Appendix A : Protocol

https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=112260

Appendix B: Search strategy (up to October 3rd, 2018)

Literature search

PubMed:

("influenza, human"[MeSH Terms] OR "influenzavirus a"[MeSH Terms] OR "influenzavirus b"[MeSH Terms] OR flu[Title/Abstract] OR influenza*[Title/Abstract] OR "influenza vaccines"[MeSH Terms]) AND ("Vaccines"[Mesh:noexp] OR "Vaccines, Attenuated"[Mesh] OR "Vaccines, Inactivated"[Mesh:noexp] OR "Vaccines, Subunit"[Mesh] OR "Vaccines, Synthetic"[Mesh] OR "Viral Vaccines"[Mesh:noexp] OR vaccin*[Title/Abstract] OR inocul*[Title/Abstract] OR immuni*[Title/Abstract] OR "immunization"[MeSH Terms] OR "vaccination"[MeSH Terms] OR "adjuvants, immunologic"[MeSH Terms] OR adjuvant*[Title/Abstract] OR immunostimul*[Title/Abstract] OR immunomodul*[Title/Abstract] OR immunotherap*[Title/Abstract] OR "influenza vaccines"[MeSH Terms]) AND ("Dose-Response Relationship, Immunologic"[Mesh] OR "immunogenicity, vaccine"[MeSH Terms] OR "immunity, humoral"[MeSH Terms] OR "adaptive immunity"[MeSH:noexp] OR "antibody formation"[MeSH:noexp] OR "safety"[MeSH:noexp] OR "immunology"[MeSH Subheading] OR "adverse effects"[MeSH Subheading] OR hemagglutin*[Title/Abstract] OR Microneutrali*[Title/Abstract] OR immunogen*[Title/Abstract] OR efficacy[Title/Abstract] OR adverse effect*[Title/Abstract] OR AEFI[Title/Abstract] OR SAE[Title/Abstract]) AND ("aged"[MeSH Terms] OR "age factors"[MeSH Terms] OR "middle aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms] OR "young adult"[MeSH Terms] OR "adult"[MeSH Terms] OR adult*[Title/Abstract]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals[mh] NOT humans[mh]))

CINAHL

((MH "Influenza") OR "influenza" OR (MH "Influenza A Virus") OR (MH "Influenza B Virus") OR (MH "Influenza Vaccine") OR (MH "Influenza, Human") OR (MH "Influenza, Seasonal") OR influenza* OR flu OR influenza vaccin*) **AND** ((MH "Immunization") OR "vaccination" OR (MH "Influenza Vaccine") OR (MH "Vaccines") OR (MH "Viral Vaccines") OR (MH "Attitude to Vaccines") OR (MH "Immunotherapy") OR (MH "Immunization, Secondary") OR Vaccin* OR inocul* OR immuni* OR adjuvant* OR immunostimul* OR immunomodul* OR immunotherap*) **AND** ((MH "Treatment Outcomes") OR "hemagglutin*" OR "Microneutrali*" OR "immunogen*" OR "efficacy" OR "adverse effect*" OR "adverse event*" OR "AEFI" OR "SAE" OR "antibod*" OR "safety" OR "reactogenicity") **AND** ((MH "Random Assignment") or (MH "Random Sample+") or (MH "Crossover Design") or (MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Control (Research)+") or (MH "Control Group") or (MH "Factorial Design") or (MH "Quasi-Experimental Studies+") or (MH "Placebos") or (MH "Meta Analysis") or (MH "Sample Size") or (MH "Research, Nursing") or (MH "Research Question") or (MH "Research Methodology+") or (MH "Evaluation Research+") or (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") or (MH "Nursing Practice, Research-Based") or (MH "Solomon Four-Group Design") or (MH "One-Shot Case Study") or (MH "Pretest-Posttest Design+") or (MH "Static Group Comparison") or (MH "Study Design") or (MH "Clinical Research+")) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)

(Academic publications)

Embase

1. exp influenza/
2. exp Influenza virus A/
3. exp Influenza virus B/
4. Influenza virus/
5. flu.tw.
6. "influenza*".tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. vaccine/
9. live vaccine/
10. inactivated vaccine/
11. subunit vaccine/
12. recombinant vaccine/
13. virus vaccine/
14. exp immunization/
15. exp vaccination/
16. exp immunological adjuvant/
17. influenza vaccine/
18. "vaccin*".tw.
19. inocul*.tw.
20. immuni*.tw.
21. adjuvant*.tw.
22. immunostimul*.tw.
23. immunomodul*.tw.
24. immunotherap*.tw.
25. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp dose response/
27. vaccine immunogenicity/
28. exp humoral immunity/
29. adaptive immunity/
30. antibody production/
31. safety/
32. side effect.fs.
33. adverse drug reaction.fs.
34. hemagglutin*.tw.
35. Microneutrali*.tw.
36. immunogen*.tw.
37. efficacy.tw.
38. adverse effect*.tw.
39. AEFI.tw.
40. SAE.tw.
41. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42. infant/
43. child/ or preschool child/ or school child/
44. adolescent/
45. 42 or 43 or 44
46. adult/ or aged/
47. 45 not 46

48. exp animal/ or nonhuman/
49. exp human/
50. 48 not 49
51. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw.
52. 7 and 25 and 41 and 51
53. 52 not 47
54. 53 not 50
55. limit 54 to yr="2010 -Current"
56. limit 55 to (english or french)
57. limit 56 to embase

Web of Science

# 5	2,779	(#4 AND #3 AND #2 AND #1) AND **LANGUAGE:** (English OR French) AND **DOCUMENT TYPES:** (Article) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2010-2018
# 4	2,342,818	(TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2010-2018
# 3	1,166,035	(TS=(hemagglutin* OR Microneutrali* OR immunogen* OR efficacy OR adverse effect* OR adverse event* OR AEFI OR SAE OR antibod* OR safety OR reactogenicity)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2010-2018
# 2	417,224	(TS=(Vaccin* OR inocul* OR immuni* OR adjuvant* OR immunostimul* OR immunomodul* OR immunotherap*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2010-2018
# 1	60,932	(TS= (influenza* OR flu OR influenza vaccin*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2010-2018

Clinical trials search:

Clinical Study Data Request : (ClinicalStudyDataRequest.com)

Influenza vaccine

ClinicalTrials.gov : (https://clinicaltrials.gov/)

immunogenicity OR efficacy OR safety OR reactogenicity OR adverse events OR adverse effects OR antibody titer | Influenza OR influenza, A OR influenza, B OR influenza, human OR Influenza vaccine | Adult, Older Adult | Phase 3 | Start date on or after 01/01/2010

European Organisation for Research and treatment of Cancer Clinical Trials Database: (https://www.eortc.org/clinical-trials-database/)

influenza vaccine

European Union Clinical Trials Register: (**https://www.clinicaltrialsregister.eu**)

(influenza OR flu) AND vaccine

World Health Organization International Clinical Registry Platform: (https://www.who.int/clinical-trials-registry-platform)

No keyword, a list of studies was uploaded on 3rd October 2018.

Health Canada's Clinical Trials Database: (https://health-products.canada.ca/ctdb-bdec/index-eng.jsp)

Key words: Influenza vaccine

Appendix C:

Table C1: Exclusion criteria for chronic medical conditions and previous influenza vaccination history for each included study (N=18)

Study ID	Exclusion criteria for chronic medical conditions (non-exhaustive list)	Previous influenza vaccination history[a] N (%)
Sanofi Pasteur		
GQM01	Immunocompromised persons	814 (51.9%)
GQM04	Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion/ immunocompromised persons	626 (40.0%)
GQM07	Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion/ immunocompromised persons	118 (39.3%)
GQM11	Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion/ immunocompromised persons	1065 (47.9%)
QID01	Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion/ immunocompromised persons	1272 (37.9%)
QIV03	Any condition that in the opinion of the investigator would pose a health risk to the subject or could interfere with the evaluation of the vaccine/ immunocompromised persons	NA
QIV06	Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion/ immunocompromised persons	NA
RPV03C	Chronic disease that is unstable or any intercurrent illness that might interfere with the ability to participate fully in the study; or interfere with evaluation of the vaccine.	532 (55.8%)
GlaxoSmithKline (GSK)		
112963	Uncontrolled medical condition/immunocompromised persons	1173 (68.7%)

Study ID	Exclusion criteria for chronic medical conditions (non-exhaustive list)	Previous influenza vaccination history[a] N (%)
201251	Any condition which, in the opinion of the investigator, prevents the subject from participating in the study/immunocompromised persons	34 (28.3%)
114269	Chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality/Immunocompromised persons	3669 (78.8%)
117036	Any condition which, in the opinion of the investigator, prevents the subject from participating in the study/immunocompromised persons	600 (72.4%)
CSL Seqirus		
CSLCT-QIV-13-01	Any clinically significant disease or finding that, in the investigator's opinion, precluded study participation /immunocompromised persons.	3 039 (87.3%)
V118-18	Any underlying medical condition with fatal prognosis within 12 months/immunocompromised persons.	4 064 (59.9%)
V58-23	Chronic illness that would interfere with the subject's safety and/or could interfere with the evaluation of study vaccine/immunocompromised persons	458 (29.4%)
V70-27	Immunocompromised persons	153 (2.6%)
V118-20	Any clinical condition that, in the opinion of the Investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study/immunocompromised persons.	1 541 (86.7%)
V130-01	Chronic illness that, in the opinion of the investigator, would interfere with the subject's safety during study participation and/or compliance with study-related procedures and/or with the evaluation of study vaccine/ immunocompromised persons	666 (24.9%)

a. QM01: participants with history of having ever received an influenza vaccine from 2008/2009 to 2010/2011 seasons. GQM04: participants with history of having ever received an influenza vaccine from 2009/2010 to 2011/2012 seasons. GQM07: participants with history of influenza vaccine for the 2014-2015 season. GQM11: participants with history of having ever received an influenza vaccine from 2011/2012 to 2013/2014 seasons. QID01: participants with history of influenza vaccine in the previous year. RPV03C: Participants with history of influenza vaccine in the previous 3 years. 112963: Participants with history of having ever received an influenza vaccine during the 3 prior seasons. 201251: Participants with history of having ever received an influenza vaccine during 4 prior seasons 114269/117036/117276: Participants with history of having ever received an influenza vaccine during 3 prior seasons. CLSCTQIV-13-01/V118-01/V118-20: Participants with previous influenza vaccination in the past 5 years. V58-23/V70-27/V130-01: Previous influenza vaccination without precision.

Appendix D: Flow chart

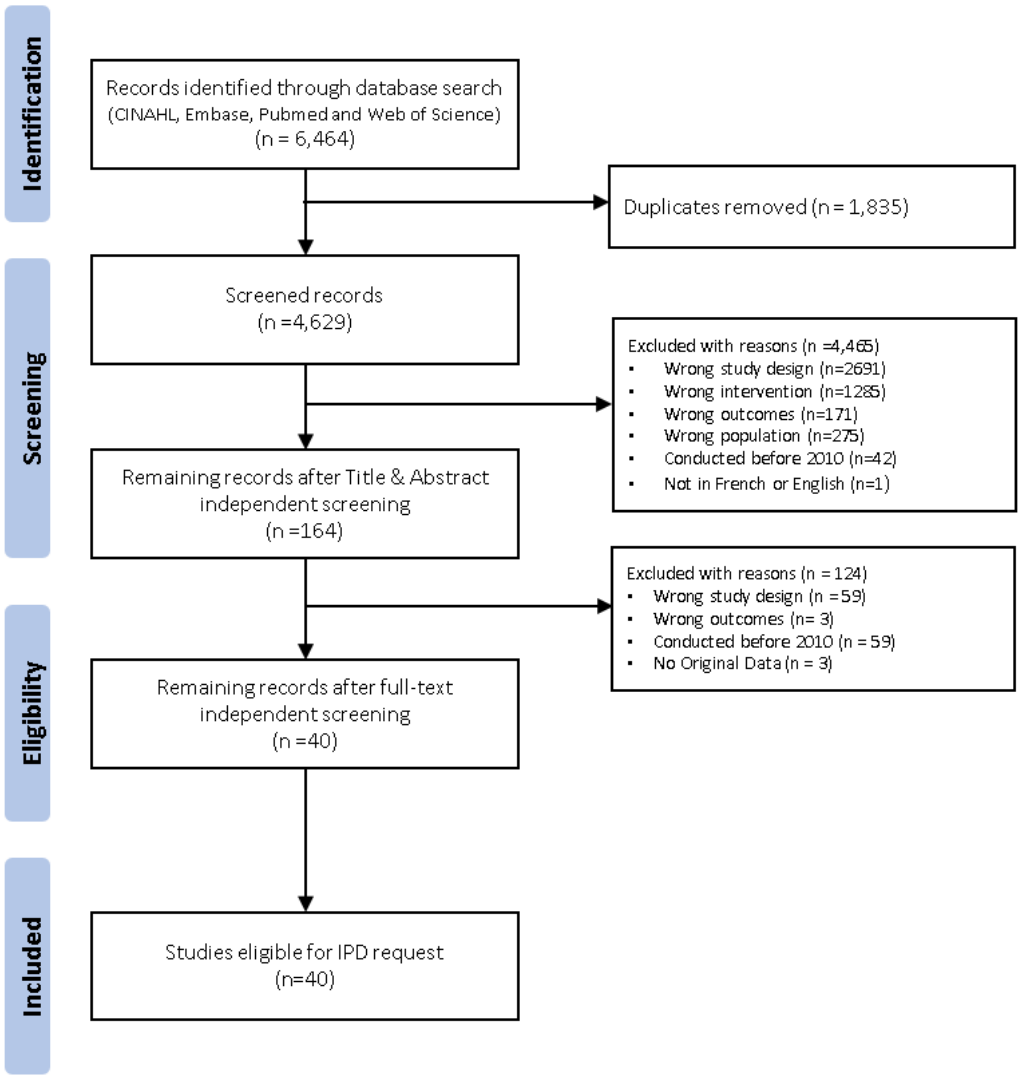

Figure D1: Study selection flowchart from literature search

Appendix E

Table E1: Definitions of safety outcomes assessed in included studies (N=18)

Study ID	Safety outcomes of interest available	Injection site reactions (ISR) collected	Criteria for severe ISR (Grade 3)	Systemic reactions collected	Criteria for severe systemic reactions (Grade 3)
Sanofi Pasteur					
GQM01	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related): 6 months	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm Induration ≥ 25 mm Ecchymosis ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
GQM04	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related): 6 months	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm Induration ≥ 25 mm Ecchymosis ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
GQM07	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related): 21 days	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm Induration ≥ 25 mm Ecchymosis ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
GQM11	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related) : 6 months	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm Induration ≥ 25 mm Ecchymosis ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C

Study ID	Safety outcomes of interest available	Injection site reactions (ISR) collected	Criteria for severe ISR (Grade 3)	Systemic reactions collected	Criteria for severe systemic reactions (Grade 3)
QID01	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 28 days Serious adverse events (n related): 6 months	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm Induration ≥ 25 mm Ecchymosis ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
QIV03	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related): 21 days	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
QIV06	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 28 days Serious adverse events (n related): during the study	Pain Erythema ≥ 25 mm Swelling ≥ 25 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Shivering	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
RPV03C	Unsolicited events (n related): 28 days Serious adverse events (n related): from vaccination to next visit	NA	NA	NA	NA
GlaxoSmithKline (GSK)					

Study ID	Safety outcomes of interest available	Injection site reactions (ISR) collected	Criteria for severe ISR (Grade 3)	Systemic reactions collected	Criteria for severe systemic reactions (Grade 3)
112963	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 30 days Serious adverse events (n related): 6 months	Pain Erythema > 20 mm Swelling > 20 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Gastro-intestinal Myalgia Shivering Arthralgia Fatigue	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
201251	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related) : 21 days	Pain Erythema > 20 mm Swelling > 20 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Gastro-intestinal Myalgia Shivering Arthralgia Fatigue	Symptoms that prevent normal, everyday activities. Fever > 39˚C
114269	Any solicited reactions Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 21 days Serious adverse events (n related): 6 months	Pain Erythema > 20 mm Swelling > 20 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Gastro-intestinal Myalgia Shivering Arthralgia Fatigue	Symptoms that prevent normal, everyday activities. Fever > 39˚C
117036	Any solicited reactions: 7 days Solicited injection site reactions (Grade 3) Solicited systemic reactions (Grade 3) Details for solicited reactions Unsolicited events (n related): 30 days	Pain Erythema ≥ 20 mm Swelling ≥ 20 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Swelling > 100 mm	Fever ≥ 38˚C Headache Gastro-intestinal Myalgia Shivering Arthralgia Fatigue	Symptoms that prevent normal, everyday activities. Fever > 39˚C
CSL Seqirus					
CSLCT-QIV-13-01	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 6 months	Pain Erythema ≥ 20 mm Swelling/Lump ≥ 20 mm	Symptoms that prevent normal, everyday activities. Erythema ≥ 100 mm Swelling ≥ 100 mm	Fever ≥ 38˚C Headache Malaise Myalgia Nausea Vomiting Chills	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C

Study ID	Safety outcomes of interest available	Injection site reactions (ISR) collected	Criteria for severe ISR (Grade 3)	Systemic reactions collected	Criteria for severe systemic reactions (Grade 3)
V118-18	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 12 months	Pain Erythema ≥ 1 mm Induration ≥ 1 mm Ecchymosis ≥ 1 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Arthralgia Myalgia Nausea Vomiting Chills Diarrhea Fatigue Loss of appetite	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C
V58-23	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 21 days	Pain Erythema, size ND Induration, size ND Ecchymosis, size ND	Symptoms that prevent normal, everyday activities Erythema, size ND Induration, size ND Ecchymosis, size ND	Chills Headache Arthralgia Myalgia Nausea Vomiting Loss of appetite Diarrhea Fatigue	Symptoms that prevent normal, everyday activities.
V70-27	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 12 months	Pain Erythema, size ND Swelling, size ND Induration, size ND Tenderness	Symptoms that prevent normal, everyday activities Erythema > 100 mm Swelling > 100 mm Induration > 100 mm	Fever ≥ 38˚C Headache Arthralgia Myalgia Nausea Vomiting Chills Diarrhea Fatigue	Symptoms that prevent normal, everyday activities. Fever ≥ 40.5˚C
V118-20	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 6 months	Pain Erythema ≥ 1 mm Induration ≥ 1 mm Ecchymosis ≥ 1 mm	Symptoms that prevent normal, everyday activities. Erythema > 100 mm Induration > 100 mm Ecchymosis > 100 mm	Fever ≥ 38˚C Headache Arthralgia Myalgia Nausea Vomiting Chills Diarrhea Fatigue Loss of appetite	Symptoms that prevent normal, everyday activities. Fever ≥ 39˚C

Study ID	Safety outcomes of interest available	Injection site reactions (ISR) collected	Criteria for severe ISR (Grade 3)	Systemic reactions collected	Criteria for severe systemic reactions (Grade 3)
V130-01	Solicited injection site reactions (Grade 3): 7 days Solicited systemic reactions (Grade 3): 7 days Details for solicited reactions Serious adverse events: 6 months	Pain Erythema, size ND Induration, size ND Ecchymosis, size ND	Symptoms that prevent normal, everyday activities Erythema, size ND Induration, size ND Ecchymosis, size ND	Fever ≥ 38˚C Headache Arthralgia Myalgia Nausea Vomiting Chills Diarrhea Fatigue Loss of appetite	Symptoms that prevent normal, everyday activities. Fever, size ND

NA: Not available ND: not defined

Appendix F:

Figure F1: Risk of bias assessment of included studies (N=18) as per ROBINS-1 tool.

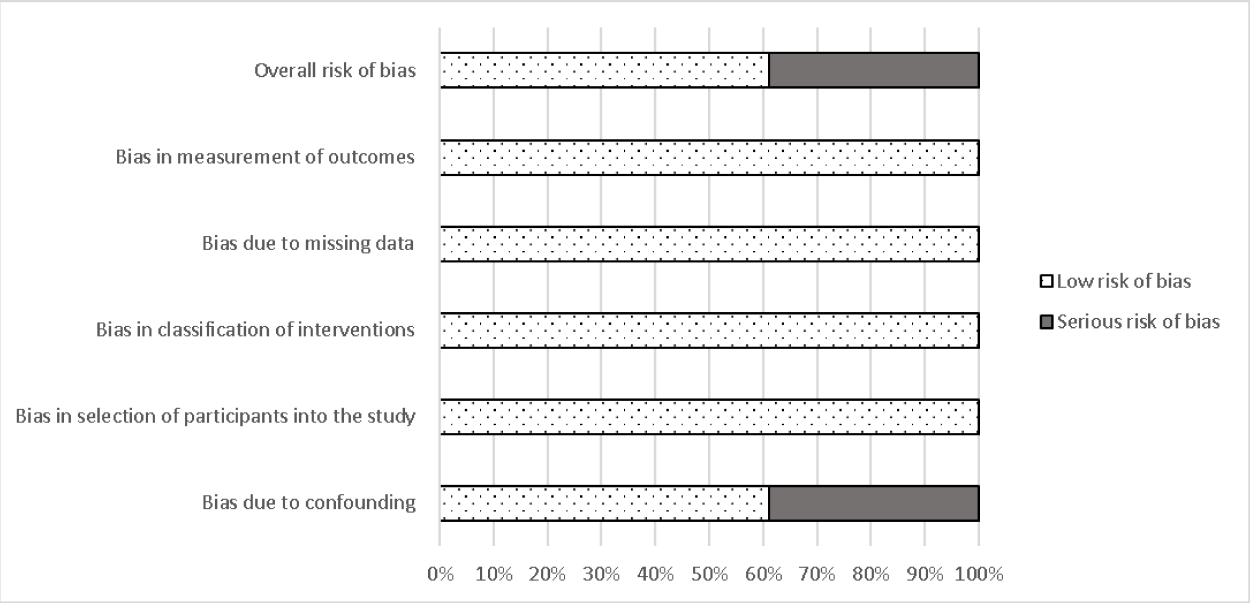

Table F1: Certainty of evidence using GRADE approach

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Females	Males	Relative (95% CI)	Absolute (95% CI)		
Injection site reactions (follow-up: 7 days)												
17	observational studies	serious[a]	serious[b]	not serious	not serious	none	9057/20295 (44.6%)	4695/13860 (33.9%)	**RR 1.34** (1.27 to 1.42)	**115 more per 1 000** (from 91 more to 142 more)	⨁⨁◯◯ Low	IMPORTANT
Systemic reactions (follow-up: 7 days)												
17	observational studies	serious[a]	not serious	not serious	not serious	none	7392/20086 (36.8%)	3900/13659 (28.6%)	**RR 1.26** (1.22 to 1.30)	**74 more per 1 000** (from 63 more to 86 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

a. Risk of bias has been assessed using the ROBINS-I tool. Six studies were deemed at serious risk of confounding as there is no possibility to stratify results according to pre-specified age groups. Otherwise, all studies were considered at low risk of bias in all other domains. In sensitivity analysis, conclusions were unchanged after stratifying results according to other age groups. We downgraded the certainty of the evidence by one level as most of information are from studies at low risk of bias.

b. Moderate heterogeneity for injection site reactions (I2=70%, P value <0.0001 among younger participants and I2=73%, P value <0.0001 among older participants. Might partially be explained by the variation in definitions used for injection site reactions between studies and the impossibility to stratify results according to pre-specified age groups in some studies. The certainty of evidence was lowered by one level.

Appendix G:

Table G1: Subgroup analyses for the association of sex and injection site reactions (ISR) following influenza vaccines (solicited period) among younger and older participants[a]

Subgroups	Number of studies	Females		Males		Risk ratio M-H, random (95% CI)	P-value for heterogeneity among subgroups
		Events	Total	Events	Total		
Younger participants							
Vaccine type							
QIV[b]	13	3557	5578	1829	3797	1.31 (1.22; 1.40)	0.40
TIV[c]	11	2277	3976	1217	2648	1.25 (1.16; 1.35)	
Risk of bias							
Low	8	4421	7232	2262	4738	1.29 (1.19; 1.40)	0.90
Serious	6	1413	2322	784	1707	1.28 (1.16; 1.42)	
Older participants							
Vaccine type							
QIV[b]	11	1300	3832	725	3071	1.41 (1.25; 1.60)	0.55
TIV[c]	9	1923	6909	924	4344	1.50 (1.28; 1.76)	
Risk of bias							
Low	8	2726	9375	1431	6326	1.33 (1.21; 1.46)	**0.05[d]**
Serious	4	497	1366	218	1089	1.73 (1.35; 2.22)	

[a] Younger participant include those aged 18-64 years and older participants those aged 65 years and over. ISR have been collected within 7 days following vaccination. Events: Number of participants reporting at least one ISR during the period. Total: Number of participants with available data for solicited symptoms See Appendix A for the list of ISR collected in each study and the criteria used. Risk assessment has been done using the risk of bias in non-randomized studies of intervention (Robins-I) assessment tool. Studies were deemed at serious risk of bias due to confounding when there was no possibility to stratify results according to pre-specified age groups.

[b] Subgroup of participants who received QIV

[c] Subgroup of participants who received TIV.

[d] A P-value < 0.10 indicates a statistically significant subgroup difference.

Appendix H:

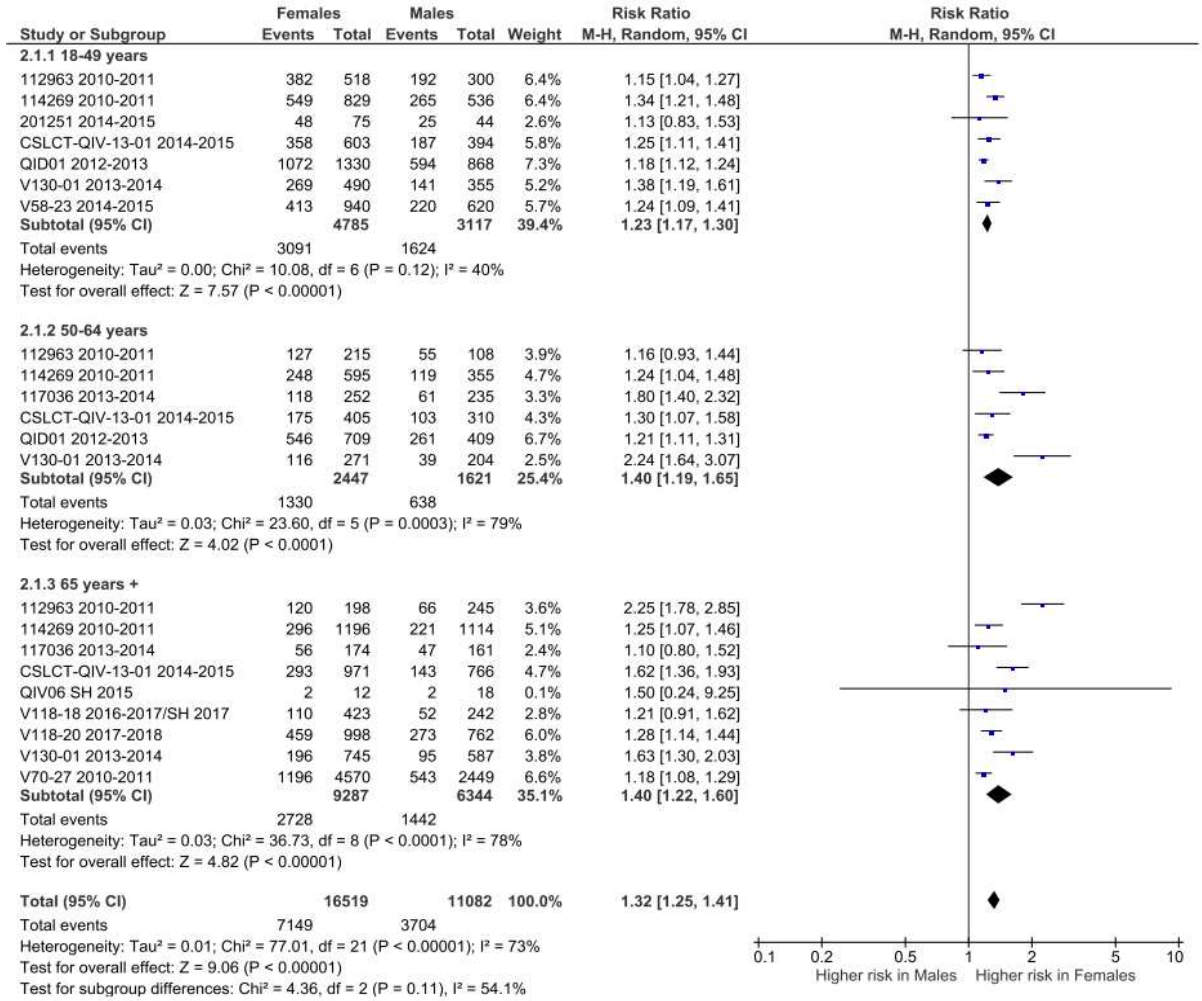

Figure H1. Risk ratio for the association of sex with injection site reactions (ISR) following influenza vaccines (solicited period) among participants aged 18-49 years, 50-64 years and 65 years and over.

Only studies for which we have the data for these age groups are included (N=12). ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season; SH denotes Southern Hemisphere influenza season if applicable. ISR have been collected within 7 days following vaccination. Events: Number of participants reporting at least one solicited local reaction during the period. Total: Number of participants with available data for solicited symptoms. See Appendix E for the list of ISR collected in each study and the criteria used.

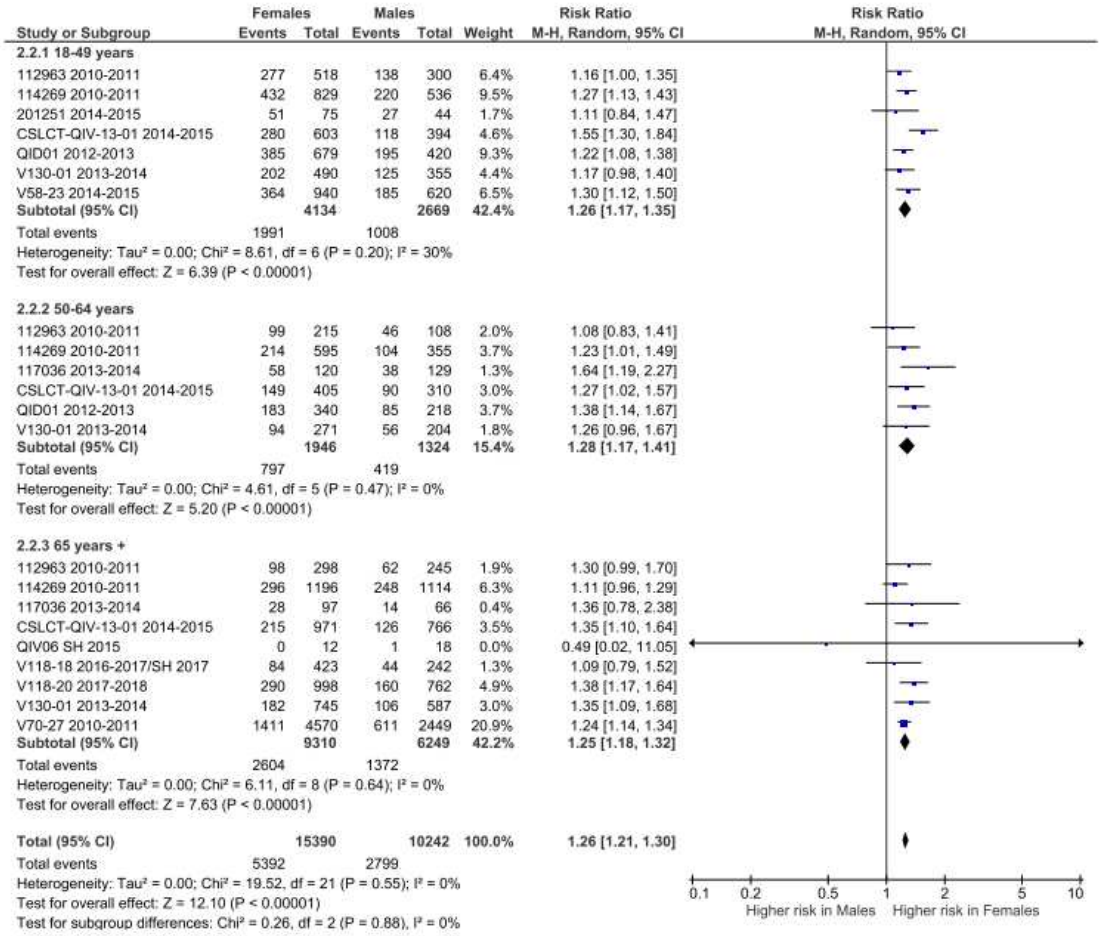

Figure H2. Risk ratio for the association of sex with systemic reactions following influenza vaccines (solicited period) among participants aged 18-49 years, 50-64 years and 65 years and over.

Only studies for which we have the data for these age groups are included (N=11). ID used for each study refers to the clinical trial number followed by the Northern hemisphere influenza season. SH: Southern Hemisphere influenza season. Local reactions have been collected within 7 days following vaccination. Events: Number of participants reporting at least one solicited systemic reaction during the period. Total: Number of participants with available data for solicited symptoms. See Appendix E for the list of systemic reactions collected in each study and the criteria used.

Appendix I:

Generalized linear mixed models:

Model 1: $\text{Log}\,(P\,[\text{Injection site reactions} = 1 \mid X_i, Z_i] = \underbrace{\beta_0 + \beta_1 \text{Sex} + \beta_2 \text{Age}}_{\text{Fixed effects}} + \underbrace{\gamma_0 + \gamma_1 \text{Sex}}_{\text{Random effects}}$

Model 2: $\text{Log}\,(P\,[\text{Systemic reactions} = 1 \mid X_i, Z_i] = \underbrace{\beta_0 + \beta_1 \text{Sex} + \beta_2 \text{Age}}_{\text{Fixed effects}} + \underbrace{\gamma_0 + \gamma_1 \text{Sex}}_{\text{Random effects}}$

Where X=fixed variables and β =the effects (fixed) of these variables

Z=random variables and γ the effects (random) of these variables

The model allows that the effect of sex could vary between studies.

Measures	Relative risk	95% Confidence intervals
Association of sex with injection site reactions	1.29	1.19; 1.39
Association of sex with systemic reactions	1.21	1.11; 1.31

Table I1: Corrections for multiple comparisons

Injection site reactions			**Systemic reactions**		
Main analysis	***P***	***P'***	**Main analysis**	***P***	***P'***
Outcomes			**Outcomes**		
Overall ISR			Overall systemic reactions		
Younger participants	0.0001	0.0028	Younger participants	0.0001	0.0019
Older participants	0.0001	0.0028	Older participants	0.0001	0.0019
Test for subgroup differences	0.1100	0.8800	Test for subgroup differences	0.7600	1.0000
Grade 3 ISR			Grade 3 systemic reactions		
Younger participants	0.0004	0.0044	Younger participants	0.0001	0.0019
Older participants	0.1400	0.8800	Older participants	0.0001	0.0019
Test for subgroup differences	0.7300	1.0000	Test for subgroup differences	**0.0300**	**0.2400**
Pain			Fever		
Younger participants	0.0001	0.0028	Younger participants	**0.0300**	**0.2400**
Older participants	0.0001	0.0028	Older participants	0.5900	1.0000
Test for subgroup differences	0.2900	1.0000	Test for subgroup differences	0.3700	1.0000
Redness			Headache		
Younger participants	0.0001	0.0028	Younger participants	0.0001	0.0019
Older participants	0.0001	0.0028	Older participants	0.0001	0.0019
Test for subgroup differences	**0.0200**	**0.2000**	Test for subgroup differences	0.8500	1.0000
Sensitivity analysis			Myalgia		
Outcomes			Younger participants	0.0002	0.0020
Overall ISR			Older participants	0.0030	0.0270
18-49 y	0.0001	0.0028	Test for subgroup differences	0.6400	1.0000
50-64 y	0.0001	0.0028	**Sensitivity analysis**		
65+ y	0.0001	0.0028	**Outcomes**		
Test for subgroup differences	0.1100	0.8800	Overall systemic reactions		
Overall ISR - younger participants			18-49 y	0.0001	0.0019
QIV vaccine	0.0001	0.0028	50-64 y	0.0001	0.0019
TIV vaccine	0.0001	0.0028	65+ y	0.0001	0.0019
Test for subgroup differences	0.4000	1.0000	Test for subgroup differences	0.8800	1.0000
Overall ISR – older participants					
QIV vaccine	0.0001	0.0028			
TIV vaccine	0.0001	0.0028			
Test for subgroup differences	0.5500	1.0000			
Overall ISR younger participants					
Low/moderate risk of bias	0.0001	0.0028			
Serious risk of bias	0.0001	0.0028			
Test for subgroup differences	0.9000	1.0000			
Overall ISR – older participants					
Low/moderate risk of bias	0.0001	0.0028			
Serious risk of bias	0.0001	0.0028			
Test for subgroup differences	**0.0500**	**0.4500**			

P': p-value adjusted for the multiple comparisons by the Holm method.