptoms classified as harms by arm after the first vaccination dose. The authors carried out nasal swabs in 10 children and found that 1 had tonsillitis and 5 had adenovirus rhinitis. Although the breakdown by arm of these is not reported as this is a RCT, what surely matters is the difference in event between arms, even for harms. This leads me to suspect that the authors did not trust their own random allocation.
Slepushkin 1991 [46]	Randomisation and attrition are not explained. The authors checked harm data against seroconversion, to ensure that for example temp was not associated with seroconversion i.e. with infection. Unfortunately no effectiveness data are reported. Follow-up not described. Problem with data collection and surveillance in school 2. In the 1993 paper the authors report efficacy as 13% (P=0.82) for two doses of CA and 73% (P=0.08) for one dose of BIV. This relates to school 1. They also report an efficacy estimate for school 2 but this is likely to be highly unreliable.
Slepushkin 1994 [47]	Interventions: There is no placebo arm reported in the third year, which is strange as there is a placebo arm reported for immunogenicity in table 2 (??). For the second year there is also a mysterious second inactivated vaccine which appears in the results tables - data not extracted. The authors do not draw clear conclusions and it is difficult to understand to what the purpose of the study was. Badly reported no clear overall denominator and safety data is reported for limited groups of participants with no clear sampling rule.
Slobodniuk 2002a [48]	The study is very difficult to interpret, there is no information on participants, community, matching, viral circulation disparity between paired sera and enrollees etc.
Vasil'eva 1982 [49]	Methods: The setting, season and viral circulation are not described. Participants: 335 children of unknown provenance. Interventions: Placebo is not described. Outcomes Serological: Paired sera taken in a non-described fashion. Outcomes Effectiveness: Breakdown by age groups and type of injection is not reported. There is no description of randomisation, allocation or attrition.
Vasil'eva 1988a [35]	Unclear rationale for subgroup sampling and sketchy description of methods. Much may have been lost in translation.
Vasil'eva 1988b [36]	Methods: Randomisation is described only to say that older children ("adolescents") were drawn individually into the randomization sequence whereas children aged 11-14 were selected on the basis of their class. It is unclear whether this means cluster randomization although denominators are roughly on a 3:1 basis. Outcomes- Safety: The basis for the sampling is unclear and it is not at all clear whether this is a random sample (data not extracted). Earlier in the report, the text reports "When the groups were formed, with the aim of evaluating the preparations' reactogenic properties and antigenic activity, the units of selection were individuals" (??). The outcomes reported in this analysis (Table 3) are very unusual (allergies, bronchitis, neuralgia, carbuncles, stomach ulcers etc.) and there is gross imbalance and inconsistencies in the denominators of the arms (centrifugal 6625, adsorptive 491, chromatographic 4655, placebo 3493 =15264). Notes: I am not happy about the large number of inconsistencies in the text and non random (or at least unexplained) sampling carried out. Terrible reporting leading to wicked loss of data. I have trying extracting data for influenza from the effectiveness text assuming a denominator of 6596 for all vaccinees and 3393 for placebo, converting percentages from the text as follows for influenza A (H1N1) 18.2%/ of those inoculated with the chromatographic preparation (4655 i.e. 847), 24.2% of those inoculated with the centrifugal (6625) preparation and 37.9% (i.e. 1603) of children in the control groups (3393, not 3493 as it says in Table 3, i.e. 1286). As the summed denominators exceed the denominator reported CDP needs to check). However these numerators do not match even remotely the 198 paired sera taken for influenza diagnosis. Too many inconsistencies.

Online supplemental Table 5. List of the randomized controlled trials included in the meta-analyses on the efficacy of influenza vaccine for healthy adults – Laboratory-confirmed cases of influenza. The studies for which there may be some discrepancy between meta-analysis inclusion criteria and extracted data (or data exclusion) are underlined.

	Villari et al. [50]	**Jefferson et al. [51]**	**Osterholm et al. [5]**
End date of the search (mm/yy)	12/2002	06/2010	02/2011
Participant's age-range (years)	15-65	16-65	All ages §
Study inclusion criteria for RCTs (all meta-analyses only included studies assessing wild-strain naturally-occurring infections)	- Published in English - At least 70% of healthy individuals aged between 15 and 65 years	- At least 75% of participants within the age range	- Vaccines licensed in USA after 1966 for LAV and 1975 for PIV - RT-PCR or culture-confirmed influenza cases as outcome - Indexed in Medline
Study exclusion criteria	- Control group receiving no intervention	- Control group receiving another influenza vaccine	- Control group receiving another influenza vaccine or no intervention
Laboratory-confirmed cases			
Individual datasets on PIV*			
Mogabgab (a), 1970 [52] (n=1402)	Not included: outcome based on a sub-sample (incorrect randomization)	Included – LCC-S	Not included: date
Mogabgab (b), 1970 [52] (n=1551)	Not included: outcome based on a sub-sample (incorrect randomization)	Included – LCC-S	Not included: date
Leibovitz, 1971 [53] (n=9616)	Not included: control group receiving no intervention	Included – LCC-S	Not included: date
Hoskins, 1973 [7] (n=724)	Included – LCC-S	Not included: influenza B vaccine as control	Not included: date
Mair (a), 1974 [54] (n=247)	Included – LCC-S	Not included: influenza B vaccine as control	Not included: date
Mair (b), 1974 [54] (n=218)	Included – LCC-S	Not included: influenza B vaccine as control	Not included: date
Hammond, 1978 [55] (n=225)	Included – LCC-S	Included – LCC-S	Not included: vaccine type
Tannock, 1984 [56] (n=57)	Included – LCC-S	Included – LCC-S	Not included: vaccine type
Couch (b), 1986 [57] (n=180)	Included – LCC-S	Not included: probably missed in the search	Not included: not indexed in Medline

Keitel (a), 1988 [58] (n=598)	Included - LCC-S (authors used a different reference as the study was published twice)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Keitel (b), 1988 [58] (n=697)	Included - LCC-S (authors used a different reference as the study was published twice)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Edwards (e), 1994 [59] (n=1756)	Included – LCC-S (n=1317) Ω	Not included: influenza B vaccine as control	Not included: influenza B vaccine as control
Edwards (f), 1994 [59] (n=2124)	Included – LCC-S (n=1592) Ω	Not included: influenza B vaccine as control	Not included: influenza B vaccine as control
Edwards (g), 1994 [59] (n=2251)	Included – LCC-S (n=1689) Ω	Not included: influenza B vaccine as control	Not included: influenza B vaccine as control
Edwards (h), 1994 [59] (n=2032)	Included – LCC-S (n=1524) Ω	Not included: influenza B vaccine as control	Not included: influenza B vaccine as control
Powers (a), 1995 [60] (n=34)	Included – LCC-S (studies were split differently in sub-trials but data coincide)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Powers (b), 1995 [60] (n=34)	Included – LCC-S (studies were split differently in sub-trials but data coincide)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Powers (c), 1995 [60] (n=59)	Included – LCC-S (studies were split differently in sub-trials but data coincide)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Keitel (a), 1997 [61] (n=830)	Included – LCC-S	Included – LCC-S (different outcome extracted γ)	Not included: mixed cultural and serological confirmation
Keitel (b), 1997 [61] (n=940)	Included – LCC-S	Included – LCC-S (different outcome extracted γ)	Not included: mixed cultural and serological confirmation
Keitel (c), 1997 [61] (n=934)	Included – LCC-S	Included – LCC-S (different outcome extracted γ)	Not included: mixed cultural and serological confirmation
Wilde, 1999 [62] (n=359)	Included – LCC-S	Not included: pneumococcal vaccine as control	Not included: mixed cultural and serological confirmation
Bridges (a), 2000 [63] (n=275)	Not included: outcome based on a sub-sample (incorrect randomization)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Bridges (b), 2000 [63] (n=278)	Not included: outcome based on a sub-sample (incorrect randomization)	Included – LCC-S	Not included: mixed cultural and serological confirmation
Ohmit, 2006 [64] (n=728)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Ohmit, 2008 [65] (n=1205)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Beran (a), 2009 [66] (n=6203)	Not included: date	Included – LCC-C (n=6143 due to an error in data extraction)	Included – LCC-C

Beran (b), 2009 [67] (n=7652)	Not included: date	Included – LCC-C γ	Included – LCC-C γ
Monto, 2009 [68] (n=1138)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Frey, 2010 [69] (n=7481)	Not included: date	Not included: date	Included – LCC-C
Jackson (a), 2010 [70] (n=3431)	Not included: date	Not included: probably missed in the search	Included – LCC-C
Jackson (b), 2010 [70] (n=4054)	Not included: date	Not included: probably missed in the search	Included – LCC-C
Individual datasets on LAV*			
Rytel, 1977 [71] (n=143)	Included – LCC-S	Included – LCC-S	Not included: mixed cultural and serological confirmation
Monto, 1982 [72] (n=284)	Included – LCC-S	Included – LCC-S	Not included: outcome only based on serology
Couch (a), 1986 [57] (n=179)	Included – LCC-S	Not included: probably missed in the search	Not included: not indexed in Medline
Edwards (a), 1994 [59] (n=1750)	Included – LCC-S (n=1311) Ω	Included – LCC-C (different data extracted γ)	Not included: placebo was an influenza vaccine
Edwards (b), 1994 [59] (n=2093)	Included – LCC-S (n=1561) Ω	Included – LCC-C (different data extracted γ)	Not included: placebo was an influenza vaccine
Edwards (c), 1994 [59] (n=2239)	Included – LCC-S (n=1676) Ω	Included – LCC-C (different data extracted γ)	Not included: placebo was an influenza vaccine
Edwards (d), 1994 [59] (n=2015)	Included – LCC-S (n=1507) Ω	Included – LCC-C (different data extracted γ)	Not included: placebo was an influenza vaccine
Ohmit, 2006 [64] (n=725)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Ohmit, 2008 [65] (n=1191)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Monto, 2009 [68] (n=1138)	Not included: date	Not included: uncertain reasons γ	Included – LCC-C
Clinically-confirmed cases			
Individual datasets on PIV*			

Maynard (a), 1968 [24] (n=250)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Maynard (b), 1968 [24] (n=238)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Waldman (f), 1969 [73] (n=120)	Included	Not included: uncertain reasons γ	Not included: outcome not considered
Waldman (h), 1969 [73] (n=28)	Included	Not included: uncertain reasons γ	Not included: outcome not considered
Waldman (a), 1969 [74] (n=583)	Included (n=524) Ω	Included	Not included: outcome not considered
Waldman (b), 1969 [74] (n=590)	Included (n=530) Ω	Included	Not included: outcome not considered
Eddy, 1970 [75] (n=1667)	Included	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Edmondson, 1970 [76] (n=1774)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Mogabgab (a), 1970 [52] (n=1402)	Included	Included (different outcome extracted but risk ratios are similar)	Not included: outcome not considered
Mogabgab (b), 1970 [52] (n=1551)	Included	Included (different outcome extracted but risk ratios are similar)	Not included: outcome not considered
Waldman (b), 1972 [77] (n=239)	Included (n=214) Ω	Included	Not included: outcome not considered
Waldman (d), 1972 [77] (n=236)	Included (n=212) Ω	Included	Not included: outcome not considered
Hoskins, 1973 [7] (n=724)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Williams (a), 1973 [78] (n=2924)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Williams (b), 1973 [78] (n=2939)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Mair (a), 1974 [54] (n=247)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Mair (b), 1974 [54] (n=218)	Included	Not included: influenza B vaccine as control	Not included: outcome not considered
Hammond, 1978 [55] (n=225)	Included	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered

Couch (b), 1986 [57] (n=180)	Included	Not included: probably missed in the search	Not included: outcome not considered
Zhilova (a), 1986 [79] (n=2203)	Not included: unclear randomization	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Zhilova (b), 1986 [79] (n=1831)	Not included: unclear randomization	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Keitel (a), 1988 [58] (n=598)	Included (authors used a different reference as the study was published twice)	Included (different outcome extracted γ)	Not included: outcome not considered
Keitel (b), 1988 [58] (n=697)	Included (authors used a different reference as the study was published twice)	Included (different outcome extracted γ)	Not included: outcome not considered
Weingarten, 1988 [80] (n=179)	Included	Included	Not included: outcome not considered
Edwards (e), 1994 [59] (n=1756)	Included – LCC-S (n=1317) Ω	Not included: influenza B vaccine as control	Not included: outcome not considered
Edwards (f), 1994 [59] (n=2124)	Included – LCC-S (n=1592) Ω	Not included: influenza B vaccine as control	Not included: outcome not considered
Edwards (g), 1994 [59] (n=2251)	Included – LCC-S (n=1689) Ω	Not included: influenza B vaccine as control	Not included: outcome not considered
Edwards (h), 1994 [59] (n=2032)	Included – LCC-S (n=1524) Ω	Not included: influenza B vaccine as control	Not included: outcome not considered
Nichol, 1995 [81] (n=825)	Included	Included	Not included: outcome not considered
Powers (a), 1995 [60] (n=50)	Included (studies were split differently in sub-trials but data coincide)	Included (n=34) Ω	Not included: outcome not considered
Powers (b), 1995 [60] (n=50)	Included (studies were split differently in sub-trials but data coincide)	Included (n=34) Ω	Not included: outcome not considered
Powers (c), 1995 [60] (n=75)	Included (studies were split differently in sub-trials but data coincide)	Included (n=59) Ω	Not included: outcome not considered
Keitel (a), 1997 [61] (n=830)	Included	Included (different outcome extracted γ)	Not included: outcome not considered
Keitel (b), 1997 [61] (n=940)	Included	Included (different outcome extracted γ)	Not included: outcome not considered
Keitel (c), 1997 [61] (n=934)	Included	Included (different outcome extracted γ)	Not included: outcome not considered
Bridges (a), 2000 [63] (n=1130)	Included	Included	Not included: outcome not considered

Bridges (b), 2000 [63] (n=1178)	Included	Included	Not included: outcome not considered
Mesa Duque, 2001 [82] (n=493)	Not included: Spanish language	Included	Not included: outcome not considered
Mixéu, 2002 [83] (n=593)	Included	Included	Not included: outcome not considered
Beran (a), 2009 [66] (n=6014)	Not included: date	Included	Not included: outcome not considered
Individual datasets on LAV*			
Slepuskin, 1967 [84] (n=3193)	Included	Not included: outcome complex to identify γ	Not included: outcome not considered
Sumarokow, 1971 [85] (n=19,887)	Not included: Russian language	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Monto, 1982 [72] (n=284)	Included	Included	Not included: outcome not considered
Couch (a), 1986 [57] (n=179)	Included	Not included: probably missed in the search	Not included: outcome not considered
Zhilova (a), 1986 [79] (n=2082)	Not included: unclear randomization	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Zhilova (b), 1986 [79] (n=1931)	Not included: unclear randomization	Included into a separate meta-analysis of unclearly defined CCC	Not included: outcome not considered
Edwards (a), 1994 [59] (n=1750)	Included (n=1311) Ω	Included	Not included: outcome not considered
Edwards (b), 1994 [59] (n=2093)	Included (n=1561) Ω	Included (different outcome extracted γ)	Not included: outcome not considered
Edwards (c), 1994 [59] (n=2239)	Included (n=1676) Ω	Included (different outcome extracted γ)	Not included: outcome not considered
Edwards (d), 1994 [59] (n=2015)	Included (n=1507) Ω	Included (different outcome extracted γ)	Not included: outcome not considered
Nichol, 1999 [86] (n=4307)	Included	Included (different outcome extracted γ)	Not included: outcome not considered
Individual datasets on AIV*			
Waldman (e), 1969 [73] (n=353)	Included	Not included: uncertain reasons γ	Not included: outcome not considered

Waldman (g), 1969 [73] (n=78)	Included	Not included: uncertain reasons γ	Not included: outcome not considered
Waldman (c), 1969 [74] (n=597)	Included (n=538) Ω	Included	Not included: outcome not considered
Waldman (d), 1969 [74] (n=590)	Included (n=530) Ω	Included	Not included: outcome not considered
Waldman (a), 1972 [77] (n=244)	Included (n=219) Ω	Included	Not included: outcome not considered
Waldman (c), 1972 [77] (n=243)	Included (n=219) Ω	Included	Not included: outcome not considered

PIV=Parenteral inactivated vaccine; LAV=Live attenuated vaccine. LCC-C=laboratory-confirmed cases, with culture confirmation; LCC-S=laboratory-confirmed cases, with culture and/or serological confirmation.

* Name of the first author, year of publication, sample included in the analysis. In all meta-analyses, when more than one treatment arm was included into the same study, the study was divided into sub-trials. When the meta-analysis included both LAV and PIV to derive an overall estimate, the placebo group should have been equally split between the sub-trials to avoid the inclusion of placebo data twice or more times. In single meta-analyses, it is thus possible that the total number of a study is different, depending upon the meta-analysis in which it has been included: the entire placebo arm is usually included if the meta-analysis is referred to only one type of vaccine (LAV or PIV), but the placebo arm could (and should) be split by the number of sub-trials if the meta-analysis is referred to both PIV and LAV. We have reported here the total sample of each trial as the placebo arm was not split. The letters under brackets are referred to the sub-trial and have been assigned by the authors of the first meta-analysis including the study.

§ Only the results on healthy adults are here considered.

Ω Because the meta-analysis was referred to both LAV and PIV, authors correctly extracted the data splitting the placebo arm into two, avoiding data replication.

γ

Slepuskin 1967: The randomized controlled trial was chaotically described within the results of a large non-randomized field trial.

Waldman (e to h) 1969, Ohmit 2006, Ohmit 2008, Monto 2009: As partially note in Osterholm et al. review, these studies fulfilled inclusion criteria by Jefferson et al. but they were not included and any explanation or mention to them was provided. If **Couch 1986** (published into a book) or **Jackson 2010** (published on March, just three months before the end of the search) might have been missed in the search, the above four studies have been published into widely circulating journals (JAMA, New England Journal of Medicine, Journal of Infectious Diseases, New England Journal of Medicine, respectively). Thus, it is unlikely that they have been missed in the search and no reasons are available for their exclusion.

Edwards (a to d) 1994 LCC: Villari et al. and Jefferson et al. extracted, respectively, the cases with symptoms and culture or serological confirmation, or the cases with symptoms and culture confirmation only. In the meta-analysis shown in the online supplemental Figures 7A, 7B and 7C we included both the cases as extracted by Villari et al. (Figure 7A, 7C), and cases as extracted by Jefferson et al. (Figure 7B, 7C).

Edwards (b to d) 1994 CCC: Villari et al. and Jefferson et al. extracted, respectively, all the cases (presenting for culture and retrospectively reported) and only those retrospectively reported. As single risk ratios were very similar, for the sake of simplicity in the meta-analysis shown in the online supplemental Figure 9 we included the cases as extracted by Jefferson et al.

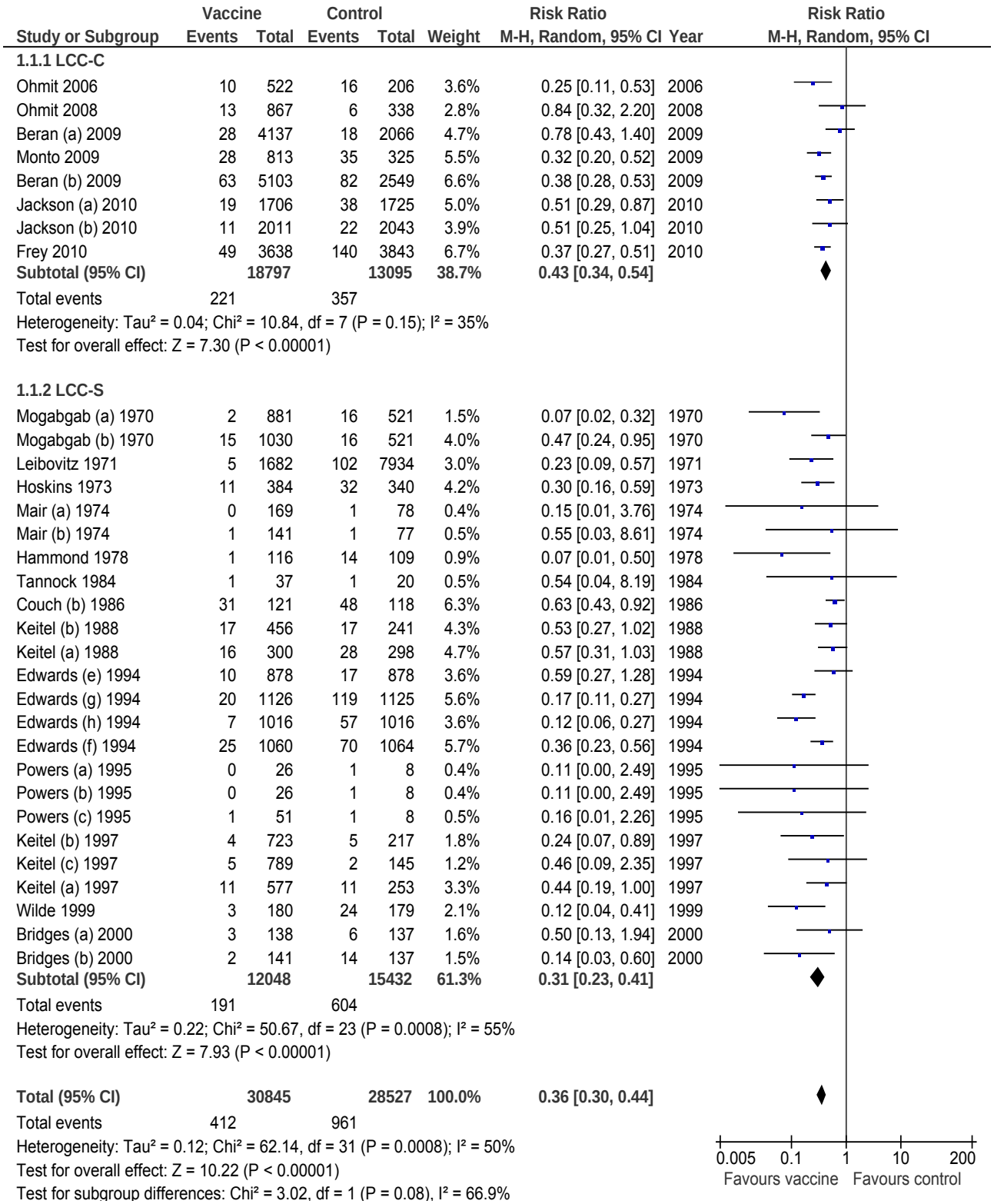
Keitel (a and b) 1988 and Keitel (a to c) 1997, CCC: Villari et al and Jefferson et al. extracted, respectively, cases defined as “any illness” and “febrile illness”. As the combined risk ratios were similar, for the sake of simplicity in the meta-analysis shown in the online supplemental Figure 8 we included the cases as extracted by Jefferson et al.

Keitel (a to c) 1997, **LCC**: Villari et al and Jefferson et al. extracted, respectively, cases defined as “any illness with culture or serological confirmation” and “febrile illness with cultural or serological confirmation”. As the combined risk ratios were similar, for the sake of simplicity in the meta-analysis shown in the online supplemental Figures 7A, 7B and 7C we included the cases as extracted by Jefferson et al.

Nichol 1999: Villari et al and Jefferson et al. extracted, respectively, the cases (both LCC and CCC) during the peak and during the total outbreak period. As the risk ratios were very similar, for the sake of simplicity in the meta-analysis shown in the online supplemental Figure 9 we included the cases as extracted by Jefferson et al.

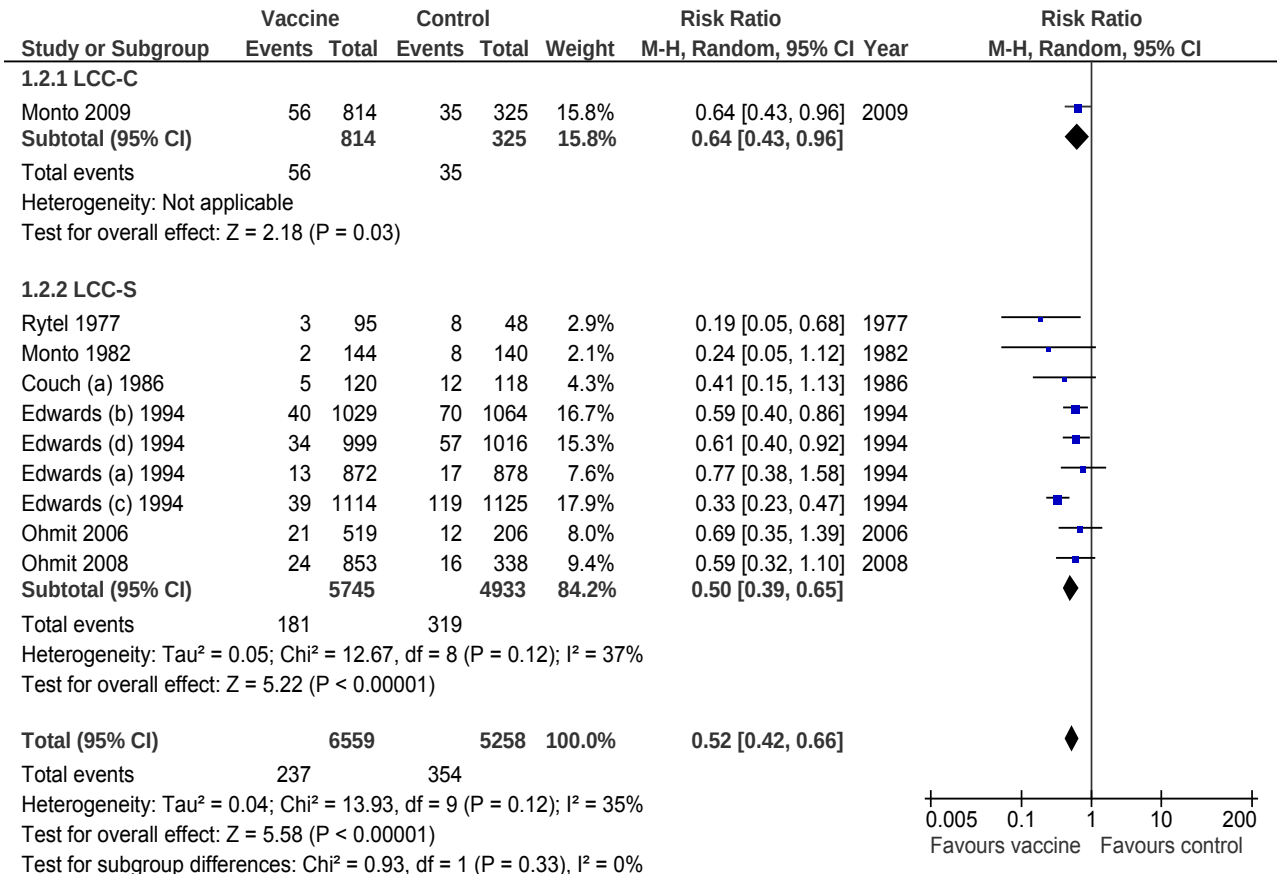
Beran (b) 2009: LCC – Data were slightly differently extracted between Osterholm et al. and Jefferson et al. The number of cases among vaccinees was 65 in Jefferson et al. meta-analysis, 63 in Osterholm et al. meta-analysis.

Online supplemental Figure 6. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines (PIV) for preventing laboratory-confirmed cases of influenza (LCC-C if cultural confirmation only; LCC-S if cultural and/or serological confirmation) in healthy adults. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

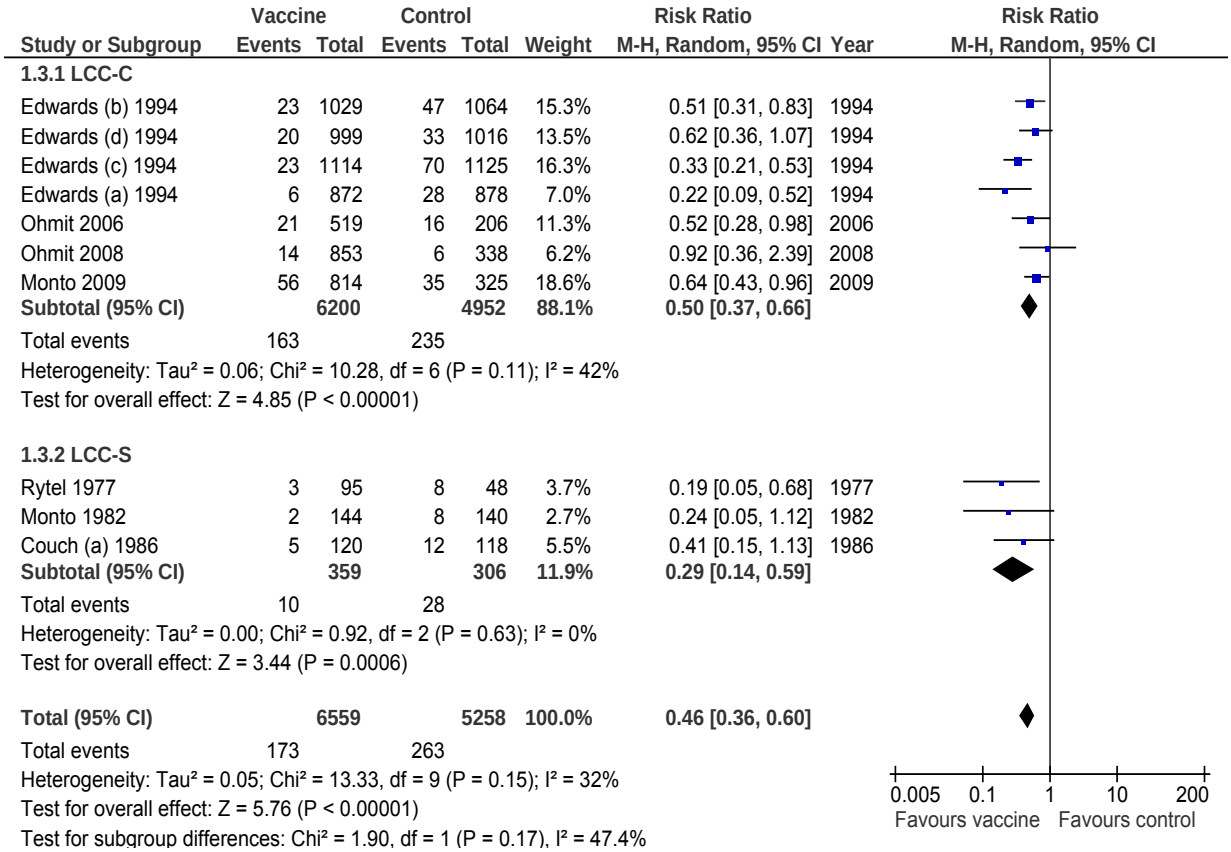


Online supplemental Figures 7A, 7B, 7C. Meta-analyses evaluating the efficacy of live attenuated vaccines (LAV) for preventing laboratory-confirmed cases of influenza (LCC-C if cultural confirmation only; LCC-S if cultural and/or serological confirmation) in healthy adults. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria (Figure 7A) or more restrictive criteria in outcome extraction (Figure 7B), In specific, some studies (Edwards 1994 all, Ohnit 2006 and Ohmit 2008) reported both LCC-C and LCC-S outcomes, and data extraction could differ depending upon inclusion criteria (with regard to outcome definition). Because the results might relevantly differ, we extracted both outcomes data from that trials and reported two separate meta-analyses. Both LCC-C and LCC-S data from these studies were separately reported in Figure 7C to enable an indirect evaluation of the influence of outcome type on vaccine efficacy.

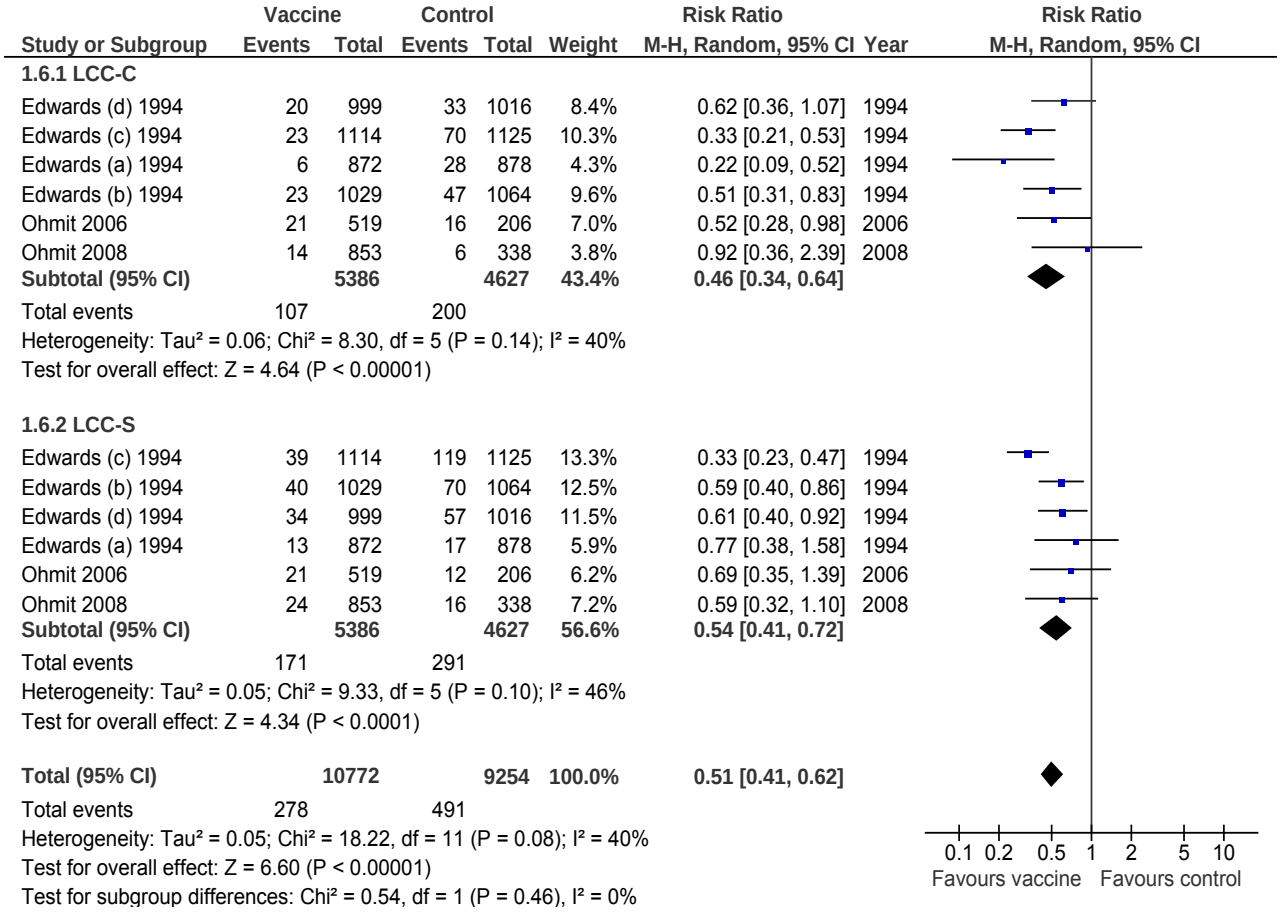
7A



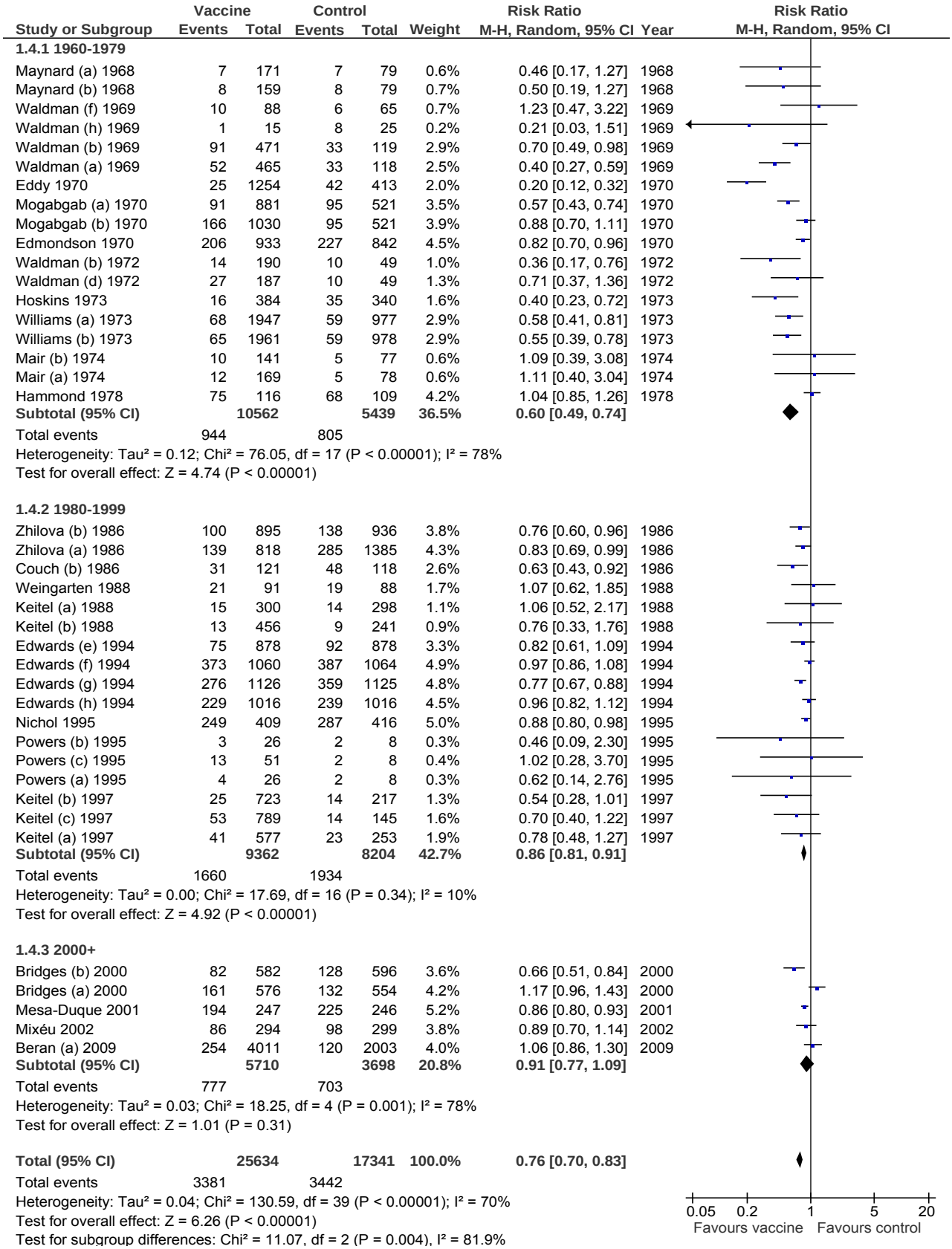
7B


Vaccine
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.3.1 LCC-C
Edwards (b) 1994 23 1029 47 1064 15.3% 0.51 [0.31, 0.83] 1994
Edwards (d) 1994 20 999 33 1016 13.5% 0.62 [0.36, 1.07] 1994
Edwards (c) 1994 23 1114 70 1125 16.3% 0.33 [0.21, 0.53] 1994
Edwards (a) 1994 6 872 28 878 7.0% 0.22 [0.09, 0.52] 1994
Ohmit 2006 21 519 16 206 11.3% 0.52 [0.28, 0.98] 2006
Ohmit 2008 14 853 6 338 6.2% 0.92 [0.36, 2.39] 2008
Monto 2009 56 814 35 325 18.6% 0.64 [0.43, 0.96] 2009
Subtotal (95% CI) 6200 4952 88.1% 0.50 [0.37, 0.66]
Total events 163 235
Heterogeneity: Tau² = 0.06; Chi² = 10.28, df = 6 (P = 0.11); I² = 42%
Test for overall effect: Z = 4.85 (P < 0.00001)
1.3.2 LCC-S
Rytel 1977 3 95 8 48 3.7% 0.19 [0.05, 0.68] 1977
Monto 1982 2 144 8 140 2.7% 0.24 [0.05, 1.12] 1982
Couch (a) 1986 5 120 12 118 5.5% 0.41 [0.15, 1.13] 1986
Subtotal (95% CI) 359 306 11.9% 0.29 [0.14, 0.59]
Total events 10 28
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)
Total (95% CI) 6559 5258 100.0% 0.46 [0.36, 0.60]
Total events 173 263
Heterogeneity: Tau² = 0.05; Chi² = 13.33, df = 9 (P = 0.15); I² = 32%
Test for overall effect: Z = 5.76 (P < 0.00001)
Test for subgroup differences: Chi² = 1.90, df = 1 (P = 0.17), I² = 47.4%
0.005 0.1 1 10 200
Favours vaccine Favours control

7C


Vaccine
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.6.1 LCC-C
Edwards (d) 1994 20 999 33 1016 8.4% 0.62 [0.36, 1.07] 1994
Edwards (c) 1994 23 1114 70 1125 10.3% 0.33 [0.21, 0.53] 1994
Edwards (a) 1994 6 872 28 878 4.3% 0.22 [0.09, 0.52] 1994
Edwards (b) 1994 23 1029 47 1064 9.6% 0.51 [0.31, 0.83] 1994
Ohmit 2006 21 519 16 206 7.0% 0.52 [0.28, 0.98] 2006
Ohmit 2008 14 853 6 338 3.8% 0.92 [0.36, 2.39] 2008
Subtotal (95% CI) 5386 4627 43.4% 0.46 [0.34, 0.64]
Total events 107 200
Heterogeneity: Tau² = 0.06; Chi² = 8.30, df = 5 (P = 0.14); I² = 40%
Test for overall effect: Z = 4.64 (P < 0.00001)
1.6.2 LCC-S
Edwards (c) 1994 39 1114 119 1125 13.3% 0.33 [0.23, 0.47] 1994
Edwards (b) 1994 40 1029 70 1064 12.5% 0.59 [0.40, 0.86] 1994
Edwards (d) 1994 34 999 57 1016 11.5% 0.61 [0.40, 0.92] 1994
Edwards (a) 1994 13 872 17 878 5.9% 0.77 [0.38, 1.58] 1994
Ohmit 2006 21 519 12 206 6.2% 0.69 [0.35, 1.39] 2006
Ohmit 2008 24 853 16 338 7.2% 0.59 [0.32, 1.10] 2008
Subtotal (95% CI) 5386 4627 56.6% 0.54 [0.41, 0.72]
Total events 171 291
Heterogeneity: Tau² = 0.05; Chi² = 9.33, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 4.34 (P < 0.0001)
Total (95% CI) 10772 9254 100.0% 0.51 [0.41, 0.62]
Total events 278 491
Heterogeneity: Tau² = 0.05; Chi² = 18.22, df = 11 (P = 0.08); I² = 40%
Test for overall effect: Z = 6.60 (P < 0.00001)
Test for subgroup differences: Chi² = 0.54, df = 1 (P = 0.46), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours vaccine Favours control

Online supplemental Figure 8. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines (PIV) for preventing clinically-confirmed cases of influenza (CCC) in healthy adults. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

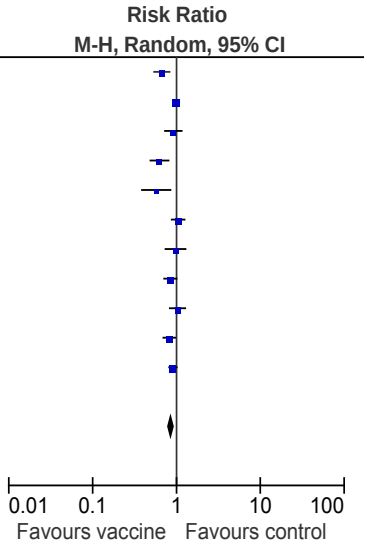


Online supplemental Figure 9. Meta-analysis evaluating the efficacy of live attenuated vaccines (LAV) for preventing clinically-confirmed cases of influenza (CCC) in healthy adults. All studies that were considered in at least one meta-analysis have been included, using the least restrictive criteria for outcome definition and sample inclusion criteria.

	Vaccine		Control			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Slepuskin 1967	201	2254	125	939	8.6%	0.67 [0.54, 0.83]	1967
Sumarokow 1971	1407	9945	1429	9942	13.9%	0.98 [0.92, 1.05]	1971
Monto 1982	70	144	74	140	7.9%	0.92 [0.73, 1.16]	1982
Zhilova (b) 1986	92	995	138	936	7.3%	0.63 [0.49, 0.80]	1986
Couch (a) 1986	28	120	48	118	4.2%	0.57 [0.39, 0.85]	1986
Zhilova (a) 1986	150	697	285	1385	9.8%	1.05 [0.88, 1.25]	1986
Edwards (a) 1994	89	872	92	878	6.5%	0.97 [0.74, 1.28]	1994
Edwards (c) 1994	201	1114	240	1125	10.1%	0.85 [0.71, 1.00]	1994
Edwards (d) 1994	148	999	146	1016	8.5%	1.03 [0.83, 1.27]	1994
Edwards (b) 1994	208	1029	262	1064	10.4%	0.82 [0.70, 0.96]	1994
Nichol 1999	751	2874	412	1433	12.7%	0.91 [0.82, 1.01]	1999
Total (95% CI)		**21043**		**18976**	**100.0%**	**0.87 [0.79, 0.95]**	
Total events	3345		3251				

Heterogeneity: Tau² = 0.02; Chi² = 33.54, df = 10 (P = 0.0002); I² = 70%

Test for overall effect: Z = 3.02 (P = 0.003)

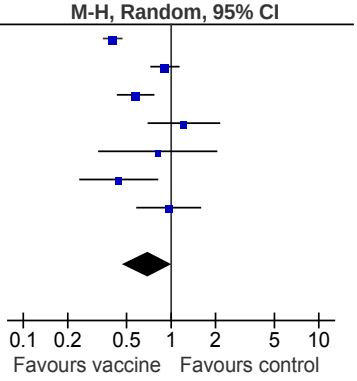


Online supplemental Figure 10. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines for preventing clinically-confirmed cases of influenza (CCC) in the elderly. Only the datasets that have been published after 2000 (the year of the search end by Vu et al. [87]) were included [88-93].

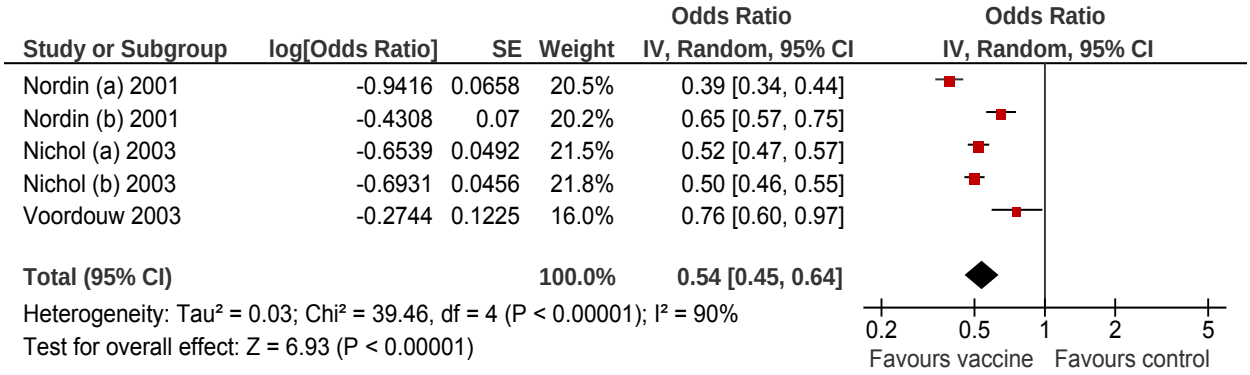
	Vaccine		No vaccination			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Deguchi 2001	256	10739	694	11723	17.8%	0.40 [0.35, 0.46]	2001
Monto 2001	247	1728	98	623	17.3%	0.91 [0.73, 1.13]	2001
Saito (a) 2002	58	331	112	368	16.6%	0.58 [0.44, 0.76]	2002
Saito (b) 2002	68	743	14	187	13.1%	1.22 [0.70, 2.12]	2002
Kaway 2003	19	3520	6	903	8.8%	0.81 [0.33, 2.03]	2003
Hara 2006	20	3169	22	1540	12.5%	0.44 [0.24, 0.81]	2006
Leung 2007	194	2943	16	234	13.9%	0.96 [0.59, 1.58]	2007
Total (95% CI)		**23173**		**15578**	**100.0%**	**0.69 [0.47, 1.01]**	
Total events	862		962				

Heterogeneity: Tau² = 0.20; Chi² = 54.50, df = 6 (P < 0.00001); I² = 89%

Test for overall effect: Z = 1.92 (P = 0.05)



Online supplemental Figure 11. Meta-analysis evaluating the efficacy of parenteral inactivated vaccines for preventing all deaths in the elderly. Only the datasets that have been published after 2000 (the year of the search end by Vu et al. [87]) were included [94-96].



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