

SUPPLEMENTAL STATEMENT –
Recombinant Influenza Vaccines

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Canadian Immunization Guide Chapter on
Influenza and Statement on Seasonal Influenza
Vaccine for 2022–2023

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



Public Health
Agency of Canada

Agence de la santé
publique du Canada

Canada

**TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP,
INNOVATION AND ACTION IN PUBLIC HEALTH.**

—Public Health Agency of Canada

Également disponible en français sous le titre :
Déclaration supplémentaire – Vaccins antigrippaux recombinants
Une déclaration d'un comité consultatif (DCC)
Comité consultatif national de l'immunisation (CCNI)
Chapitre sur la grippe du Guide canadien d'immunisation et Déclaration sur la vaccination antigrippale pour la saison
2022-2023

This publication can be made available in alternative formats upon request.

© Her Majesty the Queen in Right of Canada, as represented by the Minister of Health, 2022

Publication date: September 2022

This publication may be reproduced for personal or internal use only without permission provided the source is fully acknowledged. However, multiple copy reproduction of this publication in whole or in part for purposes of resale or redistribution requires the prior written permission from the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5 or copyright.droitdauteur@pwgsc.gc.ca.

Cat.: HP5-140/2022E-PDF

ISBN: 978-0-660-44486-4

Pub.: 220317

PREAMBLE

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI Statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

TABLE OF CONTENTS

SUMMARY OF THE INFORMATION CONTAINED IN THIS NACI SUPPLEMENTAL STATEMENT	3
I. INTRODUCTION	4
II. METHODS	6
II.1 NACI literature review	6
III. VACCINE	10
III.1 Recombinant influenza vaccine preparation authorized for use in Canada	10
III.2 Vaccine efficacy and effectiveness	10
III.3 Immunogenicity	11
III.4 Safety	14
IV. DISCUSSION	18
V. RECOMMENDATIONS	20
VI. TABLES	21
LIST OF ABBREVIATIONS	48
ACKNOWLEDGEMENTS	50
REFERENCES	51
APPENDIX A: PRISMA FLOW DIAGRAM	55
APPENDIX B: CHARACTERISTICS OF INFLUENZA VACCINES AVAILABLE FOR USE IN CANADA, 2022–2023 ^A	56

SUMMARY OF THE INFORMATION CONTAINED IN THIS NACI SUPPLEMENTAL STATEMENT

The following highlights key information for immunization providers. Please refer to the remainder of this supplemental statement for details.

1. What

Supemtek™ is a quadrivalent recombinant seasonal influenza vaccine (RIV4) that has recently been authorized for use in Canada in adults 18 years of age and older. Supemtek is the first and, to date, the only seasonal influenza vaccine made with recombinant technology available in Canada. Other influenza vaccines are made in eggs or mammalian cell cultures.

2. Who

This supplemental statement addresses the annual influenza vaccination of adults who do not have contraindications to Supemtek.

3. How

Supemtek may be considered among the quadrivalent influenza vaccines offered to adults 18 years of age and older for their annual influenza vaccination.

4. Why

Supemtek is considered effective, immunogenic, and safe in adults 18 years of age and older and has a comparable immunogenicity and safety profile to egg- and cell culture-based, inactivated, live attenuated, adjuvanted, and high-dose seasonal influenza vaccines already licensed in Canada. Supemtek can provide a broader protection against influenza when compared to trivalent vaccines as its formulation contains both influenza B lineages. In addition, it contains identical hemagglutinin proteins to target influenza strains.

I. Introduction

Influenza is a viral infection that has been estimated to cause approximately 12,200¹ hospitalizations and 3,500 deaths² in Canada annually. In the five seasons prior to the COVID-19 pandemic (2014–2015 to 2018–2019 seasons), an average of 47,000 laboratory-confirmed cases of influenza were reported to FluWatch, Canada’s national surveillance system, each year^{3–5}. The burden of influenza illness varies from year to year. Influenza activity has been at a historical low during the COVID-19 pandemic, which has been associated with various reasons including the implementation of non-pharmaceutical public health measures (e.g., masking, social distancing) against COVID-19. Only 69 confirmed cases of influenza were identified in Canada during the 2020–2021 season and no community circulation of influenza occurred⁵. A return of persistent sporadic influenza activity was observed in the 2021–2022 season. It is expected that seasonal influenza will continue to re-circulate following the relaxation of COVID-19 pandemic-related public health measures. Low exposure to influenza during the COVID-19 pandemic may lead to higher infection rates when influenza begins circulating as levels of immunity to influenza may have decreased during the pandemic⁶. An increased number of influenza infections and larger outbreaks compared to those observed during the COVID-19 pandemic when infections were reported to be at historic lows^{6,7} may occur. Additionally, the resurgence of seasonal influenza may not follow usual seasonal patterns^{5,8}. Vaccination against seasonal influenza remains the best method of preventing and limiting the spread and impact of seasonal influenza circulation.

Influenza in humans is caused by two main types of influenza virus: A, which is classified into subtypes based on hemagglutinin (HA) and neuraminidase (NA) surface proteins, and B, which consists of two antigenically distinct lineages, B/Yamagata and B/Victoria. Seasonal influenza vaccines are either trivalent or quadrivalent formulations. Trivalent influenza vaccines contain two influenza A and one influenza B strain, and quadrivalent influenza vaccines contain the three strains included in trivalent vaccines and an additional influenza B strain from the other lineage of influenza B. Each year, the National Advisory Committee on Immunization (NACI) publishes a statement on seasonal influenza vaccines, which contains recommendations and guidance on the use of influenza vaccines for the upcoming influenza season.

Supemtek (Sanofi Pasteur, Ltd.) is a quadrivalent recombinant seasonal influenza vaccine (RIV4) that was authorized for use in Canada in adults 18 years of age and older on January 14, 2021⁹. Supemtek is created using an insect cell-baculovirus expression vector system and influenza virus proteins (i.e., HA antigens)⁹. The vaccine manufacturing process involves inserting the gene for the production of the HA antigen into a baculovirus to produce a recombinant baculovirus. Insect cells [proprietary expresSF+ insect cells] are then infected with the recombinant baculovirus. The baculovirus facilitates the transportation of the genetic instructions for producing the HA antigen to the host insect cells. A single HA antigen is cloned in these host cells. The individual HA antigens are then extracted from the host cells and further purified to be formulated into the final vaccine product.

Recombinant technology is a novel platform for influenza vaccine manufacturing that aims to overcome challenges associated with egg-based vaccine production and to improve the development process and quality of seasonal influenza vaccines^{10–12}. Although Supemtek is the only seasonal influenza vaccine made with recombinant technology authorized for use in Canada, the recombinant protein technology is an established technique that has been utilized to produce vaccines for other vaccine-preventable diseases, including hepatitis B,

human papillomavirus, meningococcal group B, herpes zoster, cholera, traveller's diarrhea and COVID-19¹³. Additionally, RIV has been licensed in the United States (US) for 9 years.

The recombinant manufacturing platform offers several advantages over egg-based or cell-based vaccine production including faster production times, high vaccine purity, and reduced risk of mismatch between the vaccine and circulating viral strains^{12,14}. The recombinant production is not dependent on egg supply nor the availability of an avian or canine kidney cell substrate, as it does not require expansion of live egg-grown nor cell-grown viruses for development of a candidate vaccine virus. It therefore allows for a faster manufacturing process that can be valuable during a pandemic response or in cases of vaccine supply shortage^{11,14}. Recombinant vaccines are made from stable genetic sequences from original wild-type human isolates, so large quantities of highly purified HA can be produced in a relatively short period of time without preservatives^{11,14}.

Additionally, recombinant vaccine technology ensures an exact match of HA protein included in the vaccine to the influenza strains recommended seasonally by the World Health Organization (WHO). It is not subject to the risk of mutations related to egg-adaptive changes and therefore may potentially have higher vaccine effectiveness relative to standard egg-based influenza vaccines¹². At the time of this Statement's development, the infrastructure required for manufacturing recombinant vaccines is limited compared to the vast infrastructure for producing egg-based influenza vaccines^{15,16}. Thus, the cost of recombinant influenza vaccines (RIV) is typically greater compared to egg-based vaccines^{15,16}.

The authorization of Supemtek triggered the need for a supplemental NACI statement, as it is the first, and currently the only, RIV available in Canada, and NACI has not previously made a recommendation on RIV in any population. Supemtek (licensed in the US under the tradename Flublok® Quadrivalent) builds on the clinical development of its trivalent predecessor, Flublok (RIV3), a RIV developed by Protein Sciences, Inc. (currently operating as Sanofi Pasteur, Ltd.). Flublok and its quadrivalent formulation, Flublok Quadrivalent, have been licensed for use among adults in the US since 2013 and 2016, respectively. Supemtek has also been licensed for use in the European Union (EU) since 2020. The trivalent and quadrivalent RIV formulations have the same manufacturing process. Additionally, both formulations have a high purity of HA and similar compositions, with the differentiation being that the quadrivalent formulation has a higher content of recombinant HA (180 instead of 135 µg/dose) due to the inclusion of one additional HA antigen⁹. The Supemtek formulation comprises antigens from two influenza A subtype viruses (H1N1 and H3N2) and two influenza type B virus lineages (B/Yamagata lineage and B/Victoria lineage). Supemtek contains three times higher HA content per strain compared with cell- and egg-based standard-dose quadrivalent influenza vaccines. Despite the higher HA content, administration of the vaccine does not appear to be associated significant increase in adverse events (AEs)^{17,18}.

Guidance Objective:

The objective of this advisory committee supplemental statement is to review the available evidence on the efficacy, effectiveness, immunogenicity, and safety of Supemtek, and to provide guidance on its use among adults in Canada.

II. METHODS

In brief, the broad stages in the preparation of this NACI statement included:

- Knowledge synthesis;
- Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and certainty of effects observed across studies;
- Translation of evidence into recommendations.

Details of NACI's evidence-based process for recommendation development can be found elsewhere^{19,20}.

To develop comprehensive, appropriate immunization program recommendations, NACI considers a number of factors. In addition to critically appraising the evidence on burden of disease and vaccine characteristics such as safety, efficacy, immunogenicity and effectiveness, NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into its guidance²¹. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) to consider these programmatic factors systematically for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools, please see [A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations](#).

For this advisory committee statement, NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to organize the information and to develop recommendations. Further information on this framework can be found in the [GRADE handbook](#).

A systematic review, including scientific and grey literature, and a meta-analysis were undertaken to develop recommendations for the use of Supemtek seasonal influenza vaccine in adults 18 years of age and older in Canada. The literature review and knowledge synthesis were performed by PHAC staff and supervised by the NACI Influenza Working Group (IWG). Following critical appraisal of individual studies, proposed recommendations for vaccine use were developed. The evidence and proposed recommendations were presented to NACI for deliberation on October 27, 2021 and approved following a thorough review of the evidence. Relevant considerations, rationale for specific decisions, and knowledge gaps are described in the following sections.

II.1 NACI literature review

The policy and research questions addressed in this statement are:

Policy Question: Should Supemtek be considered alongside the influenza vaccines already recommended for use by NACI?

Research Question: What are the vaccine efficacy, effectiveness, immunogenicity, and safety of Supemtek in persons 18 years of age and older?

The literature search and data extraction were conducted according to the following PICOT framework (Population, Intervention, Comparators, Outcomes and Time):

- P (Population):** Adults (18 years of age and older)
- I (Intervention):** Quadrivalent recombinant influenza vaccine (RIV4)
- C (Comparator):** Egg-based, standard-dose quadrivalent inactivated influenza vaccine (IIV4-SD), trivalent, standard-dose inactivated influenza vaccine (IIV3-SD), high-dose (IIV3- HD) or adjuvanted trivalent inactivated influenza vaccine (IIV3-Adj), mammalian cell culture-based trivalent inactivated influenza vaccine (IIV3-cc) or quadrivalent inactivated influenza vaccine (IIV4-cc), placebo, or no comparator
- O (Outcome):** Efficacy, effectiveness, immunogenicity, safety
- T (Time)** Studies published January 2000 or later

The search strategy was developed based on the research question and PICOT illustrated above, in conjunction with a librarian from the Health Library of Health Canada and PHAC (search strategy available upon request). The EMBASE, MEDLINE, Cochrane Central, Scopus, ProQuest Public Health, and ClinicalTrials.gov, electronic databases were searched for primary research articles and case reports. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered. Searches were restricted to articles published in English or French due to the language proficiencies of the reviewers. Additionally, hand-searching of the reference lists of included articles was performed by one reviewer to identify additional relevant publications. All searches were performed on January 12, 2021, with an update to August 8, 2021.

Two reviewers independently screened the titles and abstracts of records retrieved from the database searches for potential eligibility. DistillerSR® (Evidence Partners Inc., Ottawa, Canada) was used to operationalize screening and data management. The full texts of records deemed potentially eligible were obtained and independently reviewed by both reviewers for potential inclusion in the review. Refer to Appendix A for the PRISMA Flow Diagram of study selection.

Studies were included if they met the following criteria:

1. The study population or subpopulation consisted of adults 18 years of age and older;
2. Study assessed efficacy and effectiveness, immunogenicity, or safety of RIV4;
3. Primary research studies from peer-reviewed scientific literature;
4. Case reports and case series;
5. Registered clinical trials and grey literature from international public health authorities (Australian Technical Advisory Group on Immunisation [ATAGI]; Centers for Disease Control and Prevention [CDC]; clinicaltrials.gov; European Centre for Disease Prevention and Control [ECDC]; European Medicines Agency [EMA]; Department of Health Services Research & Policy [HSRP]; International Clinical Trials Registry Platform [ICTRP]; World Health Organization [WHO]);
6. Study is published in English or French; and
7. Published in 2000 or later.

Studies were excluded if they met one or more of the following criteria:

1. The study did not present data on any of: the efficacy, effectiveness, immunogenicity, or safety of RIV4;
2. The study is in a language other than English or French;
3. The study is a non-human or in vitro study;
4. The article is not a primary research study;
5. The article is an editorial, opinion, commentary or news report;
6. The article is an economic study, clinical practice guideline, consensus conference, health technology assessment (HTA) report;
7. The article was a doctoral dissertation, master's thesis, or conference summary; or
8. The article is a duplicate.

One reviewer extracted data from the studies included for review into an evidence table using a piloted data abstraction template designed to capture information on study design, population and outcomes of interest. A second reviewer independently validated the abstracted data. Two reviewers independently assessed the risk of bias within each included study using the Cochrane tools (RoB 2.0²² for randomized trials and ROBINS-I²³ for non-randomized studies of interventions). The Joanna Briggs Institute (JBI) checklist was used to examine potential risks of bias in case reports or case series²⁴. The strength and certainty of evidence included in syntheses were assessed by two independent reviewers using the GRADE system^{25,26}. In the current review, GRADE assessment was reserved for outcomes deemed to be critical or important to decision making by the IWG based on the results of a prioritization exercise. The following critical outcomes and definitions were identified:

1. **Serious Adverse Event (SAE):** Any untoward medical occurrence that at any dose results in death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is life-threatening.
2. **Laboratory Confirmed Influenza (LCI)-Related Mortality:** A death during an influenza season resulting from a clinically compatible illness that was confirmed to be influenza by an appropriate laboratory test (e.g., reverse transcription polymerase chain reaction (RT-PCR), virus culture or antigen detection); all influenza (A and B).
3. **Laboratory Confirmed Influenza (LCI):** Symptoms of influenza with a positive laboratory diagnosis by reverse transcription polymerase chain reaction (RT-PCR), virus culture or antigen detection; all influenza (A and B).
4. **Solicited Systemic AE:** Intentionally solicited systemic reactions including but not limited to fever, malaise, muscle pain, headache or loss of appetite.
5. **Seroprotection:** Proportion of subjects achieving a hemagglutination inhibition (HI) titre of $\geq 1:40$ post-vaccination²⁷.
6. **Seroconversion:** Proportion of subjects achieving an increase from $\leq 1:10$ HI titre pre-vaccination to $\geq 1:40$ post-vaccination or achieving at least four-fold rise in HI titres²⁷.
7. **Geometric Mean Titre Ratio (GMTR):** Ratio of **Geometric Mean Titre (GMT)** post-vaccination of previously licensed vaccine to GMT post-vaccination of new vaccine²⁷.

For each outcome definition identified, the GRADE framework was used to assess the strength and certainty of the evidence. GRADE guidance was followed for determining the extent of the risk of bias for the body of evidence. Any disagreements or discrepancies during the data extraction and quality appraisal processes were resolved by discussion and consensus. The knowledge synthesis was performed by AG, AS, MX, and PD, and was supervised by the IWG.

Data were compiled by outcome to evaluate: the availability of quantitative evidence; heterogeneity with respect to comparisons, outcome definitions, and time point of measurement; and feasibility and appropriateness of meta-analysis. Meta-analyses were performed to pool study estimates for seroconversion rates and proportion of study participants who experienced an AE following immunization with Supemtek compared to other seasonal influenza vaccine recipients. Only estimates from studies deemed to be clinically and methodologically similar were pooled. A random effects model was used for all meta-analyses. Subgroup analyses were conducted by age group (18 to 49 years old, 50 to 64 years old, 65 years and older), vaccine strains, and influenza vaccine type. Potential heterogeneity between studies was assessed using the I^2 statistic, with a threshold of 50% or higher suggesting potentially important heterogeneity. Forest plots have been provided to present meta-analyses. Potential publication bias was assessed using funnel plots.

All analyses were conducted using the RevMan 5.0 meta-analysis software²⁸.

III. VACCINE

III.1 Recombinant influenza vaccine preparation authorized for use in Canada

Supemtek is an unadjuvanted RIV4 made from recombinant HA expressed in proprietary expresSF+ insect cells (derived from *Spodoptera frugiperda* cells) using baculovirus as a vector for protein expression. It is authorized for intramuscular (IM) injection and is available as a 0.5 mL single-dose, pre-filled syringe without a needle. Supemtek does not contain egg proteins, antibiotics, or preservatives. There is no gelatin added in Supemtek as a stabilizer. The single-dose, prefilled syringes also do not contain any natural rubber latex. For more information on Supemtek, refer to the product monograph⁹.

Table 1. Characteristics of Supemtek influenza vaccine

Route of Administration	Dosage	Non-medicinal Ingredients
Intramuscular	Each 0.5 mL dose contains 45 µg of HA of each of the four influenza virus strains contained in the vaccine	Sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, and polysorbate 20. Each dose may also contain residual amounts of: Baculovirus and <i>Spodoptera frugiperda</i> cell proteins, baculovirus and cellular DNA, and Triton X-100.

III.2 Vaccine efficacy and effectiveness

Two vaccine efficacy and effectiveness outcomes were ranked as critical during the outcome prioritization process: efficacy or effectiveness against laboratory-confirmed influenza (LCI)-related mortality and efficacy or effectiveness against LCI.

One peer-reviewed study that assessed the efficacy of Supemtek against LCI was identified and included in the review¹⁷ and is summarized below.

Although one effectiveness study reporting on influenza hospital encounters was identified as part of this review, the study by Izurieta et al. (2020)²⁹ was not included in the evidence synthesis because it did not provide data on LCI outcomes that were pre-specified as critical for decision making in this analysis. Therefore, the certainty of evidence from this study was not assessed and the study will not be presented further.

Peer-reviewed, published clinical data pertaining to the efficacy or effectiveness of vaccination with RIV4 during pregnancy or including breastfeeding were not available at the time of this review.

Efficacy against Laboratory-Confirmed Influenza-Related Mortality

No studies reported on the efficacy of Supemtek against LCI-related mortality and studies evaluating the efficacy of Flublok against LCI-related mortality were beyond the scope of this review.

Efficacy against Laboratory-Confirmed Influenza Infection

The study by Dunkle et al. (2017a)¹⁷ assessed the relative vaccine efficacy (rVE) of Supemtek compared to egg-based IIV4-SD against LCI infection during the 2014-2015 influenza season in the US. Specifically, Dunkle et al. (2017a) conducted a participant, care provider, investigator, and outcomes assessor-blind parallel Phase 3-4 randomized clinical trial to determine the rVE of Supemtek compared to egg-based IIV4-SD against reverse transcription polymerase chain reaction (RT-PCR) confirmed influenza infection and culture-positive influenza infection¹⁷. The clinical trial was conducted in medically stable, ambulatory adults 50 years of age and older (mean age: 63; age range: 50-96) at 40 outpatient centres across the US¹⁷. Individuals testing positive for influenza by RT-PCR or viral culture between 14 and 224 days after vaccination were classified as cases¹⁷.

The results from the study by Dunkle et al. (2017a) indicated that study participants who received Supemtek had statistically significantly lower risk of having any RT-PCR LCI infection compared to study participants who received IIV4-SD (rVE: 30%; 95% confidence interval (CI): 10 to 47%; hazard ratio [HR]: 0.69; 95% CI: 0.53 to 0.90; p=0.006)¹⁷. In separate sub-group analyses, the rVE for adults 50 years of age and older who were vaccinated with Supemtek versus IIV4-SD was statistically significant for influenza A (rVE: 36%; 95% CI: 14 to 53%) and was not statistically significant against RT-PCR LCIB (rVE: 4%; 95% CI: -72 to 46%)¹⁷. This trial was performed during the 2014-15 influenza season which was characterized by widespread circulation of antigenically mismatched influenza A(H3N2)¹⁷. The pre-specified non-inferiority criterion required a lower bound of the 95% CI for rVE greater than -20% and the pre-specified superiority criterion required a lower bound of the 95% CI for rVE greater than 9%¹⁷. A pre-specified exploratory analysis for superiority was also assessed if the primary endpoint had a lower bound 95%CI of >9%. Since the lower bound here was 10% for the primary endpoint, this pre-specified endpoint for superiority was met. However, subgroup analyses by influenza type demonstrated that adults 50 years of age and older who were vaccinated with Supemtek had statistically significantly lower risk of having any RT-PCR LCIA (rVE: 36%; 95% CI: 14 to 53%; HR: 0.64; 95% CI: 0.48 to 0.86; p=0.003)¹⁷. rVE against RT-PCR LCI for adults 50 to 64 years of age who were vaccinated with Supemtek compared to egg-based IIV4-SD was 42% (95% CI: 15 to 61%) and 17% (95% CI: -20 to 43%) for adults >64 years of age¹⁷. rVE estimates were similar between RT-PCR LCI infections and viral culture-positive influenza infections for all subgroup analyses conducted¹⁷. This study was conducted in adults aged 50 years and over and, therefore, the findings may not be directly applicable to younger adult populations. Moreover, the study presented wide CIs around the outcome measures important to this analysis. Due to the limitations of the available vaccine efficacy data, the overall quality of the body of evidence for this outcome was rated as low. Additional details regarding study characteristics and results are shown in Table 4.

III.3 Immunogenicity

Regulators in Canada, the US, and Europe accept non-inferiority immunogenicity trials that compare the HI antibody response of the new vaccine to that of an existing licensed vaccine, or placebo-controlled immunogenicity trials that assess the HI antibody response to the new vaccine. Non-inferiority and placebo-controlled immunogenicity trials are often considered sufficient by regulatory authorities when there are bridging data to correlate immunogenicity outcomes to clinical protection, or when the new vaccines are considered by the regulators to be very similar to vaccines already authorized. Serological assessments based on the GMTs of HI antibody that are used by regulators are: GMTR, seroprotection rate, and seroconversion rate. The US Food and Drug Administration (FDA) has published definitions for these serological assessments and

criteria for immunogenicity data necessary for influenza vaccine licensure²⁷, which are also used in Canada. These definitions and currently used criteria are shown in Table 3. Correlates of protection that are not based on HI antibody titres have not been well established.

Three vaccine immunogenicity outcomes were ranked as critical during the outcome prioritization process of this review: seroprotection rate, seroconversion rate, and GMTR. Although GMT was not identified as a critical outcome, evidence reporting on GMT will be presented to supplement the evidence base for immunogenicity.

Eight RCTs that assessed the immunogenicity of Supemtek compared to different influenza vaccines, including IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), IIV3-Adj (Fluad[®], Seqirus, Inc.), IIV4-SD (FluQuadri[™], Sanofi Pasteur; Fluarix Quadrivalent, GlaxoSmithKline; Fluzone Quadrivalent, Sanofi Pasteur), and IIV4-cc (Flucelvax[®] Quadrivalent, Seqirus), were identified in this review. One study was conducted among adult military beneficiaries 18 years of age and older³⁰, one study was conducted among adult participants 50 years of age and older¹⁷, three studies were conducted among adult participants 65 years of age and older^{31–33}, two studies focused on adult participants 18 to 49 years of age^{34,35}, and one study was conducted among healthcare personnel 18 to 64 years of age³⁶. Of these studies, two were conducted during the 2014-2015 influenza season^{17,34}, three were conducted over the 2017-2018 influenza season^{31,32,35}, and three were conducted over the 2018-2019 influenza season^{30,33,36}. Additional details on the immunogenicity findings from these studies are shown in Table 5. Overall, there was fair evidence (of moderate certainty) that the immunogenicity for Supemtek is non-inferior to traditional egg-based comparators, based on data in adults aged 18 years and older. Three RCTs were identified to have an unclear risk of selection bias as these studies did not specify the method of random sequence generation^{30,32,35}. Two RCTs were identified to have a moderate risk of recruitment bias as these studies were conducted at a single-centre that may not be representative of the population of interest^{31,35}. One RCT was identified to have an unclear risk of recruitment bias as it did not specify the site used for recruitment³².

Seroprotection rate

Four RCTs were identified that assessed the seroprotection rate of HI titres against HA of Supemtek at approximately three to five weeks post-vaccination^{17,31,33,36}. Of these studies, one was conducted during the 2014-2015 influenza season¹⁷, one was conducted over the 2017-2018 influenza season³¹, and two were conducted over the 2018-2019 influenza season^{33,36}. The comparator vaccines for these four studies included IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline), IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), and IIV3-Adj (Fluad, Seqirus, Inc.). Three RCTs were conducted among adult participants 50 years of age and older^{17,31,33} and one RCT was conducted among adult healthcare personnel 18 to 64 years of age³⁶. Only one RCT out of the four studies also assessed the seroprotection rate of HA of Supemtek at 56 days and 182 days post-vaccination³³. The comparator vaccines for this study included IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³³.

At approximately one month post-vaccination, the seroprotection rate in Supemtek recipients was similar to or higher than seroprotection rates for recipients of the comparator vaccines (IIV4-SD, IIV4-cc, IIV3-HD, IIV3-Adj) in adults 18 years of age and older^{17,31,33,36}. In two of the four studies, RIV4 met the non-inferiority criteria specified by the US FDA for all tested influenza strains including A(H1N1), A(H3N2), B/Yamagata lineage, and B/Victoria lineage^{33,36}. Across the four RCTs, RIV4 met non-inferiority criteria against five of seven tested strains of A(H3N2)^{17,31,33,36}. In Belongia et al. (2020), RIV4 demonstrated lower rates of seroprotection for older adults 65 to 74 years of age against two of four tested strains of A(H3N2)³¹. However, one limitation was the small

sample size of the study³¹. In the study by Dunkle et al. (2017a), RIV4 met the non-inferiority threshold for seroprotection against influenza A(H1N1), A(H3N2), and B/Yamagata lineage, but not against influenza B/Victoria lineage in adults aged 50 and older¹⁷. The FDA non-inferiority criterion required a lower bound of the 95% CI for the percentage of participants achieving seroprotection greater than or equal to 70% for adults under 65 years of age and greater than or equal to 60% for adults 65 years of age or older²⁷.

At 56 and 182 days post-vaccination, seroprotection rate against A/Michigan/45/2015 (H1N1) and B/Colorado/06/2017 (Victoria lineage) were slightly lower in Supemtek recipients compared to IIV3-HD recipients³³. However, no test of significance was conducted. At 56 and 182 days post-vaccination, seroprotection rates in Supemtek recipients against other tested influenza strains were comparable to or greater than seroprotection rates for recipients of the comparator vaccine (IIV3-HD) in adults 65 years of age and older³³. Additional details on the immunogenicity findings in adults can be found in Table 5.

Seroconversion rate

Eight RCTs were identified that assessed the seroconversion rate of HA of Supemtek at approximately three to five weeks post-vaccination^{17,30–36}. Of these studies, two were conducted during the 2014–2015 influenza season^{17,32}, three were conducted over the 2017–2018 influenza season^{31,32,35}, and three were conducted over the 2018–2019 influenza season^{30,33,36}. The comparator vaccines for these eight studies included IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus, Inc.), IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline; FluQuadri, Sanofi Pasteur; Fluzone Quadrivalent, Sanofi Pasteur), and IIV4-cc (Fluclavax Quadrivalent, Seqirus). One RCT assessed the seroconversion rate of HA of Supemtek at 56 days and 182 days post-vaccination³³. The comparator vaccines for this study included IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³³. Of the eight studies, one study was conducted among adult military beneficiaries 18 years of age and older³⁰, one study was conducted among adult participants 50 years of age and older¹⁷, three studies were conducted among adult participants 65 years of age and older^{31–33}, two studies focused on adult participants 18 to 49 years of age^{34,35}, and one study was conducted among healthcare personnel 18 to 64 years of age³⁶.

In four of the eight studies, at approximately three to five weeks post-vaccination, Supemtek demonstrated non-inferiority to IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc in the HI antibody responses against influenza A(H1N1), A(H3N2), B/Yamagata and B/Victoria lineage contained in the comparator vaccines, based on seroconversion rates^{31–33,36}. The FDA non-inferiority criterion required that the difference between the upper bound of the 95% CI of the seroconversion between the licensed vaccine and the new vaccine (i.e., seroconversion of licensed vaccine – seroconversion of new vaccine) did not exceed 10 percentage points²⁷.

There were different results in the remaining studies. The two studies by Dunkle et al. (2017) demonstrated that, compared to IIV4-SD, RIV4 met the non-inferiority threshold in HI antibody responses for 3 of the 4 virus strains. Non-inferiority, however, was not met against the B/Victoria lineage in adults 18 to 64 years of age^{17,34}. Additionally, rates of seroconversion following RIV4 did not meet the non-inferiority threshold compared to IIV4-SD against influenza A(H1N1) in adults 64 and older¹⁷. Non-inferiority could not be assessed for the remaining two RCTs as these studies did not state CIs for seroconversion estimates^{30,35}. Due to the heterogeneity in the influenza strain, vaccine type, follow-up period, and population in the seroconversion rates measured, only three of the eight studies identified could be pooled through meta-analysis. When data from three RCTs in adult participants 50 years of age and older were combined and weighted using a random effects model, there was little difference in seroconversion rates between

Supemtek and other seasonal influenza vaccine comparators (odds ratio [OR]: 1.36; 95% CI: 1.00 to 1.86; Figure 1)^{17,32,33}.

At 56 and 182 days post-vaccination, Supemtek demonstrated comparable HI antibody responses against A(H1N1), A(H3N2), B/Victoria lineage, and B/Yamagata lineage to IIV3-HD (Fluzone High-Dose, Sanofi Pasteur) in adults 65 years of age and older, based on seroconversion rates³³.

Geometric Mean Titre and Geometric Mean Titre Ratio

Eight RCTs assessed the GMT and/or GMTR of Supemtek compared to various different influenza vaccines including IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus, Inc.), IIV4-SD (FluQuadri, Sanofi Pasteur; Fluarix Quadrivalent, GlaxoSmithKline; Fluzone Quadrivalent, Sanofi Pasteur), IIV4-cc (Flucelvax Quadrivalent, Seqirus) at approximately three to twenty-six weeks (i.e., six months) following influenza vaccination were identified in this review^{17,30–37}. Of these studies, two were conducted during the 2014-2015 influenza season^{17,34,37}, three were conducted over the 2017-2018 influenza season^{31,32,35}, and three were conducted over the 2018-2019 influenza season^{30,33,36}.

Three studies assessed the GMTR of Supemtek compared to IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline; Fluzone Quadrivalent, Sanofi Pasteur) at approximately one month following vaccination in adults 18 years of age or older^{17,34,36,37}. In one study, RIV4 met the non-inferiority criteria specified by the US FDA for all tested influenza strains including A(H1N1), A(H3N2), B/Yamagata lineage, and B/Victoria lineage³⁶. In two of the three studies, seroresponses to A(H1N1), A(H3N2), and B/Yamagata lineage in RIV4 recipients aged 18 to 64 years were comparable to seroresponses in IIV4-SD recipients based on the GMTR^{17,34,37}. However, the GMTR against B/Victoria lineage for IIV4-SD recipients compared to RIV4 recipients did not meet the non-inferiority criteria set by the US FDA^{17,34,37}. The FDA non-inferiority criterion required an upper bound 95% CI on the GMTR to be less than or equal to 1.5²⁷. Geometric mean titre estimates could not be pooled during meta-analysis due to the heterogeneity between study populations (i.e., studies were conducted among different age groups).

Five RCTs assessed the GMT of Supemtek compared to various different influenza vaccines including IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus, Inc.), IIV4-SD (FluQuadri, Sanofi Pasteur; Fluarix Quadrivalent, GlaxoSmithKline; Fluzone Quadrivalent, Sanofi Pasteur), IIV4-cc (Flucelvax Quadrivalent, Seqirus) at three to eight weeks following vaccination^{30–33,35}. GMTs in Supemtek recipients were similar to or higher than GMTs for recipients of the comparator vaccines^{30–33,35}.

Additional details on the immunogenicity findings in adults can be found in Table 5.

III.4 Safety

Two vaccine safety outcomes were ranked as critical during the outcome prioritization process for this review: SAEs and solicited systemic AEs.

This review identified six peer-reviewed studies that assessed the safety of Supemtek in adults, including five RCTs and one review of post-marketing surveillance data in adults^{17,32–34,38,39}. Of these studies, two were conducted during the 2014-2015 influenza season^{17,34}, two were conducted during the 2017-2018 influenza season^{32,38}, one was conducted during the 2018-2019 influenza season³³, and one study reported data from the Vaccine Adverse Event Reporting System (VAERS) from July 1, 2017, through June 30, 2020³⁹. Among the five RCTs, one study

was conducted among adult participants 18 to 49 years of age³⁴, one study was conducted among adult participants 50 years of age and older¹⁷, and three studies focused on adult participants 65 years of age and older^{32,38,39}. Notably, no published clinical data pertaining to the safety of vaccination with RIV4 during pregnancy were available at the time of this review to inform vaccine-associated risks. Vaccine comparators used in the five RCTs included IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus, Inc.), IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline; FluQuadri, Sanofi Pasteur)^{17,32,38,39}. There was moderate certainty of evidence for the safety outcomes overall. A common concern across the studies reporting on the safety of Supemtek in adults was the imprecision of the estimates due to the lack of CIs reported in four of the five RCTs^{17,32,34,38} and the uncertainties regarding the completeness, quality, and consistency of the data reported to VAERS³⁹.

Additional details on the safety evidence presented in this review are shown in Table 6.

Serious Adverse Events

Five studies were identified that evaluated the occurrence of SAEs in recipients of Supemtek, including four RCTs^{17,32-34} and one review of post-marketing surveillance data in adults³⁹. SAEs reported across clinical trials were not considered by the investigators to be related to the trial vaccines^{17,32-34,39} and SAE rates were not significantly different between the study vaccine and the comparator vaccine(s).

One RCT examined the occurrence of SAEs in adult participants 18 to 49 years of age six months following Supemtek or IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline) administration³⁴. In this study, 1% of individuals who received Supemtek experienced at least one SAEs within six months following vaccination³⁴. The occurrence of SAEs was similar between the vaccine groups, and the study did not find any deaths or SAEs to be related to the study vaccines³⁴.

Three RCTs examined the occurrence of SAEs in adult participants 50 years of age or older^{17,32,33}. Cowling et al. (2020a) found that 6.6% of Supemtek recipients experienced hospitalization within 30 days following vaccination³². This proportion was comparable to or less than the proportion of participants who experienced hospitalization within 30 days of receiving a comparator vaccine, and all SAEs were deemed unrelated to the study vaccines³². One RCT found that 3.4% and 3.0% of adult participants 50 years of age or older experienced at least one SAE within six months of receiving Supemtek and IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline), respectively¹⁷. Common SAEs among this group of participants included cardiac disorders, musculoskeletal and connective tissue disorders, and infections and infestations¹⁷. Death occurred in 8 Supemtek recipients and in 12 IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline) recipients¹⁷. The occurrence of SAEs was similar between the vaccine groups, and the study did not find any deaths or SAEs to be related to the study vaccines¹⁷. The third RCT examined the occurrence of SAEs in adult participants 65 years of age or older within six months after receiving Supemtek or IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³³. This RCT found that 2% and 3.9% of adult participants 65 years of age or older experienced a SAE within six months after receiving Supemtek and IIV3-HD (Fluzone High-Dose, Sanofi Pasteur), respectively³³. Common SAEs found in this study included infections and infestations, metabolism and nutrition disorders, and injury, poisoning, and procedural complications³³. No SAEs were considered to be related to the study vaccines³³. When data from two RCTs in adult participants 50 years of age and older were combined and weighted using a random effects model, there was no difference in the odds of experiencing a serious adverse event following administration of Supemtek and other seasonal influenza vaccine comparators (OR: 1.01; 95% CI: 0.62 to 1.66; Figure 2)^{17,33}.

A clinical review of post-licensure surveillance data from the VAERS, which is a passive surveillance system useful for detecting safety issues related to newly licensed vaccines for use in the US, identified 849 AE reports following Supemtek administration from July 1, 2017, through June 30, 2020³⁹. Of these 849 AE reports, 39 were SAE³⁹. Notably, ten reports of Guillain-Barré syndrome were identified; two reports met Brighton Collaboration criteria level 1, five reports met Brighton Collaboration criteria level 2, and three reports met Brighton Collaboration criteria level 3³⁹. Three serious reports of anaphylaxis were identified, including two reports that met Brighton Collaboration criteria level 2, and one report that did not meet Brighton Collaboration criteria, but was diagnosed by the attending physician as an anaphylactic reaction³⁹.

Solicited Systemic Adverse Events

Four studies were identified that evaluated the occurrence of solicited systemic AEs in recipients of Supemtek, including three RCTs^{33,34,38} and one review of post-marketing surveillance data in adults³⁹. Most systemic reactions reported by the clinical trials were mild to moderate in severity and were transient in nature^{33,34,38}.

One RCT examined the proportion of adult participants 18 to 49 years of age who experienced solicited systemic AEs of any severity within 6-7 days following vaccination with Supemtek or IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline)³⁴. The proportion of participants who experienced at least one solicited systemic AE of any severity, at least one Grade 3 (i.e., severe) solicited systemic AE, and at least one Grade 4 (i.e., life-threatening) solicited systemic AE following Supemtek or the comparator vaccine IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline), were similar³⁴. Of the participants who received Supemtek, 34.1% experienced at least one solicited systemic AE of any severity, 2.3% experienced a Grade 3 (i.e., severe) solicited systemic AE, and 0% experienced a Grade 4 (i.e., life-threatening) solicited systemic AE within 6-7 days following vaccination³⁴. Common solicited systemic AEs included headache, fatigue, and muscle pain³⁴.

One RCT examined the proportion of adult participants 65 years of age or older who experienced at least one mild, moderate, or severe solicited systemic AE at one, three to four, seven to nine, and 14 to 16 days following vaccination with Supemtek, IIV4-SD (FluQuadri, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus), and IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³⁸. The proportion of participants who experienced at least one solicited systemic AE of each severity was similar between Supemtek and the comparator vaccines, including IIV4-SD (FluQuadri, Sanofi Pasteur), IIV3-Adj (Fluad, Seqirus), and IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³⁸. At one day following vaccination, 0.4%-5.0%, 0% and 0.4% of Supemtek recipients reported mild, moderate and severe solicited systemic AEs, respectively³⁸. At three to four days following vaccination, 1.5%-5.5%, 0.7%-1.1% and 0% of Supemtek recipients reported mild, moderate and severe solicited systemic AEs, respectively³⁸. At seven to nine days following vaccination, 0.3%-5.9%, 0.3%-0.7% and 0.3% of Supemtek recipients reported mild, moderate and severe solicited systemic AEs, respectively³⁸. At 14 to 16 days following vaccination, 0%-5.2%, 0%-1.6%, 0.7% of Supemtek recipients reported mild, moderate and severe solicited systemic AEs, respectively³⁸. Common solicited systemic AEs at all three time points included mild fatigue, mild muscle pain, mild feverishness, and other mild systemic AEs³⁸.

One RCT examined the proportion of adult participants 65 years of age or older who experienced at least one solicited systemic AE within six days of receiving Supemtek or IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³³. The proportion of participants who experienced at least one solicited systemic AE of any severity and at least one severe solicited systemic AE was similar between Supemtek and the comparator vaccine IIV3-HD (Fluzone High-Dose, Sanofi Pasteur)³³.

Within six days following vaccination, 25.8% (95% CI: 19.1, 33.6) of 151 Supemtek recipients experienced at least one solicited systemic AE of any severity and 2.6% (95% CI: 0.7to 6.6%) of the Supemtek recipients experienced at least one severe adverse event³³. Common solicited systemic AEs included muscle pain, fatigue, and headache³³.

A clinical review of post-licensure surveillance data from the VAERS, identified 849 adverse event reports following Supemtek administration from July 1, 2017, through June 30, 2020³⁹. Of these reports, the most common solicited systemic AEs reported included pyrexia, headache, and rash.

IV. DISCUSSION

This systematic review examined studies of the efficacy, immunogenicity, and safety of Supemtek, a recombinant seasonal influenza vaccine approved for adult use in Canada. The peer-reviewed published evidence on the efficacy of Supemtek against LCI illness was sparse. One RCT that evaluated the rVE of Supemtek was identified in this review¹⁷. The efficacy study by Dunkle et al. (2017) demonstrated that Supemtek was statistically significantly more efficacious than egg-based IIV4-SD in preventing LCI-A infection in adults 50 years of age or older. Compared to IIV4-SD, RIV4 met the non-inferiority threshold in HI antibody responses for 3 of the 4 virus strains. Non-inferiority, however, was not met against the B/Victoria lineage in adults 50 years of age and older¹⁷. The data from this clinical trial have limitations. The results may not be applicable to all influenza seasons as the study was conducted in the 2014-2015 influenza season in the US, which was A(H3N2)-dominant. Additionally, since the efficacy estimates were derived from one clinical trial conducted among adults 50 years of age or older, these efficacy estimates may not be generalizable to younger adults (e.g., adults 18 to 49 years of age). Furthermore, the CIs surrounding the efficacy estimates were wide, suggesting a risk of imprecision. A previous study by Treanor et al. (2011) found that the efficacy of Flublok, the previously FDA-approved trivalent formulation of Supemtek, was superior to a saline placebo against culture-positive influenza A, but not culture-positive influenza B in adults 18 to 49 years of age during the 2007-2008 influenza season in the US⁴⁰. The NACI IWG had prespecified vaccine efficacy against laboratory confirmed influenza-related mortality to be a critically important outcome to be considered, but no data were available for this outcome.

Eight RCTs conducted in adults that specifically assessed the immunogenicity of Supemtek were identified in this review^{17,30-36}. Overall, across the eight studies, Supemtek demonstrated non-inferiority compared to egg-based influenza vaccines against influenza A(H1N1), most strains of A(H3N2), and B/Yamagata lineage^{17,30-36}. Findings differed across studies regarding the non-inferiority of RIV4 compared to egg-based influenza vaccines against influenza B/Victoria lineage based on seroconversion rates, seroprotection rates, GMTs, and GMTR^{17,34}. The immunogenicity evidence for Supemtek builds on the clinical development program of Flublok (RIV3) in the US.

This review also examined six studies that assessed the safety of Supemtek, including five RCTs^{17,32-34,38} and one post-marketing surveillance study³⁹. The five RCTs found that Supemtek is a safe, well-tolerated, and immunogenic alternative to conventional egg-based influenza vaccines for adults (noting that no published clinical data pertaining to the safety of vaccination with RIV4 during pregnancy were available at the time of this review to inform vaccine-associated risks)^{17,32-34,38}. Post-marketing surveillance data revealed that the lack of egg proteins in Supemtek does not eliminate the risk of allergic reactions following vaccine administration, as allergic reactions can occur following exposure to any drug or vaccine⁴¹. The five RCTs did not identify an elevated risk of severe allergic reactions compared to traditional egg-based influenza vaccines^{17,32-34,38}.

Recombinant technology is a method of influenza vaccine production that is significantly different from existing egg-based and mammalian cell-culture-based technology. Recombinant technology is the quickest method of influenza vaccine production as it does not depend on the growth of candidate vaccine viruses. Unlike egg- or cell-based vaccines, recombinant technologies do not result in vaccine viruses that are adapted from growth in eggs or in cells; instead, recombinant technology ensures an exact match to the key component of the influenza strains recommended annually by the WHO. Furthermore, RIV are insulated from egg-adaptive changes and pose negligible mutation risk¹². As such, they have the potential to provide enhanced protection in some

seasons compared to standard egg-based influenza vaccines¹². Similar to mammalian cell culture-based vaccines, recombinant vaccines may offer enhanced manufacturing scalability, sterility, timeliness, and flexibility^{10–12}. The flexible and quick manufacturing process of recombinant vaccines may be helpful in a prompt response to rapid and emerging circulating seasonal influenza strains in a post-COVID-19 pandemic setting. The diversification of vaccine platforms can help to overcome influenza supply vulnerabilities and to improve vaccine-production capacity, which may be particularly helpful in an influenza pandemic setting, in cases of vaccine shortage, and in cases of egg supply shortage¹⁰.

The NACI Secretariat applied the Committee's EEFA Framework to assess the implications of ethics, equity, feasibility and acceptability of its recommendation for the use of Supemtek for the prevention of influenza in adults aged 18 years and older in Canada. There were no potential inequities or ethical considerations identified that could arise with the recommendation of Supemtek. However, acceptability of a newly approved vaccine such as Supemtek by the general public, providers and policymakers could be affected by the vaccine's real or perceived potential risks and unknowns. Potential feasibility issues identified are the limited manufacturing infrastructure and the comparatively higher cost of RIV compared to egg-based vaccines. No cost analyses or economic evaluations were conducted prior to the development of this statement and the true cost of RIV, particularly following the optimization of manufacturing infrastructure, is unknown¹⁶.

Given the novelty of RIV, ongoing monitoring of new and emerging evidence on RIV4 efficacy, effectiveness, immunogenicity, and safety will be important. As additional research data on RIV4 become available, further analyses could explore comparisons of these outcomes between seasons and against different influenza subtypes, with comparisons to existing egg-based and mammalian cell culture-based influenza vaccines.

Notably, very limited peer-reviewed, published data on the use of RIV in pregnant individuals and in other vulnerable populations are available to inform vaccine-associated risks. For example, a new study has been published on the safety of Supemtek compared to IIV4-SD in adults self-identified as ethnically Chinese and aged 18-64 years, including pregnant individuals, during the 2018-2019 influenza season in the US⁴². The study found that RIV4 has a comparable safety profile to IIV4-SD and demonstrated safety findings consistent with the studies included in this review.

In addition, safety data on the use of RIV3 in pregnant adults are available and may be considered to supplement the safety evidence base given that the trivalent and quadrivalent RIV formulations are produced using the same manufacturing platform and have overlapping compositions. For example, a supplemental safety analysis stratified on pregnancy status that was conducted as part of a retrospective cohort study evaluating the safety of RIV3 compared to IIV3 in adults aged 18 years and older during a single influenza season (2015-2016) did not detect any safety concerns⁴³. A more robust, comprehensive, and consistent body of evidence, including further data on comorbidities, pregnant individuals, health status, and other potential confounders⁴⁴, is needed to evaluate the relative effectiveness and safety of Supemtek compared to other injectable influenza vaccines.

V. RECOMMENDATIONS

Following the thorough review of available evidence summarized above, as well as the assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework, the following section outlines the evidence-informed recommendation made by NACI regarding the use of Supemtek in adults 18 years of age and older. NACI will continue to carefully monitor the scientific developments related to influenza vaccines, as well as ongoing vaccine pharmacovigilance, and will update its recommendations as required. Additional information on the strength of NACI recommendations and the grading of evidence is available in Table 3.

The following recommendation for Supemtek supplements NACI's overarching recommendation for influenza vaccination, which is available in the [NACI Seasonal Influenza Vaccine Statement](#). The overarching NACI recommendation for influenza vaccination is that an age-appropriate influenza vaccine should be offered annually to anyone 6 months of age and older (Strong NACI Recommendation), noting product-specific contraindications.

1. NACI recommends that Supemtek may be considered among the seasonal influenza vaccines offered to adults 18 years of age and older. (Discretionary NACI Recommendation)

- **NACI concludes that there is fair evidence to recommend vaccination of adults 18 years of age and older with Supemtek. (Grade B Evidence)**

Summary of Evidence and Rationale

- There is fair evidence that Supemtek is effective, safe, and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults 18 years of age and older.
- There is some evidence that Supemtek may potentially offer improved protection against laboratory-confirmed influenza A infection compared to standard egg-based influenza vaccines. However, all the relative vaccine efficacy analyses were conducted using data only from the 2014-2015 influenza season in the US, which was influenza A(H3N2)-dominant, and in adults aged 50 years and older. Therefore, no firm conclusions can be drawn at this time, and NACI will continue to monitor this issue.
- A more robust, comprehensive and consistent body of evidence, including data on comorbidities, health status, and other potential confounders, is needed to evaluate the relative effectiveness of Supemtek compared to other injectable influenza vaccines.
- There is very limited peer-reviewed, published data on the use of Supemtek in pregnant individuals.
- NACI will continue to monitor the evidence related to RIV and will update this supplemental statement as needed and as data on Supemtek from several different influenza seasons accumulates.

An updated summary of the characteristics of influenza vaccines available in Canada for the 2022–2023 influenza season can be found in Appendix B. For complete prescribing information, readers should consult the product monograph available through [Health Canada's Drug Product Database](#).

VI. TABLES

Table 2. Serological Assay Definitions and Thresholds for Protection Specified by the United States Food and Drug Administration²⁷

Serological assay	Definition	Threshold
GMTR	Ratio of GMT post-vaccination of licensed vaccine to GMT post-vaccination of new vaccine	Non-inferiority: The upper bound of the two-sided 95% CI on the ratio of the GMTs should not exceed 1.5.
Seroprotection	Proportion of subjects achieving an HI titre of $\geq 1:40$ post-vaccination	Placebo-controlled: Lower limit of the two-sided 95% CI for the percent of subjects achieving seroprotection should meet or exceed 70% (for adults <65 and children) or 60% (for adults ≥ 65)
Seroconversion	Proportion of subjects achieving an increase from $\leq 1:10$ HI titre pre-vaccination to $\geq 1:40$ post-vaccination or achieving at least four-fold rise in HI titres	Non-inferiority: Upper limit of the two-sided 95% CI on the difference between the seroconversion rates (rate of licensed vaccine – rate of new vaccine) should not exceed 10 percentage points. Placebo-controlled: Lower limit of the two-sided 95% CI for the percent of subjects achieving seroprotection should meet or exceed 40% (for adults <65 and children) or 30% (for adults ≥ 65)

Abbreviations: CI: confidence interval, GMT: geometric mean titre, GMTR: geometric mean titre ratio, HI: hemagglutination inhibition

Table 3. NACI Recommendations: Strength of Recommendation and Grade of Evidence

STRENGTH OF NACI RECOMMENDATION	GRADE OF EVIDENCE
<i>Based on factors not isolated to strength of evidence (e.g., public health need)</i>	<i>Based on assessment of the body of evidence</i>
<p>Strong “should/should not be offered”</p> <ul style="list-style-type: none"> ➤ Known/Anticipated advantages outweigh known/anticipated disadvantages (“should”), OR Known/Anticipated disadvantages outweigh known/anticipated advantages (“should not”) ➤ Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present 	A - <i>good evidence</i> to recommend
	B – <i>fair evidence</i> to recommend
	C – <i>conflicting evidence</i> , however other factors may influence decision-making
	D – <i>fair evidence</i> to recommend against
	E – <i>good evidence</i> to recommend against
	I – <i>insufficient evidence</i> (in quality or quantity), however other factors may influence decision-making
<p>Discretionary “may be considered”</p> <ul style="list-style-type: none"> ➤ Known/Anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists ➤ Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable 	A - <i>good evidence</i> to recommend
	B – <i>fair evidence</i> to recommend
	C – <i>conflicting evidence</i> , however other factors may influence decision-making
	D – <i>fair evidence</i> to recommend against
	E – <i>good evidence</i> to recommend against
	I – <i>insufficient evidence</i> (in quality or quantity), however other factors may influence decision-making

Table 4. Summary of Evidence on the Efficacy of Supemtek

STUDY DETAILS																																
Study	Vaccine	Study Design	Participants	Summary of Key Findings																												
<p>Dunkle L, Izikson R, Patriarca P, Goldenthal K, Muse D, Callahan J, Cox M, PSC12 Study Team. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. <i>New England Journal of Medicine</i>. 2017; 376(25):2427-2436.</p> <p>ClinicalTrials.gov <i>Protective Efficacy of Flublok Quadrivalent Versus Licensed Inactivated Influenza Vaccine in Adults ≥50 Years of Age</i> NCT02285998</p>	RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)	Phase III-IV RCT US Multi-centre (40 sites) 2014-2015 influenza season Funded by Protein Sciences Corporation	Adults 50 years of age or older living independently without clinically significant acute illness, not receiving ongoing immunosuppressive therapy, and with no contraindications to trial vaccines 58.5% female Mean age: 63 RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n= 4,303 IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline): n= 4,301	<p>The efficacy of RIV4 relative to IIV4-SD was calculated as $100 \times (1 - RR)$, where RR is the relative risk of influenza attack rates in the two groups (RIV4 attack rate/IIV4-SD attack rate).</p> <p>rVE for RT-PCR-positive, protocol-defined influenza-like illness (ILI):</p> <table border="1"> <thead> <tr> <th>Subgroup</th> <th>rVE estimate % (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>30 (10, 47)</td> </tr> <tr> <td>50-64 years</td> <td>42 (15, 61)</td> </tr> <tr> <td>>64 years</td> <td>17 (-20, 43)</td> </tr> <tr> <td>Influenza A</td> <td>36 (14, 53)</td> </tr> <tr> <td>Influenza B</td> <td>4 (-72, 46)</td> </tr> <tr> <td>Fever ($\geq 37.8^\circ\text{C}$)</td> <td>35 (8, 54)</td> </tr> </tbody> </table> <p>rVE for culture-positive, protocol-defined ILI:</p> <table border="1"> <thead> <tr> <th>Subgroup</th> <th>rVE estimate % (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>43 (21, 59)</td> </tr> <tr> <td>50-64 years</td> <td>44 (10, 65)</td> </tr> <tr> <td>>64 years</td> <td>42 (9, 65)</td> </tr> <tr> <td>Influenza A</td> <td>44 (22, 61)</td> </tr> <tr> <td>Influenza B</td> <td>25 (-121, 75)</td> </tr> <tr> <td>Fever ($\geq 37.8^\circ\text{C}$)</td> <td>41 (11, 61)</td> </tr> </tbody> </table>	Subgroup	rVE estimate % (95% CI)	Overall	30 (10, 47)	50-64 years	42 (15, 61)	>64 years	17 (-20, 43)	Influenza A	36 (14, 53)	Influenza B	4 (-72, 46)	Fever ($\geq 37.8^\circ\text{C}$)	35 (8, 54)	Subgroup	rVE estimate % (95% CI)	Overall	43 (21, 59)	50-64 years	44 (10, 65)	>64 years	42 (9, 65)	Influenza A	44 (22, 61)	Influenza B	25 (-121, 75)	Fever ($\geq 37.8^\circ\text{C}$)	41 (11, 61)
Subgroup	rVE estimate % (95% CI)																															
Overall	30 (10, 47)																															
50-64 years	42 (15, 61)																															
>64 years	17 (-20, 43)																															
Influenza A	36 (14, 53)																															
Influenza B	4 (-72, 46)																															
Fever ($\geq 37.8^\circ\text{C}$)	35 (8, 54)																															
Subgroup	rVE estimate % (95% CI)																															
Overall	43 (21, 59)																															
50-64 years	44 (10, 65)																															
>64 years	42 (9, 65)																															
Influenza A	44 (22, 61)																															
Influenza B	25 (-121, 75)																															
Fever ($\geq 37.8^\circ\text{C}$)	41 (11, 61)																															

Abbreviations: CI: confidence interval; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; ILI: Influenza-like illness RCT: randomized controlled trial; RIV4: quadrivalent recombinant influenza vaccine; RR: risk ratio; RT-PCR: reverse transcription polymerase chain reaction; rVE: relative vaccine efficacy; SD: standard-dose; US: United States.

Table 5. Summary of Evidence on the Immunogenicity of Supemtek

STUDY DETAILS																																
Study	Vaccine	Study Design	Participants	Summary of Key Findings																												
<p>Dawood FS, Naleway AL, Flannery B, Levine MZ, Murthy K, Sambhara S, Gangappa S, Edwards L, Ball S, Grant L, Belongia E. <i>Comparison of the Immunogenicity of Cell Culture-Based and Quadrivalent Recombinant Influenza Vaccines to Conventional Egg-Based Quadrivalent Influenza Vaccines Among Healthcare Personnel Aged 18–64 Years: A Randomized Open-Label Trial. Clinical Infectious Diseases. 2021.</i></p> <p>ClinicalTrials.gov Immunogenicity Trial of Egg-Versus Non-Egg-Based Influenza Vaccines Among HCP. NCT03722589</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase IV RCT</p>	<p>Adult healthcare personnel aged 18 to 64 years</p>	<p>Ratio of GMTs (IIV4-SD/RIV4) at 1 month post-vaccination among RIV4 recipients compared to egg-based IIV4 recipients:</p> <table border="1"> <thead> <tr> <th>Strain</th> <th>Estimate (95% CI)</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>1.5 (1.2, 1.9)</td> </tr> <tr> <td>A(H3N2)</td> <td>3.0 (2.4, 3.7)</td> </tr> <tr> <td>B/Yam</td> <td>1.1 (0.9, 1.4)</td> </tr> <tr> <td>B/Vic</td> <td>1.1 (0.9, 1.3)</td> </tr> </tbody> </table>	Strain	Estimate (95% CI)	A(H1N1)	1.5 (1.2, 1.9)	A(H3N2)	3.0 (2.4, 3.7)	B/Yam	1.1 (0.9, 1.4)	B/Vic	1.1 (0.9, 1.3)																		
		Strain	Estimate (95% CI)																													
		A(H1N1)	1.5 (1.2, 1.9)																													
		A(H3N2)	3.0 (2.4, 3.7)																													
B/Yam	1.1 (0.9, 1.4)																															
B/Vic	1.1 (0.9, 1.3)																															
<p>US Multi-centre (2 sites)</p>	<p>82.4% female</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n=202 Mean age: 43</p>	<p>Seroconversion rate in adults 18 to 64 years of age, 1 month post-vaccination, in the intention-to-treat population:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="4">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4 (Fluzone)</th> <th>IIV4 (Fluarix)</th> <th>IIV4-CC</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>29 (23, 35)</td> <td>10 (5, 15)</td> <td>23 (15, 30)</td> <td>18 (13, 22)</td> </tr> <tr> <td>A(H3N2)</td> <td>55 (49, 62)</td> <td>16 (10, 23)</td> <td>8 (3, 12)</td> <td>17 (13, 21)</td> </tr> <tr> <td>B/Yam</td> <td>20 (15, 26)</td> <td>9 (4, 14)</td> <td>10 (5, 15)</td> <td>9 (6, 13)</td> </tr> <tr> <td>B/Vic</td> <td>14 (10, 19)</td> <td>10 (5, 15)</td> <td>9 (4, 14)</td> <td>8 (5, 11)</td> </tr> </tbody> </table>	Strain	Estimate % (95% CI)				RIV4	IIV4 (Fluzone)	IIV4 (Fluarix)	IIV4-CC	A(H1N1)	29 (23, 35)	10 (5, 15)	23 (15, 30)	18 (13, 22)	A(H3N2)	55 (49, 62)	16 (10, 23)	8 (3, 12)	17 (13, 21)	B/Yam	20 (15, 26)	9 (4, 14)	10 (5, 15)	9 (6, 13)	B/Vic	14 (10, 19)	10 (5, 15)	9 (4, 14)	8 (5, 11)
Strain	Estimate % (95% CI)																															
	RIV4	IIV4 (Fluzone)	IIV4 (Fluarix)	IIV4-CC																												
A(H1N1)	29 (23, 35)	10 (5, 15)	23 (15, 30)	18 (13, 22)																												
A(H3N2)	55 (49, 62)	16 (10, 23)	8 (3, 12)	17 (13, 21)																												
B/Yam	20 (15, 26)	9 (4, 14)	10 (5, 15)	9 (6, 13)																												
B/Vic	14 (10, 19)	10 (5, 15)	9 (4, 14)	8 (5, 11)																												
<p>2018-2019 influenza seasons</p>	<p>Funded by the US Centres for Disease Control and Prevention</p>	<p>IIV4-cc (Flucelvax Quad, Seqirus) n=283 Mean age: 44</p>	<p>Seroprotection rate in adults 18 to 64 years of age, 1 month post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4 (combined)</th> <th>IIV4-CC</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>85 (80, 90)</td> <td>74 (68, 80)</td> <td>80 (75, 84)</td> </tr> <tr> <td>A(H3N2)</td> <td>95 (92, 98)</td> <td>86 (81, 90)</td> <td>86 (81, 90)</td> </tr> <tr> <td>B/Yam</td> <td>88 (83, 92)</td> <td>80 (75, 85)</td> <td>83 (79, 88)</td> </tr> <tr> <td>B/Vic</td> <td>86 (81, 90)</td> <td>86 (82, 90)</td> <td>89 (86, 93)</td> </tr> </tbody> </table>	Strain	Estimate % (95% CI)			RIV4	IIV4 (combined)	IIV4-CC	A(H1N1)	85 (80, 90)	74 (68, 80)	80 (75, 84)	A(H3N2)	95 (92, 98)	86 (81, 90)	86 (81, 90)	B/Yam	88 (83, 92)	80 (75, 85)	83 (79, 88)	B/Vic	86 (81, 90)	86 (82, 90)	89 (86, 93)						
Strain	Estimate % (95% CI)																															
	RIV4	IIV4 (combined)	IIV4-CC																													
A(H1N1)	85 (80, 90)	74 (68, 80)	80 (75, 84)																													
A(H3N2)	95 (92, 98)	86 (81, 90)	86 (81, 90)																													
B/Yam	88 (83, 92)	80 (75, 85)	83 (79, 88)																													
B/Vic	86 (81, 90)	86 (82, 90)	89 (86, 93)																													
		<p>IIV4 (Fluarix, GSK Biologics) n=120 Mean age: 45</p>	<p>IIV4 (Fluzone Quadrivalent, Sanofi Pasteur) n=122 Mean age: 44</p>																													

STUDY DETAILS																																																																													
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																									
<p>Dunkle L, Izikson R, Patriarca P, Goldenthal K, Muse D, Callahan J, Cox M, PSC12 Study Team. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. New England Journal of Medicine. 2017; 376(25):2427-2436.</p> <p>ClinicalTrials.gov <i>Protective Efficacy of Flublok Quadrivalent Versus Licensed Inactivated Influenza Vaccine in Adults ≥50 Years of Age</i> NCT02285998</p>	RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)	Phase III-IV RCT US Multi-centre (40 sites) 2014-2015 influenza season Funded by Protein Sciences Corporation	Adults 50 years of age or older living independently without clinically significant acute illness, not receiving ongoing immunosuppressive therapy, and with no contraindications to trial vaccines 58.5% female Mean age: 63 RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): ≥50 age group: n= 314 50-64 age group: n= 196 ≥65 age group: n= 118 IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline): ≥50 age group: n= 300 50-64 age group: n= 209 ≥65 age group: n= 91	GMT ratio in adults 50 years of age and older, 28 days post-vaccination (IIV4/RIV4): <table border="1"> <thead> <tr> <th>Strain</th> <th>Estimate (95% CI)</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>1.15 (0.95, 1.41)</td> </tr> <tr> <td>A(H3N2)</td> <td>0.69 (0.58, 0.82)</td> </tr> <tr> <td>B/Yam</td> <td>1.04 (0.86, 1.24)</td> </tr> <tr> <td>B/Vic</td> <td>1.47 (1.24, 1.77)</td> </tr> </tbody> </table> <p>Seroconversion rate in adults within three age categories, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th rowspan="2">Age group</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> </tr> </thead> <tbody> <tr> <td rowspan="3">A(H1N1)</td> <td>≥50</td> <td>44.9 (39.3, 50.6)</td> <td>49.0 (43.2, 54.8)</td> </tr> <tr> <td>50-64</td> <td>56 (48.4, 62.7)</td> <td>54 (47.1, 61.0)</td> </tr> <tr> <td>≥65</td> <td>27 (19.3, 36.1)</td> <td>37 (27.4, 48.1)</td> </tr> <tr> <td rowspan="3">A(H3N2)</td> <td>≥50</td> <td>54.5 (48.8, 60.1)</td> <td>43.3 (37.6, 49.1)</td> </tr> <tr> <td>50-64</td> <td>63 (55.6, 69.5)</td> <td>51 (44.2, 58.2)</td> </tr> <tr> <td>≥65</td> <td>41 (31.7, 50.1)</td> <td>25 (16.7, 35.5)</td> </tr> <tr> <td rowspan="3">B/Yam</td> <td>≥50</td> <td>38.9 (33.4, 44.5)</td> <td>38.3 (32.8, 44.1)</td> </tr> <tr> <td>50-64</td> <td>43 (35.8, 50.1)</td> <td>44 (36.7, 50.6)</td> </tr> <tr> <td>≥65</td> <td>32 (23.9, 41.4)</td> <td>26 (17.7, 36.7)</td> </tr> <tr> <td rowspan="3">B/Vic</td> <td>≥50</td> <td>21.0 (16.6, 25.9)</td> <td>34.3 (29.0, 40.0)</td> </tr> <tr> <td>50-64</td> <td>26 (19.6, 32.2)</td> <td>43 (35.8, 49.6)</td> </tr> <tr> <td>≥65</td> <td>14 (8.0, 21.1)</td> <td>15 (8.7, 24.5)</td> </tr> </tbody> </table> <p>Seroprotection rate in adults 50 years and older, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>91 (87, 94)</td> <td>95 (92, 97)</td> </tr> <tr> <td>A(H3N2)</td> <td>100 (98, 100)</td> <td>98 (96, 99)</td> </tr> <tr> <td>B/Yam</td> <td>68 (63, 73)</td> <td>72 (67, 77)</td> </tr> <tr> <td>B/Vic</td> <td>50 (44, 55)</td> <td>61 (55, 66)</td> </tr> </tbody> </table>	Strain	Estimate (95% CI)	A(H1N1)	1.15 (0.95, 1.41)	A(H3N2)	0.69 (0.58, 0.82)	B/Yam	1.04 (0.86, 1.24)	B/Vic	1.47 (1.24, 1.77)	Strain	Age group	Estimate % (95% CI)		RIV4	IIV4-SD	A(H1N1)	≥50	44.9 (39.3, 50.6)	49.0 (43.2, 54.8)	50-64	56 (48.4, 62.7)	54 (47.1, 61.0)	≥65	27 (19.3, 36.1)	37 (27.4, 48.1)	A(H3N2)	≥50	54.5 (48.8, 60.1)	43.3 (37.6, 49.1)	50-64	63 (55.6, 69.5)	51 (44.2, 58.2)	≥65	41 (31.7, 50.1)	25 (16.7, 35.5)	B/Yam	≥50	38.9 (33.4, 44.5)	38.3 (32.8, 44.1)	50-64	43 (35.8, 50.1)	44 (36.7, 50.6)	≥65	32 (23.9, 41.4)	26 (17.7, 36.7)	B/Vic	≥50	21.0 (16.6, 25.9)	34.3 (29.0, 40.0)	50-64	26 (19.6, 32.2)	43 (35.8, 49.6)	≥65	14 (8.0, 21.1)	15 (8.7, 24.5)	Strain	Estimate % (95% CI)		RIV4	IIV4-SD	A(H1N1)	91 (87, 94)	95 (92, 97)	A(H3N2)	100 (98, 100)	98 (96, 99)	B/Yam	68 (63, 73)	72 (67, 77)	B/Vic	50 (44, 55)	61 (55, 66)
Strain	Estimate (95% CI)																																																																												
A(H1N1)	1.15 (0.95, 1.41)																																																																												
A(H3N2)	0.69 (0.58, 0.82)																																																																												
B/Yam	1.04 (0.86, 1.24)																																																																												
B/Vic	1.47 (1.24, 1.77)																																																																												
Strain	Age group	Estimate % (95% CI)																																																																											
		RIV4	IIV4-SD																																																																										
A(H1N1)	≥50	44.9 (39.3, 50.6)	49.0 (43.2, 54.8)																																																																										
	50-64	56 (48.4, 62.7)	54 (47.1, 61.0)																																																																										
	≥65	27 (19.3, 36.1)	37 (27.4, 48.1)																																																																										
A(H3N2)	≥50	54.5 (48.8, 60.1)	43.3 (37.6, 49.1)																																																																										
	50-64	63 (55.6, 69.5)	51 (44.2, 58.2)																																																																										
	≥65	41 (31.7, 50.1)	25 (16.7, 35.5)																																																																										
B/Yam	≥50	38.9 (33.4, 44.5)	38.3 (32.8, 44.1)																																																																										
	50-64	43 (35.8, 50.1)	44 (36.7, 50.6)																																																																										
	≥65	32 (23.9, 41.4)	26 (17.7, 36.7)																																																																										
B/Vic	≥50	21.0 (16.6, 25.9)	34.3 (29.0, 40.0)																																																																										
	50-64	26 (19.6, 32.2)	43 (35.8, 49.6)																																																																										
	≥65	14 (8.0, 21.1)	15 (8.7, 24.5)																																																																										
Strain	Estimate % (95% CI)																																																																												
	RIV4	IIV4-SD																																																																											
A(H1N1)	91 (87, 94)	95 (92, 97)																																																																											
A(H3N2)	100 (98, 100)	98 (96, 99)																																																																											
B/Yam	68 (63, 73)	72 (67, 77)																																																																											
B/Vic	50 (44, 55)	61 (55, 66)																																																																											

STUDY DETAILS																																																																									
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																					
<p>Belongia E, Levine M, Olaiya O, Gross F, King J, Flannery B, McLean H. <i>Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A(H3N2) viruses in adults 65 to 74 years, 2017–2018. Vaccine. 2020; 38(15):3121-3128.</i></p> <p>ClinicalTrials.gov <i>Open-Label Influenza Vaccine Evaluation (OLIVE)</i> NCT02872311</p>	RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)	Open label RCT US Single-centre 2017-2018 influenza season Funding by Centres for Disease Control and Prevention to the Marshfield Clinic Research Institute	Adults 65 to 74 Years of Age 56% female Mean age: 70 RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n=30 IIV3-HD (Fluzone High- Dose, Sanofi Pasteur): n=29 IIV3-Adj (Fluad, Seqirus): n=30	GMT in adults 65 to 74 years of age, 28±5 days post-vaccination: <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> <th>IIV3-Adj</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>56.4 (39.3, 81.1)</td> <td>53.2 (32.2, 87.7)</td> <td>42.7 (25.8, 70.6)</td> </tr> <tr> <td>A(H3N2)²</td> <td>80.1 (52.9, 121.2)</td> <td>52.3 (28.4, 96.6)</td> <td>45.6 (25.9, 80.4)</td> </tr> <tr> <td>A(H3N2)³</td> <td>71.6 (44.5, 115.0)</td> <td>51.4 (28.6, 92.5)</td> <td>42.8 (25.3, 72.4)</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>48.5 (27.6, 85.2)</td> <td>28.6 (17.4, 47.0)</td> <td>22.7 (16.4, 31.4)</td> </tr> </tbody> </table> <p>¹ A/Hong Kong/4801/2014 ² A/Singapore/INFIMH-16–0019/2016 ³ A/Kentucky/29/2017 ⁴ A/Kansas/14/2017</p> Seroconversion rate in adults 65 to 74 years of age, 28±5 days post-vaccination: <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> <th>IIV3-Adj</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>13.3 (3.8, 30.7)</td> <td>3.5 (0.09, 17.8)</td> <td>6.7 (0.8, 22.1)</td> </tr> <tr> <td>A(H3N2)²</td> <td>26.7 (10.8, 42.5)</td> <td>6.9 (0.9, 22.8)</td> <td>10.0 (2.1, 26.5)</td> </tr> <tr> <td>A(H3N2)³</td> <td>40.0 (22.7, 57.5)</td> <td>6.9 (0.9, 22.8)</td> <td>13.3 (3.8, 30.7)</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>33.3 (16.5, 50.2)</td> <td>3.5 (0.1, 17.8)</td> <td>6.7 (0.8, 22.1)</td> </tr> </tbody> </table> <p>¹ A/Hong Kong/4801/2014 ² A/Singapore/INFIMH-16–0019/2016 ³ A/Kentucky/29/2017 ⁴ A/Kansas/14/2017</p> Seroprotection rate in adults 65 to 74 years of age, 28±5 days post-vaccination: <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> <th>IIV3-Adj</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>70.0 (53.6, 86.4)</td> <td>58.6 (40.1, 76.6)</td> <td>50.0 (32.1, 67.9)</td> </tr> <tr> <td>A(H3N2)²</td> <td>80.0 (65.7, 94.3)</td> <td>62.1 (44.4, 79.7)</td> <td>53.3 (35.5, 71.2)</td> </tr> <tr> <td>A(H3N2)³</td> <td>76.7 (61.5, 91.8)</td> <td>65.5 (48.2, 82.8)</td> <td>60.0 (42.5, 77.5)</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>60.0 (40.6, 77.3)</td> <td>51.7 (33.5, 69.9)</td> <td>30.0 (13.6, 46.4)</td> </tr> </tbody> </table> <p>¹ A/Hong Kong/4801/2014 ² A/Singapore/INFIMH-16–0019/2016 ³ A/Kentucky/29/2017 ⁴ A/Kansas/14/2017</p>	Strain	Estimate (95% CI)			RIV4	IIV3-HD	IIV3-Adj	A(H3N2) ¹	56.4 (39.3, 81.1)	53.2 (32.2, 87.7)	42.7 (25.8, 70.6)	A(H3N2) ²	80.1 (52.9, 121.2)	52.3 (28.4, 96.6)	45.6 (25.9, 80.4)	A(H3N2) ³	71.6 (44.5, 115.0)	51.4 (28.6, 92.5)	42.8 (25.3, 72.4)	A(H3N2) ⁴	48.5 (27.6, 85.2)	28.6 (17.4, 47.0)	22.7 (16.4, 31.4)	Strain	Estimate % (95% CI)			RIV4	IIV3-HD	IIV3-Adj	A(H3N2) ¹	13.3 (3.8, 30.7)	3.5 (0.09, 17.8)	6.7 (0.8, 22.1)	A(H3N2) ²	26.7 (10.8, 42.5)	6.9 (0.9, 22.8)	10.0 (2.1, 26.5)	A(H3N2) ³	40.0 (22.7, 57.5)	6.9 (0.9, 22.8)	13.3 (3.8, 30.7)	A(H3N2) ⁴	33.3 (16.5, 50.2)	3.5 (0.1, 17.8)	6.7 (0.8, 22.1)	Strain	Estimate % (95% CI)			RIV4	IIV3-HD	IIV3-Adj	A(H3N2) ¹	70.0 (53.6, 86.4)	58.6 (40.1, 76.6)	50.0 (32.1, 67.9)	A(H3N2) ²	80.0 (65.7, 94.3)	62.1 (44.4, 79.7)	53.3 (35.5, 71.2)	A(H3N2) ³	76.7 (61.5, 91.8)	65.5 (48.2, 82.8)	60.0 (42.5, 77.5)	A(H3N2) ⁴	60.0 (40.6, 77.3)	51.7 (33.5, 69.9)	30.0 (13.6, 46.4)
Strain	Estimate (95% CI)																																																																								
	RIV4	IIV3-HD	IIV3-Adj																																																																						
A(H3N2) ¹	56.4 (39.3, 81.1)	53.2 (32.2, 87.7)	42.7 (25.8, 70.6)																																																																						
A(H3N2) ²	80.1 (52.9, 121.2)	52.3 (28.4, 96.6)	45.6 (25.9, 80.4)																																																																						
A(H3N2) ³	71.6 (44.5, 115.0)	51.4 (28.6, 92.5)	42.8 (25.3, 72.4)																																																																						
A(H3N2) ⁴	48.5 (27.6, 85.2)	28.6 (17.4, 47.0)	22.7 (16.4, 31.4)																																																																						
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD	IIV3-Adj																																																																						
A(H3N2) ¹	13.3 (3.8, 30.7)	3.5 (0.09, 17.8)	6.7 (0.8, 22.1)																																																																						
A(H3N2) ²	26.7 (10.8, 42.5)	6.9 (0.9, 22.8)	10.0 (2.1, 26.5)																																																																						
A(H3N2) ³	40.0 (22.7, 57.5)	6.9 (0.9, 22.8)	13.3 (3.8, 30.7)																																																																						
A(H3N2) ⁴	33.3 (16.5, 50.2)	3.5 (0.1, 17.8)	6.7 (0.8, 22.1)																																																																						
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD	IIV3-Adj																																																																						
A(H3N2) ¹	70.0 (53.6, 86.4)	58.6 (40.1, 76.6)	50.0 (32.1, 67.9)																																																																						
A(H3N2) ²	80.0 (65.7, 94.3)	62.1 (44.4, 79.7)	53.3 (35.5, 71.2)																																																																						
A(H3N2) ³	76.7 (61.5, 91.8)	65.5 (48.2, 82.8)	60.0 (42.5, 77.5)																																																																						
A(H3N2) ⁴	60.0 (40.6, 77.3)	51.7 (33.5, 69.9)	30.0 (13.6, 46.4)																																																																						

STUDY DETAILS																																																																									
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																					
<p>Shinde V, Cai R, Plested J, Cho I, Fiske J, Pham X, Zhu M, Cloney-Clark S, Wang N, Zhou H, Zhou B, Patel N, Massare M, Fix A, Spindler M, Thomas D, Smith G, Fries L, Glenn G. <i>Induction of Cross-Reactive Hemagglutination Inhibiting Antibody and Polyfunctional CD4+ T-Cell Responses by a Recombinant Matrix-M–Adjuvanted Hemagglutinin Nanoparticle Influenza Vaccine. Clinical Infectious Diseases. 2020.</i></p> <p>ClinicalTrials.gov <i>Phase 2 Dose and Formulation Confirmation of Quad-NIV in Older Adults</i> NCT03658629</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase II, observer blind RCT</p> <p>US Multi-centre (14 sites)</p> <p>2018-2019 influenza season</p> <p>Funded by Novavax Inc.</p>	<p>Clinically stable adults aged ≥65 years</p> <p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n=144</p> <p>Mean age: 72.9</p> <p>57.6% female</p> <p>IIV3-HD (Fluzone High- Dose, Sanofi Pasteur); n= 143</p> <p>Mean age: 72.5</p> <p>64.7% female</p>	<p>GMT in adults 65 years of age and older, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>82.1 (71.6, 94.2)</td> <td>96.9 (84.5, 111.1)</td> </tr> <tr> <td>A(H3N2)</td> <td>66.6 (54.9, 80.9)</td> <td>46.5 (38.6, 55.9)</td> </tr> <tr> <td>B/Yam</td> <td>102.0 (88.6, 117.4)</td> <td>64.5 (57.3, 72.6)</td> </tr> <tr> <td>B/Vic</td> <td>83.3 (73.2, 94.9)</td> <td>93.2 (81.6, 106.5)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>158.8 (132.2, 190.9)</td> <td>133.4 (111.2,160.0)</td> </tr> <tr> <td>A(H3N2)²</td> <td>64.3 (53.5, 77.2)</td> <td>46.1 (38.7, 55.1)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>GMT in adults 65 years of age and older, 56 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>65.2 (57.9, 73.5)</td> <td>78.6 (69.2, 89.4)</td> </tr> <tr> <td>A(H3N2)</td> <td>49.3 (42.0, 57.9)</td> <td>38.9 (33.7, 45.1)</td> </tr> <tr> <td>B/Yam</td> <td>85.5 (73.7, 99.1)</td> <td>60.9 (53.6, 69.2)</td> </tr> <tr> <td>B/Vic</td> <td>60.7 (53.6, 68.7)</td> <td>70.9 (62.2, 80.7)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>123.8 (104.8, 146.2)</td> <td>108.3 (92.4, 126.9)</td> </tr> <tr> <td>A(H3N2)²</td> <td>55.7 (46.6, 66.6)</td> <td>41.7 (35.4, 49.2)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>GMT in adults 65 years of age and older, 182 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>53.9 (47.8, 60.7)</td> <td>65.6 (58.8, 73.1)</td> </tr> <tr> <td>A(H3N2)</td> <td>58.7 (51.5, 66.9)</td> <td>52.3 (46.6, 58.8)</td> </tr> <tr> <td>B/Yam</td> <td>63.0 (56.7, 69.9)</td> <td>57.3 (52.2, 63.1)</td> </tr> <tr> <td>B/Vic</td> <td>52.4 (46.7, 58.7)</td> <td>63.3 (56.7, 70.6)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>93.8 (79.3, 111.0)</td> <td>81.2 (69.5, 94.8)</td> </tr> <tr> <td>A(H3N2)²</td> <td>34.4 (29.1, 40.7)</td> <td>29.2 (25.0, 34.0)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p>	Strain	Estimate (95% CI)		RIV4	IIV3-HD	A(H1N1)	82.1 (71.6, 94.2)	96.9 (84.5, 111.1)	A(H3N2)	66.6 (54.9, 80.9)	46.5 (38.6, 55.9)	B/Yam	102.0 (88.6, 117.4)	64.5 (57.3, 72.6)	B/Vic	83.3 (73.2, 94.9)	93.2 (81.6, 106.5)	A(H3N2) ¹	158.8 (132.2, 190.9)	133.4 (111.2,160.0)	A(H3N2) ²	64.3 (53.5, 77.2)	46.1 (38.7, 55.1)	Strain	Estimate (95% CI)		RIV4	IIV3-HD	A(H1N1)	65.2 (57.9, 73.5)	78.6 (69.2, 89.4)	A(H3N2)	49.3 (42.0, 57.9)	38.9 (33.7, 45.1)	B/Yam	85.5 (73.7, 99.1)	60.9 (53.6, 69.2)	B/Vic	60.7 (53.6, 68.7)	70.9 (62.2, 80.7)	A(H3N2) ¹	123.8 (104.8, 146.2)	108.3 (92.4, 126.9)	A(H3N2) ²	55.7 (46.6, 66.6)	41.7 (35.4, 49.2)	Strain	Estimate (95% CI)		RIV4	IIV3-HD	A(H1N1)	53.9 (47.8, 60.7)	65.6 (58.8, 73.1)	A(H3N2)	58.7 (51.5, 66.9)	52.3 (46.6, 58.8)	B/Yam	63.0 (56.7, 69.9)	57.3 (52.2, 63.1)	B/Vic	52.4 (46.7, 58.7)	63.3 (56.7, 70.6)	A(H3N2) ¹	93.8 (79.3, 111.0)	81.2 (69.5, 94.8)	A(H3N2) ²	34.4 (29.1, 40.7)	29.2 (25.0, 34.0)
Strain	Estimate (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	82.1 (71.6, 94.2)	96.9 (84.5, 111.1)																																																																							
A(H3N2)	66.6 (54.9, 80.9)	46.5 (38.6, 55.9)																																																																							
B/Yam	102.0 (88.6, 117.4)	64.5 (57.3, 72.6)																																																																							
B/Vic	83.3 (73.2, 94.9)	93.2 (81.6, 106.5)																																																																							
A(H3N2) ¹	158.8 (132.2, 190.9)	133.4 (111.2,160.0)																																																																							
A(H3N2) ²	64.3 (53.5, 77.2)	46.1 (38.7, 55.1)																																																																							
Strain	Estimate (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	65.2 (57.9, 73.5)	78.6 (69.2, 89.4)																																																																							
A(H3N2)	49.3 (42.0, 57.9)	38.9 (33.7, 45.1)																																																																							
B/Yam	85.5 (73.7, 99.1)	60.9 (53.6, 69.2)																																																																							
B/Vic	60.7 (53.6, 68.7)	70.9 (62.2, 80.7)																																																																							
A(H3N2) ¹	123.8 (104.8, 146.2)	108.3 (92.4, 126.9)																																																																							
A(H3N2) ²	55.7 (46.6, 66.6)	41.7 (35.4, 49.2)																																																																							
Strain	Estimate (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	53.9 (47.8, 60.7)	65.6 (58.8, 73.1)																																																																							
A(H3N2)	58.7 (51.5, 66.9)	52.3 (46.6, 58.8)																																																																							
B/Yam	63.0 (56.7, 69.9)	57.3 (52.2, 63.1)																																																																							
B/Vic	52.4 (46.7, 58.7)	63.3 (56.7, 70.6)																																																																							
A(H3N2) ¹	93.8 (79.3, 111.0)	81.2 (69.5, 94.8)																																																																							
A(H3N2) ²	34.4 (29.1, 40.7)	29.2 (25.0, 34.0)																																																																							

STUDY DETAILS																																																																									
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																					
				<p>Seroconversion rate in adults 65 years of age and older, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>21.5 (15.1, 29.1)</td> <td>16.8 (11.1, 23.9)</td> </tr> <tr> <td>A(H3N2)</td> <td>45.1 (36.8, 53.6)</td> <td>21.7 (15.2, 29.3)</td> </tr> <tr> <td>B/Yam</td> <td>27.8 (20.6, 35.8)</td> <td>3.5 (1.1, 8.0)</td> </tr> <tr> <td>B/Vic</td> <td>19.4 (13.3, 26.9)</td> <td>21.0 (14.6, 28.6)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>39.6 (31.5, 48.1)</td> <td>21.7 (15.2, 29.3)</td> </tr> <tr> <td>A(H3N2)²</td> <td>43.1 (34.8, 51.6)</td> <td>18.2 (12.2, 25.5)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>Seroconversion rate in adults 65 years of age and older, 56 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>7.8 (4.0, 13.5)</td> <td>5.0 (2.0, 10.0)</td> </tr> <tr> <td>A(H3N2)</td> <td>26.2 (19.2, 34.3)</td> <td>9.3 (5.0, 15.4)</td> </tr> <tr> <td>B/Yam</td> <td>18.4 (12.4, 25.8)</td> <td>2.1 (0.4, 6.1)</td> </tr> <tr> <td>B/Vic</td> <td>4.3 (1.6, 9.0)</td> <td>5.7 (2.5, 10.9)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>26.2 (19.2, 34.3)</td> <td>12.1 (7.2, 18.7)</td> </tr> <tr> <td>A(H3N2)²</td> <td>22.0 (15.5, 29.7)</td> <td>5.7 (2.5, 10.9)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>Seroconversion rate in adults 65 years of age and older, 182 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>2.1 (0.4, 6.1)</td> <td>2.1 (0.4, 6.1)</td> </tr> <tr> <td>A(H3N2)</td> <td>29.8 (22.4, 38.1)</td> <td>12.8 (7.7, 19.4)</td> </tr> <tr> <td>B/Yam</td> <td>2.8 (0.8, 7.1)</td> <td>0 (0.0, 2.6)</td> </tr> <tr> <td>B/Vic</td> <td>3.5 (1.2, 8.1)</td> <td>2.8 (0.8, 7.1)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>12.8 (7.7, 19.4)</td> <td>4.3 (1.6, 9.0)</td> </tr> <tr> <td>A(H3N2)²</td> <td>10.6 (6.1, 16.9)</td> <td>2.1 (0.4, 6.1)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p>	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	21.5 (15.1, 29.1)	16.8 (11.1, 23.9)	A(H3N2)	45.1 (36.8, 53.6)	21.7 (15.2, 29.3)	B/Yam	27.8 (20.6, 35.8)	3.5 (1.1, 8.0)	B/Vic	19.4 (13.3, 26.9)	21.0 (14.6, 28.6)	A(H3N2) ¹	39.6 (31.5, 48.1)	21.7 (15.2, 29.3)	A(H3N2) ²	43.1 (34.8, 51.6)	18.2 (12.2, 25.5)	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	7.8 (4.0, 13.5)	5.0 (2.0, 10.0)	A(H3N2)	26.2 (19.2, 34.3)	9.3 (5.0, 15.4)	B/Yam	18.4 (12.4, 25.8)	2.1 (0.4, 6.1)	B/Vic	4.3 (1.6, 9.0)	5.7 (2.5, 10.9)	A(H3N2) ¹	26.2 (19.2, 34.3)	12.1 (7.2, 18.7)	A(H3N2) ²	22.0 (15.5, 29.7)	5.7 (2.5, 10.9)	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	2.1 (0.4, 6.1)	2.1 (0.4, 6.1)	A(H3N2)	29.8 (22.4, 38.1)	12.8 (7.7, 19.4)	B/Yam	2.8 (0.8, 7.1)	0 (0.0, 2.6)	B/Vic	3.5 (1.2, 8.1)	2.8 (0.8, 7.1)	A(H3N2) ¹	12.8 (7.7, 19.4)	4.3 (1.6, 9.0)	A(H3N2) ²	10.6 (6.1, 16.9)	2.1 (0.4, 6.1)
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	21.5 (15.1, 29.1)	16.8 (11.1, 23.9)																																																																							
A(H3N2)	45.1 (36.8, 53.6)	21.7 (15.2, 29.3)																																																																							
B/Yam	27.8 (20.6, 35.8)	3.5 (1.1, 8.0)																																																																							
B/Vic	19.4 (13.3, 26.9)	21.0 (14.6, 28.6)																																																																							
A(H3N2) ¹	39.6 (31.5, 48.1)	21.7 (15.2, 29.3)																																																																							
A(H3N2) ²	43.1 (34.8, 51.6)	18.2 (12.2, 25.5)																																																																							
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	7.8 (4.0, 13.5)	5.0 (2.0, 10.0)																																																																							
A(H3N2)	26.2 (19.2, 34.3)	9.3 (5.0, 15.4)																																																																							
B/Yam	18.4 (12.4, 25.8)	2.1 (0.4, 6.1)																																																																							
B/Vic	4.3 (1.6, 9.0)	5.7 (2.5, 10.9)																																																																							
A(H3N2) ¹	26.2 (19.2, 34.3)	12.1 (7.2, 18.7)																																																																							
A(H3N2) ²	22.0 (15.5, 29.7)	5.7 (2.5, 10.9)																																																																							
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	2.1 (0.4, 6.1)	2.1 (0.4, 6.1)																																																																							
A(H3N2)	29.8 (22.4, 38.1)	12.8 (7.7, 19.4)																																																																							
B/Yam	2.8 (0.8, 7.1)	0 (0.0, 2.6)																																																																							
B/Vic	3.5 (1.2, 8.1)	2.8 (0.8, 7.1)																																																																							
A(H3N2) ¹	12.8 (7.7, 19.4)	4.3 (1.6, 9.0)																																																																							
A(H3N2) ²	10.6 (6.1, 16.9)	2.1 (0.4, 6.1)																																																																							

STUDY DETAILS																																																																									
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																					
				<p>Seroprotection rate in adults 65 years of age and older, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>89.6 (83.4, 94.1)</td> <td>93.0 (87.5, 96.6)</td> </tr> <tr> <td>A(H3N2)</td> <td>72.9 (64.9, 80.0)</td> <td>64.3 (55.9, 72.2)</td> </tr> <tr> <td>B/Yam</td> <td>94.4 (89.3, 97.6)</td> <td>88.1 (81.6, 92.9)</td> </tr> <tr> <td>B/Vic</td> <td>93.1 (87.6, 96.6)</td> <td>95.8 (91.1, 98.4)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>93.1 (87.6, 96.6)</td> <td>92.3 (86.7, 96.1)</td> </tr> <tr> <td>A(H3N2)²</td> <td>72.9 (64.9, 80.0)</td> <td>65.0 (56.6, 72.8)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>Seroprotection rate in adults 65 years of age and older, 56 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>75.9 (68.0, 82.7)</td> <td>85 (78.0, 90.5)</td> </tr> <tr> <td>A(H3N2)</td> <td>57.4 (48.8, 65.7)</td> <td>45 (36.6, 53.6)</td> </tr> <tr> <td>B/Yam</td> <td>87.9 (81.4, 92.8)</td> <td>81.4 (74.0, 87.5)</td> </tr> <tr> <td>B/Vic</td> <td>65.2 (56.8, 73.1)</td> <td>73.6 (65.5, 80.7)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>91.5 (85.6, 95.5)</td> <td>94.3 (89.1, 97.5)</td> </tr> <tr> <td>A(H3N2)²</td> <td>53.9 (45.3, 62.3)</td> <td>42.1 (33.9, 50.8)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p> <p>Seroprotection rate in adults 65 years of age and older, 182 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>59.6 (51.0, 67.7)</td> <td>68.8 (60.5, 76.3)</td> </tr> <tr> <td>A(H3N2)</td> <td>67.4 (59.0, 75.0)</td> <td>63.8 (55.3, 71.7)</td> </tr> <tr> <td>B/Yam</td> <td>75.2 (67.2, 82.1)</td> <td>73.8 (65.7, 80.8)</td> </tr> <tr> <td>B/Vic</td> <td>62.4 (53.9, 70.4)</td> <td>78.0 (70.3, 84.5)</td> </tr> <tr> <td>A(H3N2)¹</td> <td>77.3 (69.5, 83.9)</td> <td>73.0 (64.9, 80.2)</td> </tr> <tr> <td>A(H3N2)²</td> <td>31.9 (24.3, 40.3)</td> <td>24.8 (17.9, 32.8)</td> </tr> </tbody> </table> <p>¹ A/Switzerland/9715293/2013 (Drift Strain) ² A/Wisconsin/19/2017 (Drift Strain)</p>	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	89.6 (83.4, 94.1)	93.0 (87.5, 96.6)	A(H3N2)	72.9 (64.9, 80.0)	64.3 (55.9, 72.2)	B/Yam	94.4 (89.3, 97.6)	88.1 (81.6, 92.9)	B/Vic	93.1 (87.6, 96.6)	95.8 (91.1, 98.4)	A(H3N2) ¹	93.1 (87.6, 96.6)	92.3 (86.7, 96.1)	A(H3N2) ²	72.9 (64.9, 80.0)	65.0 (56.6, 72.8)	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	75.9 (68.0, 82.7)	85 (78.0, 90.5)	A(H3N2)	57.4 (48.8, 65.7)	45 (36.6, 53.6)	B/Yam	87.9 (81.4, 92.8)	81.4 (74.0, 87.5)	B/Vic	65.2 (56.8, 73.1)	73.6 (65.5, 80.7)	A(H3N2) ¹	91.5 (85.6, 95.5)	94.3 (89.1, 97.5)	A(H3N2) ²	53.9 (45.3, 62.3)	42.1 (33.9, 50.8)	Strain	Estimate % (95% CI)		RIV4	IIV3-HD	A(H1N1)	59.6 (51.0, 67.7)	68.8 (60.5, 76.3)	A(H3N2)	67.4 (59.0, 75.0)	63.8 (55.3, 71.7)	B/Yam	75.2 (67.2, 82.1)	73.8 (65.7, 80.8)	B/Vic	62.4 (53.9, 70.4)	78.0 (70.3, 84.5)	A(H3N2) ¹	77.3 (69.5, 83.9)	73.0 (64.9, 80.2)	A(H3N2) ²	31.9 (24.3, 40.3)	24.8 (17.9, 32.8)
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	89.6 (83.4, 94.1)	93.0 (87.5, 96.6)																																																																							
A(H3N2)	72.9 (64.9, 80.0)	64.3 (55.9, 72.2)																																																																							
B/Yam	94.4 (89.3, 97.6)	88.1 (81.6, 92.9)																																																																							
B/Vic	93.1 (87.6, 96.6)	95.8 (91.1, 98.4)																																																																							
A(H3N2) ¹	93.1 (87.6, 96.6)	92.3 (86.7, 96.1)																																																																							
A(H3N2) ²	72.9 (64.9, 80.0)	65.0 (56.6, 72.8)																																																																							
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	75.9 (68.0, 82.7)	85 (78.0, 90.5)																																																																							
A(H3N2)	57.4 (48.8, 65.7)	45 (36.6, 53.6)																																																																							
B/Yam	87.9 (81.4, 92.8)	81.4 (74.0, 87.5)																																																																							
B/Vic	65.2 (56.8, 73.1)	73.6 (65.5, 80.7)																																																																							
A(H3N2) ¹	91.5 (85.6, 95.5)	94.3 (89.1, 97.5)																																																																							
A(H3N2) ²	53.9 (45.3, 62.3)	42.1 (33.9, 50.8)																																																																							
Strain	Estimate % (95% CI)																																																																								
	RIV4	IIV3-HD																																																																							
A(H1N1)	59.6 (51.0, 67.7)	68.8 (60.5, 76.3)																																																																							
A(H3N2)	67.4 (59.0, 75.0)	63.8 (55.3, 71.7)																																																																							
B/Yam	75.2 (67.2, 82.1)	73.8 (65.7, 80.8)																																																																							
B/Vic	62.4 (53.9, 70.4)	78.0 (70.3, 84.5)																																																																							
A(H3N2) ¹	77.3 (69.5, 83.9)	73.0 (64.9, 80.2)																																																																							
A(H3N2) ²	31.9 (24.3, 40.3)	24.8 (17.9, 32.8)																																																																							

STUDY DETAILS																															
Study	Vaccine	Study Design	Participants	Summary of Key Findings																											
<p>Dunkle L, Izikson R, Patriarca P, Goldenthal K, Muse D, Cox M. <i>Randomized Comparison of Immunogenicity and Safety of Quadrivalent Recombinant Versus Inactivated Influenza Vaccine in Healthy Adults 18–49 Years of Age. The Journal of Infectious Diseases.</i> 2017;216(10):1219-1226.</p> <p>ClinicalTrials.gov <i>Safety and Immunogenicity of Flublok Quadrivalent vs IIV4 in Adults 18-49 Years of Age</i> NCT02290509</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase III RCT</p> <p>US Multi-centre (10 sites)</p> <p>2014-2015 influenza season</p> <p>Funded by Protein Sciences Corporation</p>	<p>Ambulatory, medically stable adults aged 18 to 49 years with no contraindications to either study vaccine.</p> <p>64.7% female</p> <p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n= 969</p> <p>Mean age: 33.3</p> <p>IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline): n= 323</p> <p>Mean age: 34.0</p>	<p>GMT ratio in adults 18-49 years of age, 28 days post-vaccination (IIV4/RIV4):</p> <table border="1"> <thead> <tr> <th>Strain</th> <th>Estimate (95% CI)</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>0.81 (0.71, 0.92)</td> </tr> <tr> <td>A(H3N2)</td> <td>0.50 (0.44, 0.57)</td> </tr> <tr> <td>B/Yam</td> <td>0.86 (0.74, 0.99)</td> </tr> <tr> <td>B/Vic</td> <td>1.49 (1.29, 1.71)</td> </tr> </tbody> </table> <p>Seroconversion rates in adults 18-49 years of age, 28 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>66.7 (63.6, 69.6)</td> <td>63.5 (58.0, 68.7)</td> </tr> <tr> <td>A(H3N2)</td> <td>72.1 (69.2, 74.9)</td> <td>57.0 (51.4, 62.4)</td> </tr> <tr> <td>B/Yam</td> <td>59.6 (56.5, 62.8)</td> <td>60.4 (54.8, 65.7)</td> </tr> <tr> <td>B/Vic</td> <td>40.6 (37.4, 43.7)</td> <td>58.2 (52.6, 63.6)</td> </tr> </tbody> </table>	Strain	Estimate (95% CI)	A(H1N1)	0.81 (0.71, 0.92)	A(H3N2)	0.50 (0.44, 0.57)	B/Yam	0.86 (0.74, 0.99)	B/Vic	1.49 (1.29, 1.71)	Strain	Estimate % (95% CI)		RIV4	IIV4-SD	A(H1N1)	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)	A(H3N2)	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)	B/Yam	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)	B/Vic	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)
Strain	Estimate (95% CI)																														
A(H1N1)	0.81 (0.71, 0.92)																														
A(H3N2)	0.50 (0.44, 0.57)																														
B/Yam	0.86 (0.74, 0.99)																														
B/Vic	1.49 (1.29, 1.71)																														
Strain	Estimate % (95% CI)																														
	RIV4	IIV4-SD																													
A(H1N1)	66.7 (63.6, 69.6)	63.5 (58.0, 68.7)																													
A(H3N2)	72.1 (69.2, 74.9)	57.0 (51.4, 62.4)																													
B/Yam	59.6 (56.5, 62.8)	60.4 (54.8, 65.7)																													
B/Vic	40.6 (37.4, 43.7)	58.2 (52.6, 63.6)																													

<p>Wang W, Alvarado-Facundo E, Vassell R, Collins L, Colombo R, Ganesan A, Geaney C, Hrcir D, Lalani T, Markelz A, Maves R, McClenathan B, Mende K, Richard S, Schofield C, Seshadri S, Spooner C, Utz G, Warkentien T, Levine M, Coles C, Burgess T, Eichelberger M, Weiss D. <i>Comparison of A(H3N2) Neutralizing Antibody Responses Elicited by 2018–2019 Season Quadrivalent Influenza Vaccines Derived from Eggs, Cells, and Recombinant Hemagglutinin. Clinical Infectious Diseases. 2020.</i></p> <p>ClinicalTrials.gov <i>A Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED)</i> NCT03734237</p>	<p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Open label, phase IV RCT</p> <p>US Multi-centre (5 sites)</p> <p>2018-2019 influenza season</p> <p>Funded by US Food and Drug Administration, Department of Defense, and Centres for Disease Control and Prevention</p>	<p>Adult military healthcare beneficiaries aged 18 to 83 years</p> <p>47.4 female</p> <p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur) n= 51</p> <p>Mean age: 48.3</p> <p>IIV4-SD (Fluarix), GlaxoSmithKline Biologicals): n= 46</p> <p>Mean age: 48.1</p> <p>IIV4-cc (Flucelvax Quadrivalent, Seqirus, Inc.): n= 36</p> <p>Mean age: 45.7</p>	<p>GMT in adults 18-83 years of age, 21-35 days post vaccination:</p> <table border="1" data-bbox="1129 203 1549 706"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV4-cc</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>192</td> <td>60</td> <td>108</td> </tr> <tr> <td>A(H3N2)²</td> <td>282</td> <td>56</td> <td>71</td> </tr> <tr> <td>A(H3N2)³</td> <td>308</td> <td>105</td> <td>138</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>70</td> <td>40</td> <td>35</td> </tr> <tr> <td>A(H3N2)⁵</td> <td>181</td> <td>41</td> <td>55</td> </tr> <tr> <td>A(H3N2)⁶</td> <td>293</td> <td>104</td> <td>118</td> </tr> <tr> <td>A(H3N2)⁷</td> <td>458</td> <td>231</td> <td>313</td> </tr> <tr> <td>A(H3N2)⁸</td> <td>175</td> <td>63</td> <td>99</td> </tr> <tr> <td>A(H3N2)⁹</td> <td>668</td> <td>366</td> <td>439</td> </tr> <tr> <td>A(H3N2)¹⁰</td> <td>183</td> <td>74</td> <td>86</td> </tr> <tr> <td>A(H3N2)¹¹</td> <td>370</td> <td>146</td> <td>211</td> </tr> <tr> <td>A(H3N2)¹²</td> <td>1011</td> <td>480</td> <td>511</td> </tr> </tbody> </table> <p>¹ A/North Carolina/04/2016 (cell) ² A/Hong Kong/4801/2014 (cell) ³ A/Abu Dhabi/240/2018 wild type ⁴ A/Kansas/14/2017 wild type ⁵ A/Singapore/INFIMH-16-0019/2016 wild type ⁶ A/Singapore/INFIMH-16-0019/2016 T160K mutation ⁷ A/Singapore/INFIMH-16-0019/2016 L194P mutation ⁸ A/Singapore/INFIMH-16-0019/2016 D225G mutation ⁹ A/Singapore/INFIMH-16-0019/2016 T160K and L194P mutations ¹⁰ A/Singapore/INFIMH-16-0019/2016 T160K and D225G mutations ¹¹ A/Singapore/INFIMH-16-0019/2016 L194P and D225G mutations ¹² A/Singapore/INFIMH-16-0019/2016 NIB-104 (egg)</p>	Strain	Estimate			RIV4	IIV4-SD	IIV4-cc	A(H3N2) ¹	192	60	108	A(H3N2) ²	282	56	71	A(H3N2) ³	308	105	138	A(H3N2) ⁴	70	40	35	A(H3N2) ⁵	181	41	55	A(H3N2) ⁶	293	104	118	A(H3N2) ⁷	458	231	313	A(H3N2) ⁸	175	63	99	A(H3N2) ⁹	668	366	439	A(H3N2) ¹⁰	183	74	86	A(H3N2) ¹¹	370	146	211	A(H3N2) ¹²	1011	480	511
Strain	Estimate																																																										
	RIV4	IIV4-SD	IIV4-cc																																																								
A(H3N2) ¹	192	60	108																																																								
A(H3N2) ²	282	56	71																																																								
A(H3N2) ³	308	105	138																																																								
A(H3N2) ⁴	70	40	35																																																								
A(H3N2) ⁵	181	41	55																																																								
A(H3N2) ⁶	293	104	118																																																								
A(H3N2) ⁷	458	231	313																																																								
A(H3N2) ⁸	175	63	99																																																								
A(H3N2) ⁹	668	366	439																																																								
A(H3N2) ¹⁰	183	74	86																																																								
A(H3N2) ¹¹	370	146	211																																																								
A(H3N2) ¹²	1011	480	511																																																								

STUDY DETAILS																																																											
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																							
				<p>Seroconversion rate in adults 18-83 years of age, 21-35 days post vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="3">Estimate %</th> </tr> <tr> <th>RIV4</th> <th>IIV4 -SD</th> <th>IIV4- cc</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>43.1</td> <td>8.7</td> <td>8.3</td> </tr> <tr> <td>A(H3N2)²</td> <td>62.7</td> <td>6.5</td> <td>13.9</td> </tr> <tr> <td>A(H3N2)³</td> <td>52.9</td> <td>4.3</td> <td>11.1</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>21.6</td> <td>2.2</td> <td>0</td> </tr> <tr> <td>A(H3N2)⁵</td> <td>56.9</td> <td>4.3</td> <td>16.7</td> </tr> <tr> <td>A(H3N2)⁶</td> <td>47.1</td> <td>4.3</td> <td>8.3</td> </tr> <tr> <td>A(H3N2)⁷</td> <td>25.5</td> <td>4.3</td> <td>5.6</td> </tr> <tr> <td>A(H3N2)⁸</td> <td>33.3</td> <td>4.3</td> <td>8.3</td> </tr> <tr> <td>A(H3N2)⁹</td> <td>25.5</td> <td>6.5</td> <td>5.6</td> </tr> <tr> <td>A(H3N2)¹⁰</td> <td>39.2</td> <td>4.3</td> <td>2.8</td> </tr> <tr> <td>A(H3N2)¹¹</td> <td>41.1</td> <td>4.3</td> <td>5.6</td> </tr> <tr> <td>A(H3N2)¹²</td> <td>47.1</td> <td>8.7</td> <td>13.9</td> </tr> </tbody> </table> <p>¹ A/North Carolina/04/2016 (cell) ² A/Hong Kong/4801/2014 (cell) ³ A/Abu Dhabi/240/2018 wild type ⁴ A/Kansas/14/2017 wild type ⁵ A/Singapore/INFIMH-16-0019/2016 wild type ⁶ A/Singapore/INFIMH-16-0019/2016 T160K mutation ⁷ A/Singapore/INFIMH-16-0019/2016 L194P mutation ⁸ A/Singapore/INFIMH-16-0019/2016 D225G mutation ⁹ A/Singapore/INFIMH-16-0019/2016 T160K and L194P mutations ¹⁰ A/Singapore/INFIMH-16-0019/2016 T160K and D225G mutations ¹¹ A/Singapore/INFIMH-16-0019/2016 L194P and D225G mutations ¹² A/Singapore/INFIMH-16-0019/2016 NIB-104 (egg)</p>	Strain	Estimate %			RIV4	IIV4 -SD	IIV4- cc	A(H3N2) ¹	43.1	8.7	8.3	A(H3N2) ²	62.7	6.5	13.9	A(H3N2) ³	52.9	4.3	11.1	A(H3N2) ⁴	21.6	2.2	0	A(H3N2) ⁵	56.9	4.3	16.7	A(H3N2) ⁶	47.1	4.3	8.3	A(H3N2) ⁷	25.5	4.3	5.6	A(H3N2) ⁸	33.3	4.3	8.3	A(H3N2) ⁹	25.5	6.5	5.6	A(H3N2) ¹⁰	39.2	4.3	2.8	A(H3N2) ¹¹	41.1	4.3	5.6	A(H3N2) ¹²	47.1	8.7	13.9
Strain	Estimate %																																																										
	RIV4	IIV4 -SD	IIV4- cc																																																								
A(H3N2) ¹	43.1	8.7	8.3																																																								
A(H3N2) ²	62.7	6.5	13.9																																																								
A(H3N2) ³	52.9	4.3	11.1																																																								
A(H3N2) ⁴	21.6	2.2	0																																																								
A(H3N2) ⁵	56.9	4.3	16.7																																																								
A(H3N2) ⁶	47.1	4.3	8.3																																																								
A(H3N2) ⁷	25.5	4.3	5.6																																																								
A(H3N2) ⁸	33.3	4.3	8.3																																																								
A(H3N2) ⁹	25.5	6.5	5.6																																																								
A(H3N2) ¹⁰	39.2	4.3	2.8																																																								
A(H3N2) ¹¹	41.1	4.3	5.6																																																								
A(H3N2) ¹²	47.1	8.7	13.9																																																								

STUDY DETAILS																																																														
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																										
<p>Cowling B, Perera R, Valkenburg S, Leung N, Iuliano A, Tam, Wong J, Fang V, Li A, So H, Ip D, Azziz-Baumgartner E, Fry A, Levine M, Gangappa S, Sambhara S, Barr G, Skowronski D, Peiris J, Thompson M. <i>Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. Clinical Infectious Diseases. 2020;71(7):1704-1714.</i></p> <p>ClinicalTrials.gov <i>Immunogenicity of Alternative Annual Influenza Vaccination Strategies in Older Adults in Hong Kong (PIVOT)</i> NCT03330132</p>	<p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase IV RCT</p> <p>Hong Kong</p> <p>2017-2018 influenza season</p> <p>Funded by the Centres for Disease Control and Prevention</p>	<p>Community-dwelling older adults who were 65–82 years of age, residing in Hong Kong, and had not already received northern hemisphere 2017–2018 formulation of influenza vaccination.</p> <p>60.6% female</p> <p>Mean age: n/a</p> <p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur): n=200</p> <p>IIV4-SD (FluQuadri, Sanofi Pasteur): n= 200</p> <p>IIV3-Adj (Fluad, Seqirus): n= 200</p> <p>IIV3-HD (Fluzone High-Dose, Sanofi Pasteur): n= 200</p>	<p>GMT in adults 65-82 years of age, 30 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="4">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>85 (69, 105)</td> <td>69 (58, 83)</td> <td>94 (78, 114)</td> <td>125 (102, 152)</td> </tr> <tr> <td>A(H3N2)</td> <td>254 (218, 295)</td> <td>158 (135, 186)</td> <td>207 (178, 241)</td> <td>214 (183, 250)</td> </tr> <tr> <td>B/Yam</td> <td>131 (111, 155)</td> <td>121 (104, 141)</td> <td>63 (54, 74)</td> <td>68 (57, 81)</td> </tr> <tr> <td>B/Vic</td> <td>90 (76, 107)</td> <td>89 (75, 105)</td> <td>95 (81, 112)</td> <td>132 (112, 157)</td> </tr> </tbody> </table> <p>Seroconversion rate in adults 65-82 years of age, 30 days post vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="4">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H1N1)</td> <td>60 (53, 67)</td> <td>42 (36, 50)</td> <td>60 (53, 67)</td> <td>59 (52, 66)</td> </tr> <tr> <td>A(H3N2)</td> <td>56 (48, 63)</td> <td>41 (34, 48)</td> <td>48 (40, 55)</td> <td>54 (46, 61)</td> </tr> <tr> <td>B/Yam</td> <td>42 (36, 50)</td> <td>42 (36, 50)</td> <td>12 (8, 18)</td> <td>15 (10, 21)</td> </tr> <tr> <td>B/Vic</td> <td>44 (37, 51)</td> <td>48 (41, 56)</td> <td>44 (37, 51)</td> <td>52 (45, 60)</td> </tr> </tbody> </table>	Strain	Estimate (95% CI)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	A(H1N1)	85 (69, 105)	69 (58, 83)	94 (78, 114)	125 (102, 152)	A(H3N2)	254 (218, 295)	158 (135, 186)	207 (178, 241)	214 (183, 250)	B/Yam	131 (111, 155)	121 (104, 141)	63 (54, 74)	68 (57, 81)	B/Vic	90 (76, 107)	89 (75, 105)	95 (81, 112)	132 (112, 157)	Strain	Estimate (95% CI)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	A(H1N1)	60 (53, 67)	42 (36, 50)	60 (53, 67)	59 (52, 66)	A(H3N2)	56 (48, 63)	41 (34, 48)	48 (40, 55)	54 (46, 61)	B/Yam	42 (36, 50)	42 (36, 50)	12 (8, 18)	15 (10, 21)	B/Vic	44 (37, 51)	48 (41, 56)	44 (37, 51)	52 (45, 60)
Strain	Estimate (95% CI)																																																													
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																																										
A(H1N1)	85 (69, 105)	69 (58, 83)	94 (78, 114)	125 (102, 152)																																																										
A(H3N2)	254 (218, 295)	158 (135, 186)	207 (178, 241)	214 (183, 250)																																																										
B/Yam	131 (111, 155)	121 (104, 141)	63 (54, 74)	68 (57, 81)																																																										
B/Vic	90 (76, 107)	89 (75, 105)	95 (81, 112)	132 (112, 157)																																																										
Strain	Estimate (95% CI)																																																													
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																																										
A(H1N1)	60 (53, 67)	42 (36, 50)	60 (53, 67)	59 (52, 66)																																																										
A(H3N2)	56 (48, 63)	41 (34, 48)	48 (40, 55)	54 (46, 61)																																																										
B/Yam	42 (36, 50)	42 (36, 50)	12 (8, 18)	15 (10, 21)																																																										
B/Vic	44 (37, 51)	48 (41, 56)	44 (37, 51)	52 (45, 60)																																																										

STUDY DETAILS																																																	
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																													
<p>Gouma S, Zost S, Parkhouse K, Branche A, Topham D, Cobey S, Hensley S. <i>Comparison of Human H3N2 Antibody Responses Elicited by Egg-Based, Cell-Based, and Recombinant Protein-Based Influenza Vaccines During the 2017–2018 Season. Clinical Infectious Diseases.</i> 2020;71(6):1447-1453.</p> <p>ClinicalTrials.gov Comparison of Three Licensed Influenza Vaccines NCT03068949</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase IV RCT</p>	<p>Healthy adults aged 18 to 49 years</p>	<p>GMT in adults 18-49 years of age, 28 days post vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="4">Estimate (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-cc</th> <th>IIV4-SD</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>146 (95, 224)</td> <td>47 (29, 76)</td> <td>33 (20, 55)</td> <td>129 (57, 290)</td> </tr> <tr> <td>A(H3N2)²</td> <td>117 (76, 179)</td> <td>42 (27, 68)</td> <td>27 (18, 40)</td> <td>108 (49, 242)</td> </tr> <tr> <td>A(H3N2)³</td> <td>1401 (876, 2242)</td> <td>630 (411, 967)</td> <td>612 (366, 1023)</td> <td>2297 (1230, 4289)</td> </tr> <tr> <td>A(H3N2)⁴</td> <td>167 (115, 243)</td> <td>71 (44–114)</td> <td>39 (23, 65)</td> <td>164 (81, 329)</td> </tr> <tr> <td>H1N1</td> <td>186 (107, 323)</td> <td>138 (75, 251)</td> <td>90 (51, 159)</td> <td>217 (97, 484)</td> </tr> </tbody> </table> <p>¹ A/Hong Kong/4801/2014 ² A/Pennsylvania/49/2018 ³ A/Hong Kong/4801/2014 egg-adapted ⁴ A/Singapore/GP2050/2015 cell/adapted</p> <p>Seroconversion rate in adults 18-49 years of age, 28 days post vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Strain</th> <th colspan="2">Estimate %</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>A(H3N2)¹</td> <td>52</td> <td>38</td> </tr> <tr> <td>A(H3N2)²</td> <td>61</td> <td>38</td> </tr> </tbody> </table> <p>¹ A/Hong Kong/4801/2014 ² A/Pennsylvania/49/2018</p>	Strain	Estimate (95% CI)				RIV4	IIV4-cc	IIV4-SD	IIV3-HD	A(H3N2) ¹	146 (95, 224)	47 (29, 76)	33 (20, 55)	129 (57, 290)	A(H3N2) ²	117 (76, 179)	42 (27, 68)	27 (18, 40)	108 (49, 242)	A(H3N2) ³	1401 (876, 2242)	630 (411, 967)	612 (366, 1023)	2297 (1230, 4289)	A(H3N2) ⁴	167 (115, 243)	71 (44–114)	39 (23, 65)	164 (81, 329)	H1N1	186 (107, 323)	138 (75, 251)	90 (51, 159)	217 (97, 484)	Strain	Estimate %		RIV4	IIV3-HD	A(H3N2) ¹	52	38	A(H3N2) ²	61	38
		Strain	Estimate (95% CI)																																														
RIV4	IIV4-cc		IIV4-SD	IIV3-HD																																													
A(H3N2) ¹	146 (95, 224)	47 (29, 76)	33 (20, 55)	129 (57, 290)																																													
A(H3N2) ²	117 (76, 179)	42 (27, 68)	27 (18, 40)	108 (49, 242)																																													
A(H3N2) ³	1401 (876, 2242)	630 (411, 967)	612 (366, 1023)	2297 (1230, 4289)																																													
A(H3N2) ⁴	167 (115, 243)	71 (44–114)	39 (23, 65)	164 (81, 329)																																													
H1N1	186 (107, 323)	138 (75, 251)	90 (51, 159)	217 (97, 484)																																													
Strain	Estimate %																																																
	RIV4	IIV3-HD																																															
A(H3N2) ¹	52	38																																															
A(H3N2) ²	61	38																																															
		<p>US</p> <p>2017-2018 influenza season</p> <p>Funded by National Institute of Allergy and Infectious Diseases at the National Institutes of Health</p>	<p>57.6% female</p> <p>Mean age: n/a</p> <p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur) n= 23</p> <p>IIV3-HD (Fluzone High- Dose; Sanofi Pasteur): n= 16</p> <p>IIV4-cc (Flucelvax Quadrivalent, Seqirus, Inc.): n= 23</p> <p>IIV3- HD (Fluzone High-Dose; Sanofi Pasteur): n=16</p>																																														

Abbreviations: CI: confidence interval; GMT: geometric mean titre; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV4-cc: cell-culture based quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; N/A: not applicable; RCT: randomized controlled trial; RIV4: quadrivalent recombinant influenza vaccine; US: United States.

Table 6. Summary of Evidence on the Safety of Supemtek

STUDY DETAILS																																																																								
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																				
<p>Dunkle L, Izikson R, Patriarca P, Goldenthal K, Muse D, Callahan J, Cox M, PSC12 Study Team. <i>Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. New England Journal of Medicine. 2017; 376(25):2427-2436.</i></p> <p>ClinicalTrials.gov <i>Protective Efficacy of Flublok Quadrivalent Versus Licensed Inactivated Influenza Vaccine in Adults ≥50 Years of Age</i> NCT02285998</p>	RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)	Phase III-IV RCT US Multi-centre (40 sites) 2014-2015 influenza season Funded by Protein Sciences Corporation	Adults 50 years of age or older living independently without clinically significant acute illness, not receiving ongoing immunosuppressive therapy, and with no contraindications to trial vaccines 58.5% female Mean age: 63 RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur): n= 4,328 IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline): n= 4,344	Proportion of reported SAEs according to System Organ Class in adults 50 years of age and older reporting within 182 days (6 months) post-vaccination:																																																																				
				<table border="1"> <thead> <tr> <th rowspan="2">SAEs¹</th> <th colspan="2">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> </tr> </thead> <tbody> <tr> <td>Any SAE²</td> <td>3.4</td> <td>3.0</td> </tr> <tr> <td>Infections and infestations</td> <td>0.4</td> <td>0.6</td> </tr> <tr> <td>Cardiac disorders</td> <td>0.5</td> <td>0.4</td> </tr> <tr> <td>Musculoskeletal and connective tissue disorders</td> <td>0.5</td> <td>0.4</td> </tr> <tr> <td>Nervous system disorders</td> <td>0.4</td> <td>0.3</td> </tr> <tr> <td>Gastrointestinal disorders</td> <td>0.5</td> <td>0.2</td> </tr> <tr> <td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td> <td>0.2</td> <td>0.5</td> </tr> <tr> <td>General disorders and administration site conditions</td> <td>0.3</td> <td>0.2</td> </tr> <tr> <td>Respiratory, thoracic and mediastinal disorders</td> <td>0.3</td> <td>0.2</td> </tr> <tr> <td>Injury, poisoning and procedural complications</td> <td>0.2</td> <td>0.2</td> </tr> <tr> <td>Metabolism and nutrition disorders</td> <td>0.2</td> <td>0.2</td> </tr> <tr> <td>Vascular disorders</td> <td>0.1</td> <td>0.1</td> </tr> <tr> <td>Surgical and medical procedures</td> <td>0.2</td> <td>0.1</td> </tr> <tr> <td>Renal and urinary disorders</td> <td>0.2</td> <td>0.0</td> </tr> <tr> <td>Hepatobiliary disorders</td> <td>0.0</td> <td>0.1</td> </tr> <tr> <td>Reproductive system and breast disorders</td> <td>0.0</td> <td>0.1</td> </tr> <tr> <td>Blood and lymphatic system disorders</td> <td>0.1</td> <td>0</td> </tr> <tr> <td>Investigations</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Psychiatric disorders</td> <td>0.0</td> <td>0.1</td> </tr> <tr> <td>Ear and labyrinth disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Skin and subcutaneous tissue disorders</td> <td>0.0</td> <td>0.0</td> </tr> </tbody> </table>	SAEs ¹	Proportion (%)		RIV4	IIV4-SD	Any SAE ²	3.4	3.0	Infections and infestations	0.4	0.6	Cardiac disorders	0.5	0.4	Musculoskeletal and connective tissue disorders	0.5	0.4	Nervous system disorders	0.4	0.3	Gastrointestinal disorders	0.5	0.2	Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.2	0.5	General disorders and administration site conditions	0.3	0.2	Respiratory, thoracic and mediastinal disorders	0.3	0.2	Injury, poisoning and procedural complications	0.2	0.2	Metabolism and nutrition disorders	0.2	0.2	Vascular disorders	0.1	0.1	Surgical and medical procedures	0.2	0.1	Renal and urinary disorders	0.2	0.0	Hepatobiliary disorders	0.0	0.1	Reproductive system and breast disorders	0.0	0.1	Blood and lymphatic system disorders	0.1	0	Investigations	0.0	0.0	Psychiatric disorders	0.0	0.1	Ear and labyrinth disorders	0.0	0.0	Skin and subcutaneous tissue disorders	0.0	0.0
				SAEs ¹		Proportion (%)																																																																		
					RIV4	IIV4-SD																																																																		
				Any SAE ²	3.4	3.0																																																																		
				Infections and infestations	0.4	0.6																																																																		
				Cardiac disorders	0.5	0.4																																																																		
				Musculoskeletal and connective tissue disorders	0.5	0.4																																																																		
				Nervous system disorders	0.4	0.3																																																																		
				Gastrointestinal disorders	0.5	0.2																																																																		
				Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.2	0.5																																																																		
				General disorders and administration site conditions	0.3	0.2																																																																		
				Respiratory, thoracic and mediastinal disorders	0.3	0.2																																																																		
				Injury, poisoning and procedural complications	0.2	0.2																																																																		
				Metabolism and nutrition disorders	0.2	0.2																																																																		
				Vascular disorders	0.1	0.1																																																																		
				Surgical and medical procedures	0.2	0.1																																																																		
				Renal and urinary disorders	0.2	0.0																																																																		
				Hepatobiliary disorders	0.0	0.1																																																																		
				Reproductive system and breast disorders	0.0	0.1																																																																		
Blood and lymphatic system disorders	0.1	0																																																																						
Investigations	0.0	0.0																																																																						
Psychiatric disorders	0.0	0.1																																																																						
Ear and labyrinth disorders	0.0	0.0																																																																						
Skin and subcutaneous tissue disorders	0.0	0.0																																																																						
				¹ Events coded according to MedDRA, Version 17 ² Subjects may have reported more than one SAE term																																																																				

<p>Dunkle L, Izikson R, Patriarca P, Goldenthal K, Muse D, Cox M. <i>Randomized Comparison of Immunogenicity and Safety of Quadrivalent Recombinant Versus Inactivated Influenza Vaccine in Healthy Adults 18–49 Years of Age. The Journal of Infectious Diseases.</i> 2017;216(10):1219-1226.</p> <p>ClinicalTrials.gov <i>Safety and Immunogenicity of Flublok Quadrivalent vs IIV4 in Adults 18-49 Years of Age</i> NCT02290509</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase III RCT</p> <p>US Multi-centre (10 sites)</p> <p>2014-2015 influenza season</p> <p>Funded by Protein Sciences Corporation</p>	<p>Ambulatory, medically stable adults aged 18-49 years with no contraindications to either study vaccine.</p> <p>64.7% female</p> <p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur):</p> <p>SAEs population, n= 998</p> <p>Systemic AEs population, n= 994</p> <p>Mean age: 33.3</p> <p>IIV4-SD (Fluarix Quadrivalent, GlaxoSmithKline):</p> <p>SAEs population, n= 332</p> <p>Systemic AEs population, n= 332</p> <p>Mean age: 34.0</p>	<p>Proportion of SAEs in adults 18-49 years of age, within 182 days (6 months) post-vaccination:</p> <table border="1" data-bbox="1071 235 1732 771"> <thead> <tr> <th rowspan="2">SAEs</th> <th colspan="2">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> </tr> </thead> <tbody> <tr><td>Any SAE</td><td>1.0</td><td>0.6</td></tr> <tr><td>Myocardial infarction</td><td>0.2</td><td>0.0</td></tr> <tr><td>Gastrointestinal haemorrhage</td><td>0.0</td><td>0.3</td></tr> <tr><td>Pancreatitis</td><td>0.0</td><td>0.30</td></tr> <tr><td>Small intestinal obstruction</td><td>0.1</td><td>0.0</td></tr> <tr><td>Cholecystitis</td><td>0.0</td><td>0.3</td></tr> <tr><td>Appendicitis</td><td>0.1</td><td>0.0</td></tr> <tr><td>Periumbilical abscess</td><td>0.1</td><td>0.0</td></tr> <tr><td>Road traffic accident</td><td>0.1</td><td>0.0</td></tr> <tr><td>Neck pain</td><td>0.1</td><td>0.0</td></tr> <tr><td>Metabolic encephalopathy</td><td>0.1</td><td>0.0</td></tr> <tr><td>Abortion spontaneous</td><td>0.1</td><td>0</td></tr> <tr><td>Ovarian cyst</td><td>0.1</td><td>0</td></tr> <tr><td>Arm amputation</td><td>0.1</td><td>0</td></tr> </tbody> </table> <p>Proportion of reported systemic AEs in adults 18-49 years of age, within 7 days post-vaccination:</p> <table border="1" data-bbox="1071 860 2005 1274"> <thead> <tr> <th rowspan="3">Systemic AE</th> <th colspan="6">Proportion (%)</th> </tr> <tr> <th colspan="3">RIV4</th> <th colspan="3">IIV4-SD</th> </tr> <tr> <th>Any Severity</th> <th>Grade 3</th> <th>Grade 4</th> <th>Any Severity</th> <th>Grade 3</th> <th>Grade 4</th> </tr> </thead> <tbody> <tr><td>Any systemic reaction¹</td><td>34.1</td><td>2.3</td><td>0</td><td>35.8</td><td>2.7</td><td>0.3</td></tr> <tr><td>Fatigue</td><td>16.5</td><td>0.5</td><td>0</td><td>16.6</td><td>1.2</td><td>0</td></tr> <tr><td>Shivering/chills</td><td>6.9</td><td>0.5</td><td>0</td><td>6.0</td><td>1.2</td><td>0</td></tr> <tr><td>Joint pain</td><td>9.5</td><td>0.9</td><td>0</td><td>10.2</td><td>0.6</td><td>0</td></tr> <tr><td>Muscle pain</td><td>12.8</td><td>0.9</td><td>0</td><td>11.7</td><td>0.9</td><td>0</td></tr> <tr><td>Headache</td><td>20.3</td><td>1.3</td><td>0</td><td>21.1</td><td>1.8</td><td>0.3</td></tr> <tr><td>Nausea</td><td>9.0</td><td>0.6</td><td>0.1</td><td>9.3</td><td>1.2</td><td>0</td></tr> <tr><td>Fever^{2,3}</td><td>1.5</td><td>0.4</td><td>0</td><td>0.6</td><td>0.3</td><td>0</td></tr> </tbody> </table> <p>¹ The grading system systemic AE was as follows: Grade 1, mild; Grade 2, moderate; Grade 3: severe; Grade 4: life threatening.</p> <p>² For fever, the denominators were 990 and 327 for the RIV4 and IIV4-SD groups, respectively.</p> <p>³ The grading system for fever was as follows: Grade 1, 38–38.4°C (100.4–101.1°F); Grade 2, >38.4–38.9°C (101.2–102.0°F); Grade 3, >38.9–40°C (102.1–104°F); Grade 4, >40°C (>104°F).</p>	SAEs	Proportion (%)		RIV4	IIV4-SD	Any SAE	1.0	0.6	Myocardial infarction	0.2	0.0	Gastrointestinal haemorrhage	0.0	0.3	Pancreatitis	0.0	0.30	Small intestinal obstruction	0.1	0.0	Cholecystitis	0.0	0.3	Appendicitis	0.1	0.0	Periumbilical abscess	0.1	0.0	Road traffic accident	0.1	0.0	Neck pain	0.1	0.0	Metabolic encephalopathy	0.1	0.0	Abortion spontaneous	0.1	0	Ovarian cyst	0.1	0	Arm amputation	0.1	0	Systemic AE	Proportion (%)						RIV4			IIV4-SD			Any Severity	Grade 3	Grade 4	Any Severity	Grade 3	Grade 4	Any systemic reaction ¹	34.1	2.3	0	35.8	2.7	0.3	Fatigue	16.5	0.5	0	16.6	1.2	0	Shivering/chills	6.9	0.5	0	6.0	1.2	0	Joint pain	9.5	0.9	0	10.2	0.6	0	Muscle pain	12.8	0.9	0	11.7	0.9	0	Headache	20.3	1.3	0	21.1	1.8	0.3	Nausea	9.0	0.6	0.1	9.3	1.2	0	Fever ^{2,3}	1.5	0.4	0	0.6	0.3	0
SAEs	Proportion (%)																																																																																																																													
	RIV4	IIV4-SD																																																																																																																												
Any SAE	1.0	0.6																																																																																																																												
Myocardial infarction	0.2	0.0																																																																																																																												
Gastrointestinal haemorrhage	0.0	0.3																																																																																																																												
Pancreatitis	0.0	0.30																																																																																																																												
Small intestinal obstruction	0.1	0.0																																																																																																																												
Cholecystitis	0.0	0.3																																																																																																																												
Appendicitis	0.1	0.0																																																																																																																												
Periumbilical abscess	0.1	0.0																																																																																																																												
Road traffic accident	0.1	0.0																																																																																																																												
Neck pain	0.1	0.0																																																																																																																												
Metabolic encephalopathy	0.1	0.0																																																																																																																												
Abortion spontaneous	0.1	0																																																																																																																												
Ovarian cyst	0.1	0																																																																																																																												
Arm amputation	0.1	0																																																																																																																												
Systemic AE	Proportion (%)																																																																																																																													
	RIV4			IIV4-SD																																																																																																																										
	Any Severity	Grade 3	Grade 4	Any Severity	Grade 3	Grade 4																																																																																																																								
Any systemic reaction ¹	34.1	2.3	0	35.8	2.7	0.3																																																																																																																								
Fatigue	16.5	0.5	0	16.6	1.2	0																																																																																																																								
Shivering/chills	6.9	0.5	0	6.0	1.2	0																																																																																																																								
Joint pain	9.5	0.9	0	10.2	0.6	0																																																																																																																								
Muscle pain	12.8	0.9	0	11.7	0.9	0																																																																																																																								
Headache	20.3	1.3	0	21.1	1.8	0.3																																																																																																																								
Nausea	9.0	0.6	0.1	9.3	1.2	0																																																																																																																								
Fever ^{2,3}	1.5	0.4	0	0.6	0.3	0																																																																																																																								

STUDY DETAILS																																											
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																							
<p>Cowling B, Perera R, Valkenburg S, Leung N, Iuliano A, Tam, Wong J, Fang V, Li A, So H, Ip D, Azziz-Baumgartner E, Fry A, Levine M, Gangappa S, Sambhara S, Barr I, Skowronski D, Peiris J, Thompson M. <i>Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. Clinical Infectious Diseases.</i> 2020;71(7):1704-1714.</p> <p>ClinicalTrials.gov <i>Immunogenicity of Alternative Annual Influenza Vaccination Strategies in Older Adults in Hong Kong (PIVOT)</i> NCT03330132</p>	RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)	Phase IV RCT Hong Kong 2017-2018 influenza season Funded by the Centres for Disease Control and Prevention	Community-dwelling older adults who were 65-82 years of age, residing in Hong Kong, and had not already received northern hemisphere 2017–2018 formulation of influenza vaccination. 60.8% female Mean age: n/a RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur): n= 335 IIV4-SD (FluQuadri, Sanofi Pasteur) : n= 508 IIV3-Adj (Fluad, Seqirus): n= 508 IIV3-HD (Fluzone High-Dose, Sanofi Pasteur): n= 510	Proportion of reported hospitalizations in adults 65-82 years of age reporting throughout the study. No other SAE was identified by the authors and hospitalizations were deemed unrelated to the study vaccines. <table border="1" style="margin-top: 10px;"> <thead> <tr> <th rowspan="2">Hospitalizations</th> <th colspan="4">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>6.6</td> <td>8.1</td> <td>9.3</td> <td>7.1</td> </tr> <tr> <td colspan="5">Time since vaccination</td> </tr> <tr> <td><1 month</td> <td>0.6</td> <td>1.4</td> <td>0.6</td> <td>1.0</td> </tr> <tr> <td>1-3 months</td> <td>1.2</td> <td>1.8</td> <td>2.6</td> <td>1.4</td> </tr> <tr> <td>4-6 months</td> <td>4.2</td> <td>3.9</td> <td>4.7</td> <td>2.5</td> </tr> <tr> <td>>6 months</td> <td>0.0</td> <td>0.2</td> <td>0.6</td> <td>0.4</td> </tr> </tbody> </table>	Hospitalizations	Proportion (%)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	Overall	6.6	8.1	9.3	7.1	Time since vaccination					<1 month	0.6	1.4	0.6	1.0	1-3 months	1.2	1.8	2.6	1.4	4-6 months	4.2	3.9	4.7	2.5	>6 months	0.0	0.2	0.6	0.4
Hospitalizations	Proportion (%)																																										
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																							
Overall	6.6	8.1	9.3	7.1																																							
Time since vaccination																																											
<1 month	0.6	1.4	0.6	1.0																																							
1-3 months	1.2	1.8	2.6	1.4																																							
4-6 months	4.2	3.9	4.7	2.5																																							
>6 months	0.0	0.2	0.6	0.4																																							

<p>Cowling B, Thompson M, Ng T, Fang V, Perera R, Leung N, Chen Y, So H, Ip D, Iuliano A. <i>Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults. The Journal of Infectious Diseases.</i> 2020;222(8):1383-1391.</p> <p>ClinicalTrials.gov <i>Immunogenicity of Alternative Annual Influenza Vaccination Strategies in Older Adults in Hong Kong (PIVOT)</i> NCT03330132</p>	<p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Hong Kong</p> <p>2017-2018 influenza season</p> <p>Funded by the Centres for Disease Control and Prevention</p>	<p>65–82 years of age, residing in Hong Kong, and had not already received northern hemisphere 2017–2018 formulation of influenza vaccination.</p> <p>60.8% female</p> <p>Mean age: n/a</p> <p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur):</p> <p>1 day population, n= 280</p> <p>3-4 days population, n= 273</p> <p>7-9 days population, n= 307</p> <p>14-16 days population, n= 305</p> <p>IIV4-SD (FluQuadri, Sanofi Pasteur) :</p> <p>1 day population, n= 429</p> <p>3-4 days population, n= 414</p> <p>7-9 days population, n= 456</p>	<p>Proportion of reported systemic AEs in adults 65-82 years of age, within 1 day post-vaccination:</p> <table border="1" data-bbox="1073 233 1860 808"> <thead> <tr> <th rowspan="2">Systemic AEs^{1,2}</th> <th colspan="4">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr><td>Fatigue (mild)</td><td>3.2</td><td>3.7</td><td>5.2</td><td>5.0</td></tr> <tr><td>Feverishness (mild)</td><td>0.4</td><td>1.4</td><td>2.9</td><td>2.1</td></tr> <tr><td>Muscle pain (mild)</td><td>1.1</td><td>1.9</td><td>1.8</td><td>1.2</td></tr> <tr><td>Nausea (mild)</td><td>0.7</td><td>0.2</td><td>0.9</td><td>0.5</td></tr> <tr><td>Others (mild)</td><td>5.0</td><td>6.8</td><td>5.9</td><td>7.3</td></tr> <tr><td>Fatigue (moderate)</td><td>0</td><td>0.5</td><td>1.1</td><td>0</td></tr> <tr><td>Feverishness (moderate)</td><td>0</td><td>0</td><td>0.2</td><td>0.2</td></tr> <tr><td>Muscle pain (moderate)</td><td>0</td><td>0.9</td><td>0</td><td>0.2</td></tr> <tr><td>Nausea (moderate)</td><td>0</td><td>0</td><td>0.2</td><td>0.2</td></tr> <tr><td>Others (moderate)</td><td>0</td><td>0.2</td><td>1.1</td><td>1.2</td></tr> <tr><td>Fatigue (severe)</td><td>0</td><td>0</td><td>0.5</td><td>0</td></tr> <tr><td>Feverishness (severe)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Muscle pain (severe)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Nausea (severe)</td><td>0</td><td>0</td><td>0</td><td>0</td></tr> <tr><td>Others (severe)</td><td>0.4</td><td>0.5</td><td>0.2</td><td>0.5</td></tr> </tbody> </table> <p>¹ Mild: symptom is easily tolerated and does not interfere with any usual activities; moderate: symptom interferes with usual activities; severe: participant cannot carry out usual activities.</p> <p>² Other symptoms included sore throat, headache, runny nose, cough, dry eyes and upset stomach</p>	Systemic AEs ^{1,2}	Proportion (%)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	Fatigue (mild)	3.2	3.7	5.2	5.0	Feverishness (mild)	0.4	1.4	2.9	2.1	Muscle pain (mild)	1.1	1.9	1.8	1.2	Nausea (mild)	0.7	0.2	0.9	0.5	Others (mild)	5.0	6.8	5.9	7.3	Fatigue (moderate)	0	0.5	1.1	0	Feverishness (moderate)	0	0	0.2	0.2	Muscle pain (moderate)	0	0.9	0	0.2	Nausea (moderate)	0	0	0.2	0.2	Others (moderate)	0	0.2	1.1	1.2	Fatigue (severe)	0	0	0.5	0	Feverishness (severe)	0	0	0	0	Muscle pain (severe)	0	0	0	0	Nausea (severe)	0	0	0	0	Others (severe)	0.4	0.5	0.2	0.5
Systemic AEs ^{1,2}	Proportion (%)																																																																																							
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																																																																				
Fatigue (mild)	3.2	3.7	5.2	5.0																																																																																				
Feverishness (mild)	0.4	1.4	2.9	2.1																																																																																				
Muscle pain (mild)	1.1	1.9	1.8	1.2																																																																																				
Nausea (mild)	0.7	0.2	0.9	0.5																																																																																				
Others (mild)	5.0	6.8	5.9	7.3																																																																																				
Fatigue (moderate)	0	0.5	1.1	0																																																																																				
Feverishness (moderate)	0	0	0.2	0.2																																																																																				
Muscle pain (moderate)	0	0.9	0	0.2																																																																																				
Nausea (moderate)	0	0	0.2	0.2																																																																																				
Others (moderate)	0	0.2	1.1	1.2																																																																																				
Fatigue (severe)	0	0	0.5	0																																																																																				
Feverishness (severe)	0	0	0	0																																																																																				
Muscle pain (severe)	0	0	0	0																																																																																				
Nausea (severe)	0	0	0	0																																																																																				
Others (severe)	0.4	0.5	0.2	0.5																																																																																				

			<p>14-16 day population, n= 458</p> <p>IIV3-Adj (Fluad, Seqirus):</p> <p>1 day population, n= 442</p> <p>3-4 days population, n= 419</p> <p>7-9 days population, n= 462</p> <p>14-16 days population, n= 453</p> <p>IIV3-HD (Fluzone High-Dose, Sanofi Pasteur):</p> <p>1 day population, n= 424</p> <p>3-4 days population, n= 407</p> <p>7-9 days population, n= 463</p> <p>14-16 days population, n= 449</p>	<p>Proportion of reported systemic AEs in adults 65-82 years of age, within 3-4 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Systemic AEs^{1,2}</th> <th colspan="4">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>Fatigue (mild)</td> <td>2.9</td> <td>2.7</td> <td>1.7</td> <td>4.2</td> </tr> <tr> <td>Feverishness (mild)</td> <td>1.5</td> <td>0.5</td> <td>1.0</td> <td>1.0</td> </tr> <tr> <td>Muscle pain (mild)</td> <td>1.5</td> <td>2.2</td> <td>0.7</td> <td>1.7</td> </tr> <tr> <td>Nausea (mild)</td> <td>1.5</td> <td>0.5</td> <td>0.5</td> <td>0.7</td> </tr> <tr> <td>Others (mild)</td> <td>5.5</td> <td>5.8</td> <td>3.3</td> <td>5.4</td> </tr> <tr> <td>Fatigue (moderate)</td> <td>1.1</td> <td>0.7</td> <td>1.7</td> <td>0</td> </tr> <tr> <td>Feverishness (moderate)</td> <td>0</td> <td>0.2</td> <td>0</td> <td>0.2</td> </tr> <tr> <td>Muscle pain (moderate)</td> <td>0</td> <td>0.2</td> <td>0</td> <td>0.7</td> </tr> <tr> <td>Nausea (moderate)</td> <td>0</td> <td>0</td> <td>0</td> <td>0.2</td> </tr> <tr> <td>Others (moderate)</td> <td>0.7</td> <td>1.0</td> <td>2.1</td> <td>1.2</td> </tr> <tr> <td>Fatigue (severe)</td> <td>0</td> <td>0</td> <td>0</td> <td>0.2</td> </tr> <tr> <td>Feverishness (severe)</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Muscle pain (severe)</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Nausea (severe)</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>Others (severe)</td> <td>0</td> <td>0.2</td> <td>0.2</td> <td>1.0</td> </tr> </tbody> </table> <p>¹ Mild: symptom is easily tolerated and does not interfere with any usual activities; moderate: symptom interferes with usual activities; severe: participant cannot carry out usual activities.</p> <p>² Other symptoms included sore throat, headache, runny nose, cough, dry eyes and upset stomach</p>	Systemic AEs ^{1,2}	Proportion (%)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	Fatigue (mild)	2.9	2.7	1.7	4.2	Feverishness (mild)	1.5	0.5	1.0	1.0	Muscle pain (mild)	1.5	2.2	0.7	1.7	Nausea (mild)	1.5	0.5	0.5	0.7	Others (mild)	5.5	5.8	3.3	5.4	Fatigue (moderate)	1.1	0.7	1.7	0	Feverishness (moderate)	0	0.2	0	0.2	Muscle pain (moderate)	0	0.2	0	0.7	Nausea (moderate)	0	0	0	0.2	Others (moderate)	0.7	1.0	2.1	1.2	Fatigue (severe)	0	0	0	0.2	Feverishness (severe)	0	0	0	0	Muscle pain (severe)	0	0	0	0	Nausea (severe)	0	0	0	0	Others (severe)	0	0.2	0.2	1.0
Systemic AEs ^{1,2}	Proportion (%)																																																																																							
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																																																																				
Fatigue (mild)	2.9	2.7	1.7	4.2																																																																																				
Feverishness (mild)	1.5	0.5	1.0	1.0																																																																																				
Muscle pain (mild)	1.5	2.2	0.7	1.7																																																																																				
Nausea (mild)	1.5	0.5	0.5	0.7																																																																																				
Others (mild)	5.5	5.8	3.3	5.4																																																																																				
Fatigue (moderate)	1.1	0.7	1.7	0																																																																																				
Feverishness (moderate)	0	0.2	0	0.2																																																																																				
Muscle pain (moderate)	0	0.2	0	0.7																																																																																				
Nausea (moderate)	0	0	0	0.2																																																																																				
Others (moderate)	0.7	1.0	2.1	1.2																																																																																				
Fatigue (severe)	0	0	0	0.2																																																																																				
Feverishness (severe)	0	0	0	0																																																																																				
Muscle pain (severe)	0	0	0	0																																																																																				
Nausea (severe)	0	0	0	0																																																																																				
Others (severe)	0	0.2	0.2	1.0																																																																																				

Systemic AEs in adults 65-82 years of age, 7-9 days post-vaccination:

Systemic AEs ^{1,2}	Proportion (%)			
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD
Fatigue (mild)	3.9	2.2	2.8	3.0
Feverishness (mild)	0.3	0.9	1.3	1.3
Muscle pain (mild)	2.0	1.3	0.9	1.1
Nausea (mild)	1.0	0.9	0.4	0.9
Others (mild)	5.9	4.2	4.5	6.0
Fatigue (moderate)	0.3	1.3	0.9	0.9
Feverishness (moderate)	0	0.7	0.2	0.2
Muscle pain (moderate)	0	0.9	0.6	0.9
Nausea (moderate)	0	0.4	0	0.2
Others (moderate)	0.7	2.0	1.1	1.3
Fatigue (severe)	0	0.4	0	0
Feverishness (severe)	0	0	0	0
Muscle pain (severe)	0	0	0	0
Nausea (severe)	0	0	0	0
Others (severe)	0.3	0.9	0.4	0.4

¹ Mild: symptom is easily tolerated and does not interfere with any usual activities; moderate: symptom interferes with usual activities; severe: participant cannot carry out usual activities.

² Other symptoms included sore throat, headache, runny nose, cough, dry eyes and upset stomach

STUDY DETAILS																																																																																								
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																																				
				<p>Systemic AEs in adults 65-82 years of age, 14-16 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">Systemic AEs^{1,2}</th> <th colspan="4">Proportion (%)</th> </tr> <tr> <th>RIV4</th> <th>IIV4-SD</th> <th>IIV3-Adj</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>Fatigue (mild)</td> <td>1.3</td> <td>1.7</td> <td>2.2</td> <td>2.4</td> </tr> <tr> <td>Feverishness (mild)</td> <td>0.7</td> <td>0.7</td> <td>0.7</td> <td>1.1</td> </tr> <tr> <td>Muscle pain (mild)</td> <td>1.0</td> <td>1.3</td> <td>0.4</td> <td>1.8</td> </tr> <tr> <td>Nausea (mild)</td> <td>0.0</td> <td>0.2</td> <td>0.2</td> <td>0.7</td> </tr> <tr> <td>Others (mild)</td> <td>5.2</td> <td>4.6</td> <td>3.5</td> <td>5.8</td> </tr> <tr> <td>Fatigue (moderate)</td> <td>0.3</td> <td>0.7</td> <td>0.7</td> <td>0.9</td> </tr> <tr> <td>Feverishness (moderate)</td> <td>0.0</td> <td>0.7</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Muscle pain (moderate)</td> <td>0.0</td> <td>0.4</td> <td>0.9</td> <td>0.2</td> </tr> <tr> <td>Nausea (moderate)</td> <td>0.0</td> <td>0.4</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Others (moderate)</td> <td>1.6</td> <td>2.8</td> <td>1.5</td> <td>2.4</td> </tr> <tr> <td>Fatigue (severe)</td> <td>0.0</td> <td>0.2</td> <td>0.2</td> <td>0.0</td> </tr> <tr> <td>Feverishness (severe)</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Muscle pain (severe)</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.2</td> </tr> <tr> <td>Nausea (severe)</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Others (severe)</td> <td>0.7</td> <td>0.9</td> <td>0.9</td> <td>0.2</td> </tr> </tbody> </table> <p>¹ Mild: symptom is easily tolerated and does not interfere with any usual activities; moderate: symptom interferes with usual activities; severe: participant cannot carry out usual activities. ² Other symptoms included sore throat, headache, runny nose, cough, dry eyes and upset stomach</p>	Systemic AEs ^{1,2}	Proportion (%)				RIV4	IIV4-SD	IIV3-Adj	IIV3-HD	Fatigue (mild)	1.3	1.7	2.2	2.4	Feverishness (mild)	0.7	0.7	0.7	1.1	Muscle pain (mild)	1.0	1.3	0.4	1.8	Nausea (mild)	0.0	0.2	0.2	0.7	Others (mild)	5.2	4.6	3.5	5.8	Fatigue (moderate)	0.3	0.7	0.7	0.9	Feverishness (moderate)	0.0	0.7	0.0	0.0	Muscle pain (moderate)	0.0	0.4	0.9	0.2	Nausea (moderate)	0.0	0.4	0.0	0.0	Others (moderate)	1.6	2.8	1.5	2.4	Fatigue (severe)	0.0	0.2	0.2	0.0	Feverishness (severe)	0.0	0.0	0.0	0.0	Muscle pain (severe)	0.0	0.0	0.0	0.2	Nausea (severe)	0.0	0.0	0.0	0.0	Others (severe)	0.7	0.9	0.9	0.2
Systemic AEs ^{1,2}	Proportion (%)																																																																																							
	RIV4	IIV4-SD	IIV3-Adj	IIV3-HD																																																																																				
Fatigue (mild)	1.3	1.7	2.2	2.4																																																																																				
Feverishness (mild)	0.7	0.7	0.7	1.1																																																																																				
Muscle pain (mild)	1.0	1.3	0.4	1.8																																																																																				
Nausea (mild)	0.0	0.2	0.2	0.7																																																																																				
Others (mild)	5.2	4.6	3.5	5.8																																																																																				
Fatigue (moderate)	0.3	0.7	0.7	0.9																																																																																				
Feverishness (moderate)	0.0	0.7	0.0	0.0																																																																																				
Muscle pain (moderate)	0.0	0.4	0.9	0.2																																																																																				
Nausea (moderate)	0.0	0.4	0.0	0.0																																																																																				
Others (moderate)	1.6	2.8	1.5	2.4																																																																																				
Fatigue (severe)	0.0	0.2	0.2	0.0																																																																																				
Feverishness (severe)	0.0	0.0	0.0	0.0																																																																																				
Muscle pain (severe)	0.0	0.0	0.0	0.2																																																																																				
Nausea (severe)	0.0	0.0	0.0	0.0																																																																																				
Others (severe)	0.7	0.9	0.9	0.2																																																																																				

STUDY DETAILS																																																									
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																					
<p>Shinde V, Cai R, Plested J, Cho I, Fiske J, Pham X, Zhu M, Cloney-Clark S, Wang N, Zhou H, Zhou B, Patel N, Massare M, Fix A, Spindler M, Thomas D, Smith G, Fries L, Glenn G.</p> <p><i>Induction of Cross-Reactive Hemagglutination Inhibiting Antibody and Polyfunctional CD4+ T-Cell Responses by a Recombinant Matrix-M–Adjuvanted Hemagglutinin Nanoparticle Influenza Vaccine. Clinical Infectious Diseases. 2020.</i></p> <p>ClinicalTrials.gov Phase 2 Dose and Formulation Confirmation of Quad-NIV in Older Adults NCT03658629</p>	<p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur)</p>	<p>Phase II, observer blind RCT</p> <p>US Multi-centre (14 sites)</p> <p>2018-2019 influenza season</p> <p>Funded by Novavax Inc.</p>	<p>Clinically stable adults aged ≥65 years</p> <p>RIV4 (Supemtek/ Flublok Quadrivalent, Sanofi Pasteur): n=151</p> <p>Mean age: 72.9</p> <p>57.6% female</p> <p>IIV3-HD (Fluzone High- Dose, Sanofi Pasteur); n= 153</p> <p>Mean age: 72.5</p> <p>64.7% female</p>	<p>SAEs in adults 65 years of age and over, 181 days post-vaccination:</p> <table border="1"> <thead> <tr> <th rowspan="2">SAEs¹</th> <th colspan="2">Proportion % (95% CI)</th> </tr> <tr> <th>RIV4</th> <th>IIV3-HD</th> </tr> </thead> <tbody> <tr> <td>Subjects with at least one SAE</td> <td>2.0 (0.4–5.7)</td> <td>3.9 (1.5–8.3)</td> </tr> <tr> <td>Infections and infestations</td> <td>0.7</td> <td>1.3</td> </tr> <tr> <td>Nervous system disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Cardiac disorders</td> <td>0.0</td> <td>0.7</td> </tr> <tr> <td>Gastrointestinal disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Injury, poisoning, and procedural complications</td> <td>1.3</td> <td>0.7</td> </tr> <tr> <td>Metabolism and nutrition disorders</td> <td>0.0</td> <td>1.3</td> </tr> <tr> <td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Respiratory, thoracic, and mediastinal disorders</td> <td>0.0</td> <td>0.7</td> </tr> <tr> <td>General disorders and administration site conditions</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Musculoskeletal and connective tissue disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Blood and lymphatic system disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Hepatobiliary disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Reproductive system and breast disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Skin and subcutaneous tissue disorders</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Vascular disorders</td> <td>0.0</td> <td>0.0</td> </tr> </tbody> </table>	SAEs ¹	Proportion % (95% CI)		RIV4	IIV3-HD	Subjects with at least one SAE	2.0 (0.4–5.7)	3.9 (1.5–8.3)	Infections and infestations	0.7	1.3	Nervous system disorders	0.0	0.0	Cardiac disorders	0.0	0.7	Gastrointestinal disorders	0.0	0.0	Injury, poisoning, and procedural complications	1.3	0.7	Metabolism and nutrition disorders	0.0	1.3	Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.0	0.0	Respiratory, thoracic, and mediastinal disorders	0.0	0.7	General disorders and administration site conditions	0.0	0.0	Musculoskeletal and connective tissue disorders	0.0	0.0	Blood and lymphatic system disorders	0.0	0.0	Hepatobiliary disorders	0.0	0.0	Reproductive system and breast disorders	0.0	0.0	Skin and subcutaneous tissue disorders	0.0	0.0	Vascular disorders	0.0	0.0
				SAEs ¹		Proportion % (95% CI)																																																			
RIV4	IIV3-HD																																																								
Subjects with at least one SAE	2.0 (0.4–5.7)	3.9 (1.5–8.3)																																																							
Infections and infestations	0.7	1.3																																																							
Nervous system disorders	0.0	0.0																																																							
Cardiac disorders	0.0	0.7																																																							
Gastrointestinal disorders	0.0	0.0																																																							
Injury, poisoning, and procedural complications	1.3	0.7																																																							
Metabolism and nutrition disorders	0.0	1.3																																																							
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0.0	0.0																																																							
Respiratory, thoracic, and mediastinal disorders	0.0	0.7																																																							
General disorders and administration site conditions	0.0	0.0																																																							
Musculoskeletal and connective tissue disorders	0.0	0.0																																																							
Blood and lymphatic system disorders	0.0	0.0																																																							
Hepatobiliary disorders	0.0	0.0																																																							
Reproductive system and breast disorders	0.0	0.0																																																							
Skin and subcutaneous tissue disorders	0.0	0.0																																																							
Vascular disorders	0.0	0.0																																																							
<p>¹ MedDRA System Organ Class and Preferred Term</p>																																																									

STUDY DETAILS																																																																																																																					
Study	Vaccine	Study Design	Participants	Summary of Key Findings																																																																																																																	
				Systemic AEs in adults 65 years of age and over, 6 days post-vaccination: <table border="1"> <thead> <tr> <th rowspan="3">Systemic AEs</th> <th colspan="4">Proportion % (95 % CI)</th> </tr> <tr> <th colspan="2">RIV4</th> <th colspan="2">IIV3-HD</th> </tr> <tr> <th>Any severity</th> <th>Severe</th> <th>Any severity</th> <th>Severe</th> </tr> </thead> <tbody> <tr> <td>All systemic AEs</td> <td>25.8 (19.1–33.6)</td> <td>2.6 (0.7–6.6)</td> <td>24.2 (17.6–31.8)</td> <td>1.3 (0.2–4.6)</td> </tr> <tr> <td>Chills</td> <td>1.3</td> <td>0.0</td> <td>3.3</td> <td>0.7</td> </tr> <tr> <td>Fatigue</td> <td>6.6</td> <td>0.7</td> <td>10.5</td> <td>0.7</td> </tr> <tr> <td>Headache</td> <td>9.3</td> <td>2.0</td> <td>9.2</td> <td>1.3</td> </tr> <tr> <td>Joint pain</td> <td>6.6</td> <td>0.0</td> <td>7.8</td> <td>0.7</td> </tr> <tr> <td>Muscle pain</td> <td>4.6</td> <td>0.0</td> <td>14.4</td> <td>0.7</td> </tr> <tr> <td>Oral temperature</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Diarrhea</td> <td>9.9</td> <td>0.7</td> <td>3.9</td> <td>0.0</td> </tr> <tr> <td>Nausea</td> <td>2.0</td> <td>0.0</td> <td>4.6</td> <td>0.7</td> </tr> <tr> <td>Vomiting</td> <td>0.7</td> <td>0.0</td> <td>0.7</td> <td>0.7</td> </tr> <tr> <td>Chest tightness</td> <td>1.3</td> <td>0.0</td> <td>0.7</td> <td>0.0</td> </tr> <tr> <td>Cough</td> <td>5.3</td> <td>0.7</td> <td>2.0</td> <td>0.0</td> </tr> <tr> <td>Difficulty breathing</td> <td>0.7</td> <td>0.7</td> <td>2.0</td> <td>0.0</td> </tr> <tr> <td>Difficulty swallowing</td> <td>1.3</td> <td>0.7</td> <td>0.7</td> <td>0.0</td> </tr> <tr> <td>Eye redness</td> <td>0.7</td> <td>0.0</td> <td>0.7</td> <td>0.0</td> </tr> <tr> <td>Eyelid swelling</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Facial swelling</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> </tr> <tr> <td>Hoarseness</td> <td>0.7</td> <td>0.0</td> <td>2.0</td> <td>0.0</td> </tr> <tr> <td>Sore throat</td> <td>3.3</td> <td>0.7</td> <td>3.9</td> <td>0.0</td> </tr> <tr> <td>Wheezing</td> <td>2.0</td> <td>0.0</td> <td>2.0</td> <td>0.0</td> </tr> </tbody> </table>	Systemic AEs	Proportion % (95 % CI)				RIV4		IIV3-HD		Any severity	Severe	Any severity	Severe	All systemic AEs	25.8 (19.1–33.6)	2.6 (0.7–6.6)	24.2 (17.6–31.8)	1.3 (0.2–4.6)	Chills	1.3	0.0	3.3	0.7	Fatigue	6.6	0.7	10.5	0.7	Headache	9.3	2.0	9.2	1.3	Joint pain	6.6	0.0	7.8	0.7	Muscle pain	4.6	0.0	14.4	0.7	Oral temperature	0.0	0.0	0.0	0.0	Diarrhea	9.9	0.7	3.9	0.0	Nausea	2.0	0.0	4.6	0.7	Vomiting	0.7	0.0	0.7	0.7	Chest tightness	1.3	0.0	0.7	0.0	Cough	5.3	0.7	2.0	0.0	Difficulty breathing	0.7	0.7	2.0	0.0	Difficulty swallowing	1.3	0.7	0.7	0.0	Eye redness	0.7	0.0	0.7	0.0	Eyelid swelling	0.0	0.0	0.0	0.0	Facial swelling	0.0	0.0	0.0	0.0	Hoarseness	0.7	0.0	2.0	0.0	Sore throat	3.3	0.7	3.9	0.0	Wheezing	2.0	0.0	2.0	0.0
Systemic AEs	Proportion % (95 % CI)																																																																																																																				
	RIV4		IIV3-HD																																																																																																																		
	Any severity	Severe	Any severity	Severe																																																																																																																	
All systemic AEs	25.8 (19.1–33.6)	2.6 (0.7–6.6)	24.2 (17.6–31.8)	1.3 (0.2–4.6)																																																																																																																	
Chills	1.3	0.0	3.3	0.7																																																																																																																	
Fatigue	6.6	0.7	10.5	0.7																																																																																																																	
Headache	9.3	2.0	9.2	1.3																																																																																																																	
Joint pain	6.6	0.0	7.8	0.7																																																																																																																	
Muscle pain	4.6	0.0	14.4	0.7																																																																																																																	
Oral temperature	0.0	0.0	0.0	0.0																																																																																																																	
Diarrhea	9.9	0.7	3.9	0.0																																																																																																																	
Nausea	2.0	0.0	4.6	0.7																																																																																																																	
Vomiting	0.7	0.0	0.7	0.7																																																																																																																	
Chest tightness	1.3	0.0	0.7	0.0																																																																																																																	
Cough	5.3	0.7	2.0	0.0																																																																																																																	
Difficulty breathing	0.7	0.7	2.0	0.0																																																																																																																	
Difficulty swallowing	1.3	0.7	0.7	0.0																																																																																																																	
Eye redness	0.7	0.0	0.7	0.0																																																																																																																	
Eyelid swelling	0.0	0.0	0.0	0.0																																																																																																																	
Facial swelling	0.0	0.0	0.0	0.0																																																																																																																	
Hoarseness	0.7	0.0	2.0	0.0																																																																																																																	
Sore throat	3.3	0.7	3.9	0.0																																																																																																																	
Wheezing	2.0	0.0	2.0	0.0																																																																																																																	

<p>Woo E, Moro P. <i>Postmarketing safety surveillance of quadrivalent recombinant influenza vaccine: Reports to the vaccine adverse event reporting system. Vaccine. 2021;39(13):1812-1817.</i></p>	<p>RIV4 (Supemtek/Flublok Quadrivalent, Sanofi Pasteur)</p> <p>US (Vaccine Adverse Event Reporting System)</p> <p>2017-2018, 2018-2019, 2019-2020 influenza seasons</p>	<p>Post-marketing safety surveillance of cases identified through VAERS</p>	<p>Persons vaccinated with RIV4 during July 1, 2017 through June 30, 2020</p> <p>Mean age: 43.7</p> <p>69.7% female</p> <p>Reports on serious adverse events: N= 39</p> <p>Reports on systemic adverse events: N= 300</p>	SAEs reported after RIV4 vaccination:	
				SAEs	Proportion (%) RIV4
				Neurological	43.6
				Guillain-Barré syndrome	25.6
				Seizure	7.7
				Exacerbation of pre-existing multiple sclerosis	5.1
				Optic papillitis	2.6
				Sensorineural hearing loss	2.6
				Immunological	15.4
				Anaphylaxis / allergic reaction	10.3
				Serum sickness-type reaction, allergic reaction to influenza vaccine	2.6
				Stevens Johnson syndrome after lisinopril and atorvastatin	2.6
				Local reaction	12.8
				Injection site reaction or local cellulitis	12.8
				Respiratory	10.3
				Exacerbation or complications of pre-existing pulmonary conditions (chronic obstructive pulmonary disease asthma, or lung transplantation)	10.3
				Cardiac or cardiovascular	7.7
				Bradycardia	2.6
				Takotsubo cardiomyopathy, cardiogenic shock, and pulseless electrical activity	2.6
				Cardiomegaly (544 g) and hypertension	2.6
				Viral-type symptoms	7.7
Flu-like symptoms, fatigue, chills, or myalgia	7.7				
Other	2.6				
Mesenteric panniculitis	2.6				

STUDY DETAILS																						
Study	Vaccine	Study Design	Participants	Summary of Key Findings																		
				Systemic AEs identified from non-serious reports after RIV4 vaccination: <table border="1"> <thead> <tr> <th colspan="2">Systemic AEs reported after RIV4</th> </tr> <tr> <th>Systemic AEs</th> <th>Proportion (%)</th> </tr> </thead> <tbody> <tr> <td>Pyrexia</td> <td>19.3</td> </tr> <tr> <td>Headache</td> <td>16.7</td> </tr> <tr> <td>Rash</td> <td>13.7</td> </tr> <tr> <td>Dizziness</td> <td>13.3</td> </tr> <tr> <td>Fatigue</td> <td>13</td> </tr> <tr> <td>Chills</td> <td>12</td> </tr> <tr> <td>Nausea</td> <td>12</td> </tr> </tbody> </table>	Systemic AEs reported after RIV4		Systemic AEs	Proportion (%)	Pyrexia	19.3	Headache	16.7	Rash	13.7	Dizziness	13.3	Fatigue	13	Chills	12	Nausea	12
Systemic AEs reported after RIV4																						
Systemic AEs	Proportion (%)																					
Pyrexia	19.3																					
Headache	16.7																					
Rash	13.7																					
Dizziness	13.3																					
Fatigue	13																					
Chills	12																					
Nausea	12																					

Abbreviations: AE: Adverse Event; CI: confidence interval; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; MedDRA: Medical Dictionary for Regulatory Activities; n/a: not applicable; RCT: randomized controlled trial; RIV: recombinant influenza vaccine; RIV4: quadrivalent recombinant influenza vaccine; SAE: Serious Adverse Event; SD: standard-dose; US: United States; VAERS: Vaccine Adverse Event Reporting System.

Figure 1. Odds of seroconversion on days 28-30 post-vaccination between RIV4 and other seasonal influenza vaccine recipients 50 years and older.

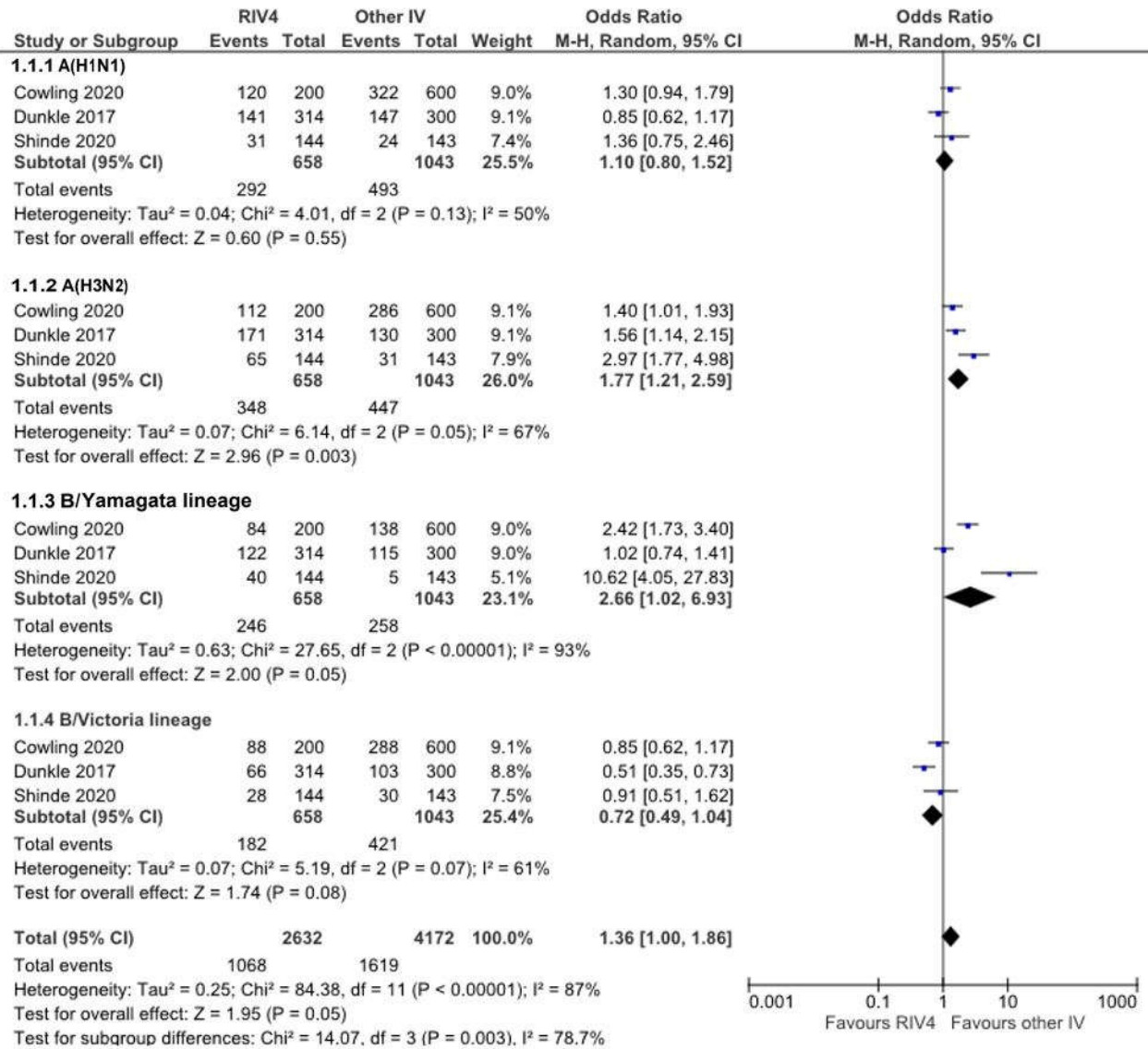
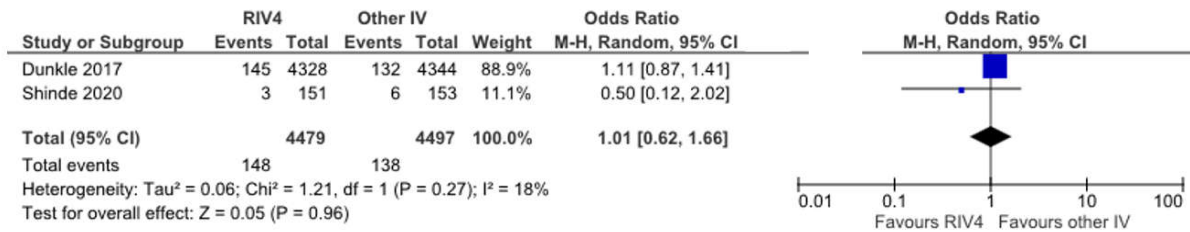


Figure 2. Odds of experiencing a SAE within 180 days of vaccination between RIV4 and other seasonal influenza vaccine recipients 50 years and older.



LIST OF ABBREVIATIONS

<i>Abbreviation</i>	<i>Term</i>
AE	Adverse event
CI	Confidence interval
EEFA	Ethics, equity, feasibility, and acceptability
FDA	Food and Drug Administration (United States)
GMT	Geometric mean titre
GMTR	Geometric mean titre ratio
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HA	Hemagglutinin
HI	Hemagglutination inhibition
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV3-Adj	Adjuvanted trivalent inactivated influenza vaccine
IIV3-cc	Cell-culture based trivalent inactivated influenza vaccine
IIV3-HD	High-dose trivalent inactivated influenza vaccine
IIV3-SD	Standard-dose trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IIV4-cc	Cell-culture based quadrivalent inactivated influenza vaccine
IIV4-SD	Standard-dose quadrivalent inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
IWG	Influenza Working Group
LCI	Laboratory-confirmed influenza
NA	Neuraminidase

NACI	National Advisory Committee on Immunization
OR	Odds ratio
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
RIV	Recombinant influenza vaccine
RIV3	Trivalent recombinant influenza vaccine
RIV4	Quadrivalent recombinant influenza vaccine
RR	Risk ratio
RT-PCR	Reverse transcription polymerase chain reaction
rVE	Relative vaccine efficacy
SAE	Serious Adverse Event
US	United States
VAERS	Vaccine Adverse Event Reporting System (US)

ACKNOWLEDGEMENTS

This supplemental statement was prepared by: A Gil, A Sinilaite, M Xi, R Harrison and J Papenburg on behalf of NACI.

NACI gratefully acknowledges the contribution of: P Doyon-Plourde, R Stirling, C Tremblay, M Tunis and K Young.

Influenza Working Group:

Members: J Papenburg (Chair), P De Wals, D Fell, I Gemmill, R Harrison, J Langley, A McGeer and D Moore.

Former members: N Dayneka, K Klein, D Kumar, J McElhaney and S Smith.

Liaison representatives: L Grohskopf (Centers for Disease Control and Prevention [CDC], United States).

Ex-officio representatives: C Bancej (Centre for Immunization and Respiratory Infectious Diseases [CIRID], PHAC), J Reiter (First Nations and Inuit Health Branch [FNIHB], Indigenous Services Canada [ISC]), B Warshawsky (Vice President's Office, Infectious Disease Prevention and Control Branch [IDPCB]), and J Xiong (Biologics and Genetic Therapies Directorate [BGTD], Health Canada [HC]).

NACI

Members: S Deeks (Chair), R Harrison (Vice-Chair), M Andrew, J Bettinger, N Brousseau, H Decaluwe, P De Wals, E Dubé, V Dubey, K Hildebrand, K Klein, J Papenburg, A Pham-Huy, B Sander, S Smith, and S Wilson.

Former NACI members: N Dayneka, C Rotstein, C Quach-Thanh.

Liaison representatives: L Bill / M Nowgesic (Canadian Indigenous Nurses Association), LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), L Dupuis (Canadian Nurses Association), D Fell (Canadian Association for Immunization Research and Evaluation), S Funnell (Indigenous Physicians Association of Canada), J Hu / N Ivers (College of Family Physicians of Canada), M Lavoie (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), A Ung (Canadian Pharmacists Association).

Ex-officio representatives: V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), C Lourenco / S Hardy (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), D MacDonald (COVID-19 Epidemiology and Surveillance, PHAC), S Ogunnaike-Cooke (CIRID, PHAC), K Robinson / D Danoff (Marketed Health Products Directorate, HC), G Poliquin (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

REFERENCES

1. Schanzer DL, McGeer A, Morris K. Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada. *Influenza Other Respir Viruses*. 2013 Sep;7(5):799–808.
2. Schanzer DL, Sevenhuysen C, Winchester B, Mersereau T. Estimating Influenza Deaths in Canada, 1992–2009. Nishiura H, editor. *PLoS ONE*. 2013 Nov 27;8(11):e80481.
3. Government of Canada [Internet]. FluWatch annual report: 2018-19 influenza season. 2020. Available from: <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/fluwatch/2018-2019/annual-report.html>
4. Government of Canada [Internet]. FluWatch annual report: 2019-2020 influenza season. 2021. Available from: <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/fluwatch/2019-2020/annual-report.html>
5. Nwosu A, Lee L, Schmidt K, Buckrell S, Sevenhuysen C, Bancej C. National Influenza Annual Report, Canada, 2020–2021, in the global context. *Can Commun Dis Rep*. 2021 Oct 14;47(10):405–13.
6. Groves HE, Papenburg J, Mehta K, Bettinger JA, Sadarangani M, Halperin SA, et al. The effect of the COVID-19 pandemic on influenza-related hospitalization, intensive care admission and mortality in children in Canada: A population-based study. *Lancet Reg Health - Am*. 2022 Mar;7:100132.
7. He D, Lui R, Wang L, Tse CK, Yang L, Stone L. Global Spatio-temporal Patterns of Influenza in the Post-pandemic Era. *Sci Rep*. 2015 Sep;5(1):11013.
8. Tang JW, Bialasiewicz S, Dwyer DE, Dilcher M, Tellier R, Taylor J, et al. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. *J Med Virol*. 2021 Jul;93(7):4099–101.
9. Sanofi Pasteur Limited [Internet]. Product monograph: Supemtek: Quadrivalent Recombinant Influenza Vaccine. 2021. Available from: https://pdf.hres.ca/dpd_pm/00059645.PDF
10. Sell TK, Gastfriend D, Watson M, Watson C, Richardson L, Cicero A, et al. Building the global vaccine manufacturing capacity needed to respond to pandemics. *Vaccine*. 2021 Mar;39(12):1667–9.
11. The Centers for Disease Control and Prevention (CDC) (US) [Internet]. Seasonal Influenza (Flu): Recombinant Flu Vaccines. Available from: https://www.cdc.gov/flu/prevent/qa_flublok-vaccine.htm
12. Barr IG, Donis RO, Katz JM, McCauley JW, Odagiri T, Trusheim H, et al. Cell culture-derived influenza vaccines in the severe 2017–2018 epidemic season: a step towards improved influenza vaccine effectiveness. *Npj Vaccines*. 2018 Dec;3(1):44.

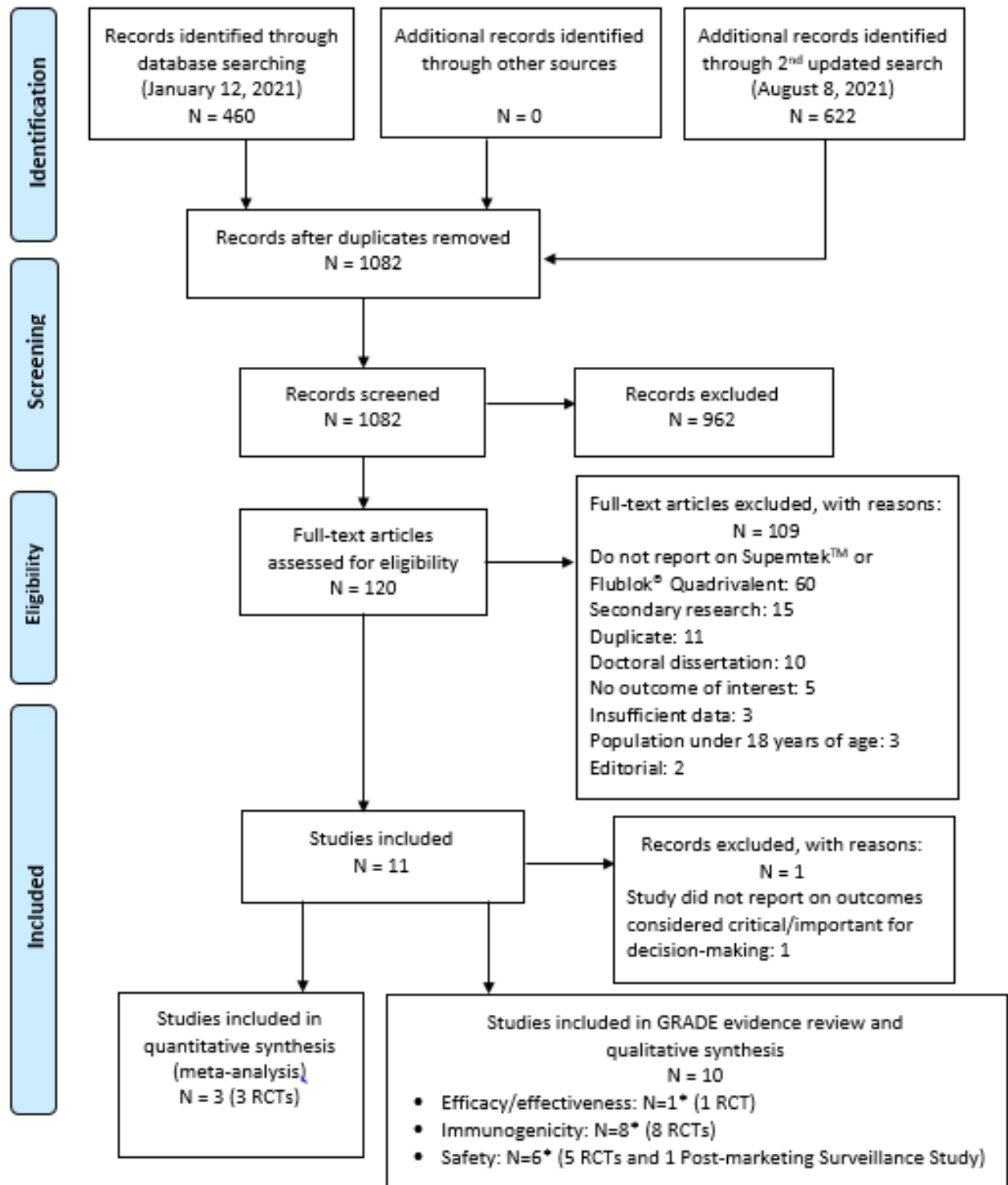
13. Government of Canada [Internet]. Canadian Immunization Guide: Part 4 - Active Vaccines. 2021. Available from: <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines.html>
14. Arunachalam AB, Post P, Rudin D. Unique features of a recombinant haemagglutinin influenza vaccine that influence vaccine performance. *Npj Vaccines*. 2021 Dec;6(1):144.
15. Centers for Disease Control and Prevention [Internet]. Archived CDC Vaccine Price List as of February 2, 2017. Available from: <https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/2017/2017-02-02.html>
16. Harding AT, Heaton NS. Efforts to Improve the Seasonal Influenza Vaccine. *Vaccines*. 2018 Mar 30;6(2):E19.
17. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. *N Engl J Med*. 2017 Jun 22;376(25):2427–36.
18. Cox MMJ, Hollister JR. FluBlok, a next generation influenza vaccine manufactured in insect cells. *Biologicals*. 2009 Jun;37(3):182–9.
19. Ismail SJ, Langley JM, Harris TM, Warshawsky BF, Desai S, FarhangMehr M. Canada's National Advisory Committee on Immunization (NACI): Evidence-based decision-making on vaccines and immunization. *Vaccine*. 2010 Apr;28:A58–63.
20. Government of Canada [Internet]. Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR. 2009. Available from: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php>
21. Ismail SJ, Hardy K, Tunis MC, Young K, Sicard N, Quach C. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. *Vaccine*. 2020 Aug;38(36):5861–76.
22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;44898.
23. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016 Oct 12;i4919.
24. The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews [Internet]. Checklist for Case Series. Available from: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Case_Series2017_0.pdf
25. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group [Internet]. GRADE Handbook. 2013. Available from: <https://gdt.gradeapro.org/app/handbook/handbook.html>
26. Hill RR. How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group [Internet]. Available from:

https://colorectal.cochrane.org/sites/colorectal.cochrane.org/files/public/uploads/how_to_grade.pdf

27. US Food and Drug Administration [Internet]. Guidance for industry: Clinical data needed to support the licensure of seasonal inactivated influenza vaccines. 2007. Available from: <https://www.fda.gov/media/73706/download>
28. Review Manager (RevMan). The Cochrane Collaboration; 2014.
29. Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, et al. Relative Effectiveness of Influenza Vaccines Among the United States Elderly, 2018–2019. *J Infect Dis*. 2020 Jun 29;222(2):278–87.
30. Wang W, Alvarado-Facundo E, Vassell R, Collins L, Colombo RE, Ganesan A, et al. Comparison of A(H3N2) Neutralizing Antibody Responses Elicited by 2018–2019 Season Quadrivalent Influenza Vaccines Derived from Eggs, Cells, and Recombinant Hemagglutinin. *Clin Infect Dis*. 2021 Dec 6;73(11):e4312–20.
31. Belongia EA, Levine MZ, Olaiya O, Gross FL, King JP, Flannery B, et al. Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A(H3N2) viruses in adults 65 to 74 years, 2017–2018. *Vaccine*. 2020 Mar;38(15):3121–8.
32. Cowling BJ, Perera RAPM, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, et al. Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. *Clin Infect Dis*. 2020 Oct 23;71(7):1704–14.
33. Shinde V, Cai R, Plested J, Cho I, Fiske J, Pham X, et al. Induction of Cross-Reactive Hemagglutination Inhibiting Antibody and Polyfunctional CD4+ T-Cell Responses by a Recombinant Matrix-M–Adjuvanted Hemagglutinin Nanoparticle Influenza Vaccine. *Clin Infect Dis*. 2021 Dec 6;73(11):e4278–87.
34. Dunkle LM, Izikson R, Patriarca PA, Goldenthal KL, Muse D, Cox MMJ. Randomized Comparison of Immunogenicity and Safety of Quadrivalent Recombinant Versus Inactivated Influenza Vaccine in Healthy Adults 18–49 Years of Age. *J Infect Dis*. 2017 Dec 5;216(10):1219–26.
35. Gouma S, Zost SJ, Parkhouse K, Branche A, Topham DJ, Cobey S, et al. Comparison of Human H3N2 Antibody Responses Elicited by Egg-Based, Cell-Based, and Recombinant Protein–Based Influenza Vaccines During the 2017–2018 Season. *Clin Infect Dis*. 2020 Sep 12;71(6):1447–53.
36. Dawood FS, Naleway AL, Flannery B, Levine MZ, Murthy K, Sambhara S, et al. Comparison of the Immunogenicity of Cell Culture–Based and Recombinant Quadrivalent Influenza Vaccines to Conventional Egg–Based Quadrivalent Influenza Vaccines Among Healthcare Personnel Aged 18–64 Years: A Randomized Open–Label Trial. *Clin Infect Dis*. 2021 Dec 6;73(11):1973–81.
37. European Medicines Agency (EMA) [Internet]. Assessment Report: Supemtek. 2021. Available from: https://www.ema.europa.eu/en/documents/assessment-report/supemtek-epar-public-assessment-report_en.pdf

38. Cowling BJ, Thompson MG, Ng TWY, Fang VJ, Perera RAPM, Leung NHL, et al. Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults. *J Infect Dis*. 2020 Sep 14;222(8):1383–91.
39. Woo EJ, Moro PL. Postmarketing safety surveillance of quadrivalent recombinant influenza vaccine: Reports to the vaccine adverse event reporting system. *Vaccine*. 2021 Mar;39(13):1812–7.
40. Treanor JJ, Sahly HE, King J, Graham I, Izikson R, Kohberger R, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: A randomized, placebo-controlled trial. *Vaccine*. 2011 Oct;29(44):7733–9.
41. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2020–21 Influenza Season. *MMWR Recomm Rep*. 2020 Aug 21;69(8):1–24.
42. Hsiao A, Hansen J, Nunley KV, Lewis N, Selmani A, Inamdar A, et al. Safety of recombinant quadrivalent influenza vaccine compared to inactivated influenza vaccine in Chinese adults: An observational study. *Vaccine*. 2022 Jan;S0264410X21016418.
43. Hansen J, Goddard K, Timbol J, Zhang L, Lewis N, Dunkle L, et al. Safety of Recombinant Influenza Vaccine Compared to Inactivated Influenza Vaccine in Adults: An Observational Study. *Open Forum Infect Dis*. 2020 Jun 1;7(6):ofaa179.
44. Renschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. *BMC Infect Dis*. 2015 Dec;15(1):429.

APPENDIX A: PRISMA FLOW DIAGRAM



*Note: some studies fit into more than one outcome category

APPENDIX B: CHARACTERISTICS OF INFLUENZA VACCINES AVAILABLE FOR USE IN CANADA, 2022–2023^a

Product name (manufacturer)	Vaccine Characteristic									
	Vaccine type	Route of administration	Authorized ages for use	Antigen content for each vaccine strain	Adjuvant	Formats available	Post-puncture shelf life for multi-dose vials	Thimerosal	Antibiotics (traces)	Production medium
Quadrivalent										
Flulaval® Tetra (GSK)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial	28 days	Yes (multi-dose vial only)	None	Egg (Avian)
Fluzone® Quadrivalent (Sanofi Pasteur)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single-dose pre-filled syringe without attached needle	Up to expiry date indicated on vial label	Yes (multi-dose vial only)	None	Egg (Avian)
Afluria® Tetra (Seqirus)	IIV4-SD (split virus)	IM	5 years and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single dose pre-filled syringe without attached needle	Up to expiry date indicated on vial label	Yes (multi-dose vial only)	Neomycin and polymyxin B	Egg (Avian)
Influvac® Tetra (BGP Pharma ULC, operating as Mylan, d.b.a. Viartis Canada)	IIV4-SD (subunit)	IM or deep subcutaneous injection	6 months and older	15 µg HA /0.5 mL dose	None	Single dose pre-filled syringe with or without attached needle	Not applicable	No	Gentamicin or neomycin and polymyxin B ^b	Egg (Avian)
Flucelvax® Quad (Seqirus)	IIV4-cc (subunit)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single dose pre-filled syringe without attached needle	28 days	Yes (multi-dose vial only)	None	Cell culture (Mammalian)
Fluzone® High-Dose Quadrivalent (Sanofi Pasteur)	IIV4-HD (split virus)	IM	65 years and older	60 µg HA /0.7 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Egg (Avian)
Supemtek™ (Sanofi Pasteur)	RIV4 (recombinant protein)	IM	18 years and older	45 µg HA /0.5 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Recombinant protein (Baculovirus Expression Vector System)

FluMist® Quadrivalent (AstraZeneca)	LAIV4 (live attenuated)	Intranasal	2–59 years	10 ^{6.5-7.5} FFU of live attenuated reassortants /0.2 mL dose (given as 0.1 mL in each nostril)	None	Single use pre-filled glass sprayer	Not applicable	No	Gentamicin	Egg (Avian)
Trivalent										
Fluad Pediatric® and Fluad® (Seqirus)	IIV3-Adj (subunit)	IM	Pediatric: 6–23 months Adult: 65 years and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	MF59	Single dose pre- filled syringe without a needle	Not applicable	No	Kanamycin and neomycin	Egg (Avian)

Abbreviations: FFU: fluorescent focus units; HA: hemagglutinin; IIV3-Adj: adjuvanted egg-based trivalent inactivated influenza vaccine; IIV4-cc: standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose egg-based quadrivalent inactivated influenza vaccine; IM: intramuscular; LAIV4: quadrivalent live attenuated influenza vaccine; NA: neuraminidase; RIV4: quadrivalent recombinant influenza vaccine.

^a Full details of the composition of each vaccine authorized for use in Canada, including other non-medicinal ingredients, and a brief description of its manufacturing process can be found in the product monograph.

^b Neomycin and polymyxin B are only used if gentamicin cannot be used. No trace amounts of neomycin or polymyxin B are present if gentamicin was used.