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INFLUENZA VACCINATION

FOR THE ELDERLY

AND ECONOMIC EVALUATION

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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DISCLOSURE

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EXECUTIVE SUMMARY

Background

Influenza infection is associated with considerable yearly morbidity and elderly population are among those at highest risk of serious outcomes. Annual influenza vaccination that is considered most-effective strategy to prevent influenza by the World Health Organization (WHO) is recommended for the elderly. Worldwide, these annual epidemics are estimated to result in about three to five million cases of severe illness, and about 290 000 to 650 000 deaths. In industrialised countries most deaths associated with influenza occurred among people age 65 or older. While a goal of reaching 75% vaccination coverage among older person by 2010 was set during 2003 World Health Assembly, only a few regions have reached this target, hence the target was extended to year 2015.

In tropical regions like Malaysia, influenza may occur throughout the year, with no clear seasonal trends, causing outbreaks more irregularly. Influenza A is usually detected more frequently than influenza B, although year-to-year variation may be considerable. The incidence of seasonal influenza remains unknown. However, there are issues with vaccinating the elderly for influenza, such as immunity conferred from vaccination is not lifelong and the presence of life threatening allergic reaction or severe allergy towards components of vaccine.

According to Drug Formulary, Ministry of Health (MOH), Influenza Vaccine (Inactivated) Injection is for prophylaxis of influenza for front liners (MOH staff and essential services personnel) and prophylaxis of influenza in high risk groups, particularly individuals who have chronic cardiovascular, pulmonary, metabolic or renal disease, or who are immunocompromised and elderly patients. Hence, this review was requested by the Head of Geriatric Unit in Hospital Queen Elizabeth to review the available evidence on influenza vaccination among the elderly and feasibility of implementing it in MOH.

Objective/aim

To assess the efficacy or effectiveness, safety, organizational and societal issues as well as cost-effectiveness of influenza vaccination in the elderly population.

Results and conclusions

A total of 301 records were identified through several databases and other sources. Five systematic review (SR) and meta-analysis (MA), five SR, one cohort, two cross-sectional studies, one case-control study and one cost-effectiveness study were included in this review.

Effectiveness

Influenza rate

There was good level of retrievable evidence to suggest that influenza vaccination was effective in reducing influenza rate in the elderly. The evidence showed vaccinated elderly experienced less influenza compared to placebo. The IVE ranged from 31% to 58% depending on the types of influenza viruses.

Influenza Like-Illness

There was good level of retrievable evidence to suggest that vaccinated elderly experienced less ILI compared with unvaccinated elderly with IVE ranged from 19% to 45% among older patients aged ≥65 years old. The influenza vaccination also prevented ILI in type 1 and type 2 diabetic patients with IVE of 13%.

Mortality

i. All-cause mortality

There was fair to good level of retrievable evidence to suggest that influenza vaccination reduced all-cause mortality with IVE of 38%-56% among diabetic patients.

ii. Influenza-related mortality

There was fair to good level of retrievable evidence to suggest vaccination reduce mortality following hospitalisation for pneumonia and influenza by 47% with IVE 25-62%. Study in US on seasonal-influenza, stated about 88.9% influenza-associated deaths averted among vaccinated group in the elderly while among French elderly population, showed that vaccination would avoid an influenza-attributable death with IVE of 35% compared to unvaccinated group.

Immune Response (Immunogenicity)

There was fair to good level of retrievable evidence to suggest better immune response (immunogenicity) for all types of vaccine which include non-adjuvanted vaccine, aluminium hydroxide-adjuvanted vaccine, and AS03A-adjuvanted vaccine.

Organisational issues

Guidelines

The WHO recommended that northern hemisphere (including Malaysia) influenza season should use both trivalent or quadrivalent vaccines that contain both influenza type A and influenza type B virus (B/Colorado/06/2017-like virus of the

B/Victoria/2/87-lineage) with a 75% vaccination coverage. In Malaysia, healthcare workers were included in annual immunization programme.

Implementation

One SR identified that among low intensity intervention, client reminder by letter or postcards showed significant positive effects to increase influenza vaccination rates for this elderly population (≥60 years old). While personalised phone calls (medium intensity intervention) and home visits, facilitators (high intensity intervention) showed significant positive effects that would increase community demand for vaccination, enhance access, and improve provider/system response.

Influenza Surveillance Programme in Malaysia

Both National Public Health Laboratory (NPHL) Sungai Buloh and the Institute of Medical Research (IMR) found that influenza A virus was the most dominantly isolated virus with 291 (59.03%) positive isolates followed by influenza B with 202 (40.97%) isolates. However, data were not stratified according to age groups.

Influenza-related hospitalisation

There was fair to good level of retrievable evidence to suggest that vaccination reduced influenza-related hospitalisation (also pneumonia) with IVE ranged from 18-49% depending on the types of influenza viruses. Vaccination also prevented all-cause hospitalisation in diabetic patients with IVE of 23% and reduced the first hospitalisation for ACS in elderly patients with CKD. Increased number of vaccination was associated with significant decreased risk of ACS hospitalisation.

The average hospital stays due to influenza for elderly (≥65 years old) was over eight days while the median length of stay for primary respiratory (influenza-related) and circulatory hospitalisations was five to six days.

Societal issues

One SR demonstrated that the ability of adults aged ≥65 years old to receive seasonal influenza vaccine was influenced by structural, intermediate, and healthcare-related social determinants which have an impact at the health system, provider and individual levels.

Safety

There was limited good level of retrievable evidence to suggest that the use of influenza vaccine was associated with non-significant adverse effects such as fever and nausea. The recent report regarding influenza-related death in South Korea was associated with the certain product brand for QIV.

Cost-effectiveness

SR on cost-effectiveness studies showing varying results ranging from being cost-effectiveness to not cost-effective in different population groups and countries. A cost-effectiveness study using societal perspective conducted in Singapore found the elderly plus some other age groups population to be the most cost-effective strategy.

Economic implication

Local economic evaluation cannot be conducted due to limitation of local data (epidemiological and costs data). Hence, the cost-effectiveness of Influenza vaccination among elderly population in Malaysia cannot be determined. Based on the financial implication analysis, the use of TIV (lowest cost) as an annual influenza vaccination is estimated to have an economic implication of approximately RM 5.447 million for a starting coverage rate of 10% (strategy 1). While in strategy 2, the lowest cost estimated for a coverage rate of 25% was RM 13.619 million per year. For strategy 3, the estimated lowest cost of TIV for elderly with diabetes mellitus with a prevalence of 41.5% a year was RM 22.61 million per year.

Methods

The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present, EBM Reviews - Cochrane Central Register of Controlled Trials - August 2019, EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to August 2019, EBM Reviews - Health Technology Assessment – 4th Quarter 2018 and EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2018. Searches were also run in EMBASE. PubMed and Google Scholar was used to search for additional web-based materials and information.

The references of retrieved articles were scrutinised for additional articles. No limits were applied. The last search was conducted on 23 January 2020.

INFLUENZA VACCINATION FOR THE ELDERLY

1. BACKGROUND

Influenza viruses is the cause of influenza (flu), a contagious respiratory illness which will lead to mild or severe illness and resulted in hospitalisation or death.[1] Influenza infection is associated with considerable yearly morbidity and the elderly population are among those at the highest risk of serious outcomes. Annual influenza vaccination among the elderly is considered as the most-effective strategy to prevent influenza by the World Health Organization (WHO).[1]

Influenza reduces the body's ability to fight other infections. Bacterial pneumonia, which is an infection of the lung, is the most common complication from influenza, especially in elderly people. Influenza can also lead to other complications for people who have heart, lung or other health conditions. These complications can sometimes be fatal. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 290 000 to 650 000 deaths. In industrialised countries, most deaths associated with influenza occur among people age 65 or older.[1] While a goal of reaching 75% vaccination coverage among older person by 2010 was set during 2003 World Health Assembly, only a few regions have reached this target, hence the target was extended to year 2015.[2]

In tropical regions like Malaysia, influenza may occur throughout the year, with no clear seasonal trends, causing outbreaks more irregularly.[4] Influenza A is usually detected more frequently than influenza B, although year-to-year variation may be considerable. The incidence of seasonal influenza remains unknown. Seroprevalence rates of 22.3% for seasonal H1N1 and 14.7% for seasonal H3N2 were reported in Kuala Lumpur, indicating that infection with influenza A is common in the general population.[3]

Most European countries recommended vaccinating at-risk group which included older population (more than 60 years old).[4] Older people was affected by flu more severely compared to younger people, as they accounted for 10 to 30 times more hospitalisation than younger patients with an attack rate estimated at five to 10% annually.[4,5] However, there are issues with vaccinating the elderly for influenza, such as immunity conferred from vaccination is not lifelong and the presence of life threatening allergic reaction or severe allergy towards components of the vaccine.[1]

According to the Drug Formulary, Ministry of Health (MOH), Malaysia, Influenza Vaccine (Inactivated) Injection is indicated for prophylaxis of influenza for front liners (MOH staff and essential services personnel) and

prophylaxis of influenza in high risk groups, particularly individuals who have chronic cardiovascular, pulmonary, metabolic or renal disease, or who are immunocompromised and elderly patients. Hence, this review was requested by the Head of Geriatric Unit in Queen Elizabeth Hospital to review the available evidence on influenza vaccination among the elderly and feasibility of implementing it in MOH.

2. OBJECTIVE / AIM

To assess the efficacy or effectiveness, safety, organizational and societal issues as well as cost-effectiveness of influenza vaccination in the elderly population.

3. TECHNICAL FEATURES

3.1 Types of Influenza

3.1.1 Seasonal Influenza

Seasonal influenza viruses circulate and disease tends to occur seasonally in the winter months, spreading from person-to-person through sneezing, coughing, or touching contaminated surfaces. It can cause mild to severe illness and even death, particularly in some high-risk individuals including pregnant women, the very young and very old, immune-compromised people, and people with chronic underlying medical conditions. It evolve continuously, which means that people can get infected multiple times throughout their lives.[6]

Seasonal influenza (or “flu”) is most often caused by type A or B influenza viruses. Currently, influenza A (H1N1) and (H3N2) are the circulating seasonal influenza A virus subtypes. This seasonal A (H1N1) virus is the same virus that caused the 2009 influenza pandemic, as it is now circulating seasonally. The other two type B influenza viruses are also circulating as seasonal influenza viruses. Another type C influenza causes milder infections and is associated with sporadic cases and minor localized outbreaks. As influenza C poses much less of a disease burden than influenza A and B, only the latter two are included in seasonal influenza vaccines.[1,2,6]

In terms of transmission, seasonal influenza spreads easily, with rapid transmission in crowded areas including nursing homes. When an infected person coughs or sneezes, droplets containing viruses (infectious droplets) are dispersed into the air and can spread up to one meter, and infect persons in close proximity who breathe these droplets in. The virus can also be spread by hands contaminated with influenza viruses. In temperate climates, seasonal epidemics occur mainly during winter, while in tropical

regions, influenza may occur throughout the year, causing outbreaks more irregularly.[2]

3.1.2 Pandemic Influenza

An influenza virus which was not previously circulating among humans and to which most people don't have immunity emerges and transmits among humans is known as pandemic influenza. It may emerge, circulate and cause large outbreaks outside of the normal influenza season.[1] Some pandemics may result in large numbers of severe infections while others will result in large numbers of milder infections, but the reasons behind these differences are not completely understood.[1]

A strain of influenza A (H1N1) virus which had not ever been seen before, emerged, spread across the world and caused the 2009 H1N1 pandemic. It has been widely circulating across the globe since 2009, and is now established in human populations as a seasonal influenza virus, as described above. Currently there is no longer a pandemic virus circulating in the world.[1]

3.1.3 Zoonotic or Variant Influenza

Influenza viruses that are routinely circulating in animals, such as avian influenza virus subtypes A(H5N1) and A(H9N2) and swine influenza virus subtypes A (H1N1) and (H3N2) can also infected humans.[1] Usually these human infections of zoonotic influenza are acquired through direct contact with infected animals or contaminated environments, and do not spread very far among humans. If such a virus acquired the capacity to spread easily among people either through adaptation or acquisition of certain genes from human viruses, it could start an epidemic or a pandemic.[1]

When viruses of subtype A (H3N2) circulating in swine, began to infect people in the USA in 2011, they were labelled “variant” (with a “v” placed after the name of the virus) in order to distinguish them from human viruses of the same subtype.[1] The variant terminology is also used for other non-seasonal influenza viruses of a subtype shared with human seasonal influenza viruses, particularly viruses of the H1 and H3 subtypes circulating in swine, when these viruses are detected in humans.[1] Other animal viruses, e.g. avian influenza A(H5N1), A(H7N7), A(H7N9), and A(H9N2), infecting people are simply called “avian influenza” or “zoonotic influenza” viruses.[1]

3.2 Population that are recommended to be vaccinated

According to World Health Organization (WHO), injected inactivated influenza vaccines are the most commonly used intervention to prevent

influenza.[1] The WHO recommends to annually vaccinate the high-risk groups. [6] They are:

- Older people aged more than 65 years
- Children aged between 6 months to 5 years
- Pregnant women at any stage of pregnancy
- Individuals with chronic medical conditions
- Health-care workers

In overseas, the vaccine was given to the seniors before the influenza season starts, usually in October. Body will takes about two weeks' time to build the immunity for best protection and this immunity lasts through the influenza season.[1,4]

3.3 Types of Influenza Vaccine

3.3.1 Trivalent Influenza Vaccine (TIV)

A synthetic vaccine consisting of three inactivated influenza viruses (IIV) or live attenuated influenza vaccine (LAIV), two different influenza type A strains (H1N1 and H3N2) and one influenza type B strain. This type of vaccine includes the standard dose, adjuvanted dose and high dose TIV.[2,7]

a. Adjuvanted Vaccine

A trivalent flu shot made with adjuvant or also known as adjuvanted vaccination (FLUAD®). FLUAD is designed specifically for people 65 years and older. It is manufactured using an egg-based process (like most flu vaccines), and is formulated with the adjuvant MF59. An adjuvant is an ingredient added to a vaccine that helps create a stronger immune response to vaccination approved for people 65 years and older, who often have a lower protective immune response after flu vaccination compared to younger, healthier people. The MF59 is an oil-in-water emulsion of squalene oil. Squalene, a naturally occurring substance found in humans, animals and plants, is highly purified for the vaccine manufacturing process. An adjuvant is an ingredient of a vaccine that helps promote a better immune response. Adjuvants also can reduce the amount of virus needed for production of a vaccine, which can allow for greater supplies of vaccine to be manufactured.[2,7]

b. High Dose Influenza Vaccine

Fluzone High-Dose is three-component (trivalent) inactivated flu vaccine, manufactured by Sanofi Pasteur Inc. Fluzone High-Dose is licensed specifically for people 65 years and older. Fluzone High-Dose contains four times the antigen (the part of the vaccine that helps your body build up protection against flu viruses) of standard-dose inactivated influenza

vaccines. The higher dose of antigen in the vaccine is intended to give older people a better immune response, and therefore, better protection against flu.[2,7]

3.3.2 Quadrivalent Influenza Vaccine (QIV)

A synthetic vaccine consisting of egg-based or cell-culture based influenza vaccine of inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), egg-based live attenuated influenza vaccine (LAIV). The quadrivalent flu vaccine is designed to protect against four different flu viruses; two influenza A viruses and two influenza B viruses.[2,7]

Examples of trivalent and quadrivalent vaccines that are available in Malaysia are Fluarix, Fluarix Tetra, FluQuadri, Inflexal V, Influvac, Influvac Tetra, SKYCellflu (quadrivalent), Synflorix, Vaxigrip and Vaxigrip Tetra. The dosage for adult is 0.5 mL (1 dose per season) via intramuscular (IM) or deep subcutaneous (SC) injection.

Figure 1: Examples of Trivalent Influenza Vaccine
Sources: Nationwide Medical Surgical, VaxServe, vaccine Ingredients

Figure 2: Examples of Quadrivalent Influenza Vaccine
Sources: Center for Infectious Disease Research and Policy, McKessen

4. METHODS

4.1. Searching

The following electronic databases were searched through the Ovid interface:

- Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials – August 2019
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to August 2019
- EBM Reviews - Health Technology Assessment – 4th Quarter 2016
- EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2016.
- EMBASE

PubMed and Google Scholar were used to search for additional literatures from the references of the retrieved articles. No limits were applied. The last search was conducted on 5th September 2019. Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection. The inclusion and exclusion criteria were:

Inclusion criteria:

Population	Elderly population, ≥ 60 years old
Interventions	Trivalent Influenza Vaccine (TIV): adjuvanted vaccine, standard dose or high dose, Quadrivalent Influenza Vaccine (QIV)
Comparators	No vaccination or placebo
Outcomes	a. Efficacy/ effectiveness: Influenza rate, Influenza-like Illness (ILI) rate, Mortality (all-cause and influenza-related mortality) b. Safety c. Organizational and Societal issue d. Cost-effectiveness
Study design	Systematic review (SR) and meta-analysis (MA), SR, Randomised Controlled Trials (RCTs), cohort and cross-sectional study

Exclusion criteria:

i. Animal / laboratory / case reports / case series
ii. Narrative review
iii. Non-English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP)[8] and were graded according to US/Canadian preventive services task force (Appendix 2). Data were extracted and summarised in evidence table as in Appendix 3.

5. RESULTS AND DISCUSSION

A total of 301 records were identified through the databases mentioned above and nine records were identified from other sources (references of retrieved articles). After removal of 105 duplicates, 205 records were screened and 130 records were excluded. Of these, 75 relevant abstracts were retrieved in full text. After applying inclusion and exclusion criteria, 60 articles were excluded with reasons (Figure 3).

There were 15 studies included in this review: five SR and MA (all for effectiveness), five SR (three for organisational and societal issues, two for economic evaluation), one cohort (effectiveness), two cross-sectional studies (effectiveness), one case-control study (effectiveness) and one cost-effectiveness study. The studies were conducted in China, Australia, USA, Europe countries, Asia, Latin and Middle-east. Figure 3 shows the number of records identified and selected for inclusion.

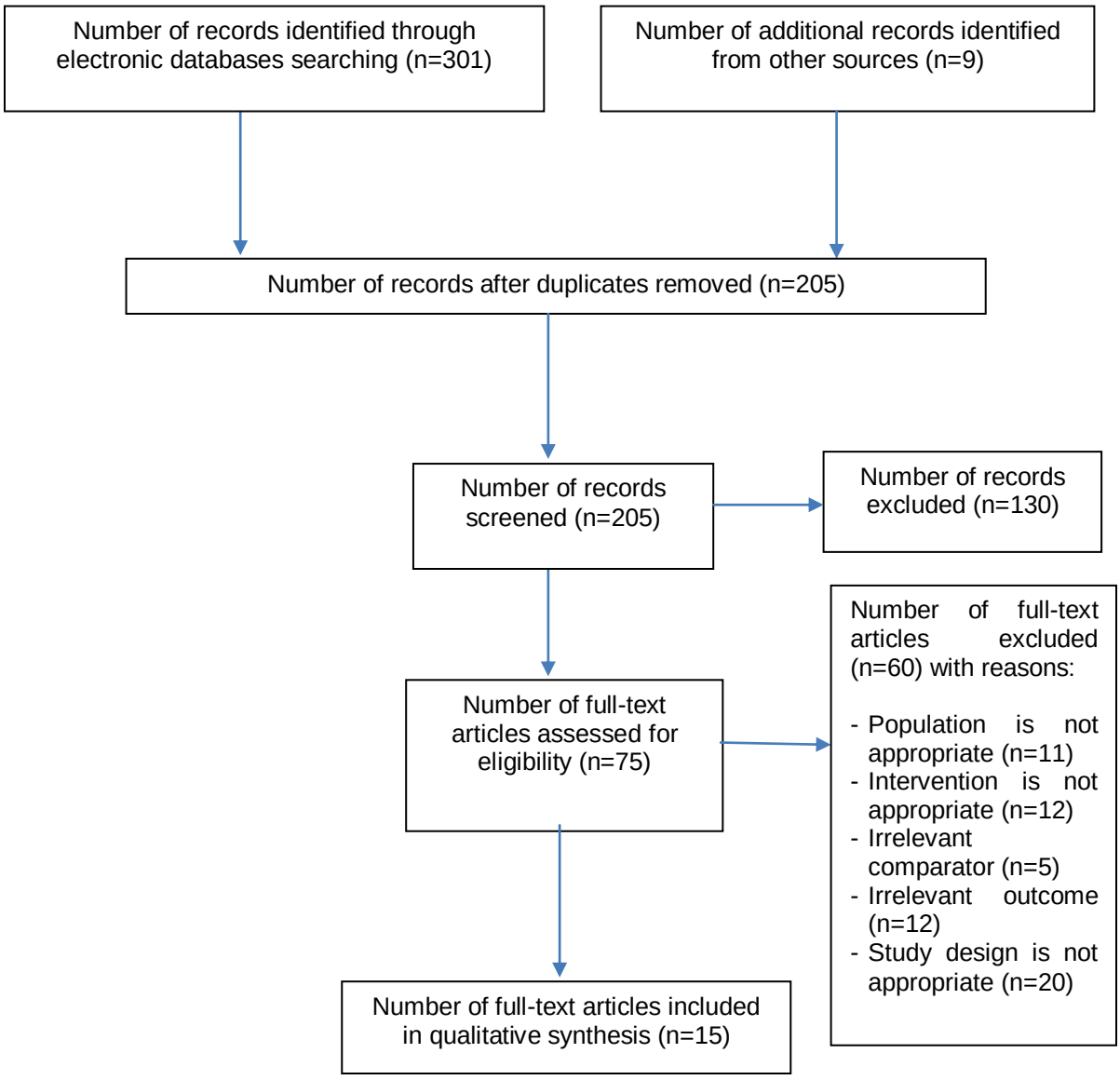

Figure 3. Flow chart of study selection

Table 1. Description of the included studies: types, intervention and comparison, duration of follow-up and outcome measures

Study	Types of vaccination (number of patients)	Intervention & Comparison (number of devices/patients)	Duration of follow-up	Outcome measures
Systematic Review (SR) and Meta-analysis (MA) of Randomised Controlled Trials, Case-control and Observational studies				
Demicheli et al. (2018)[9]	Any vaccines (n=over 5000 over 65 years old)	Vaccinated (n=NA) Placebo (n=NA)	NA	• Influenza-like illness • Influenza-related pneumonia and hospitalisation • Safety
Rondy et al. (2017)[10]	Any vaccines (n=NA over 65 years old)	Vaccinated (n=NA) Placebo (n=NA)	NA	• Influenza vaccination effectiveness
Remschmidt et al. (2015)[11]	Any vaccines (n=170,924, above 65 years old)	Vaccinated (n=NA) Placebo/unvaccinated (n=NA)	NA	• All-cause mortality • All-cause hospitalisation • Influenza or pneumonia • Influenza-like illness
Yin et al. (2011)[15]	Vaccine Type A (n=170,924, above 60 years old)	Vaccinated (n=NA) Placebo/unvaccinated (n=NA)	NA	• Immune response • Safety
Vu et al. (2002)[12]	Inactivated influenza vaccine (n=80,000 above 65 years old in living community)	Vaccinated (n=NA) Placebo/unvaccinated (n=NA)	NA	• Influenza-like illness • Hospitalised-pneumonia and influenza • Hospitalised-mortality pneumonia and influenza • All-cause mortality

Table 1. Continued

Study	Types of vaccination (number of patients)	Intervention & Comparison (number of devices/patients)	Duration of follow-up	Outcome measures
Observational studies (Cohort, cross-sectional, case-control)				
Chen et al. (2016)[22]	Any vaccines (n=4406 over 55 years old with Chronic Kidney Disease)	Vaccinated (n=2206) Unvaccinated (n=2200)	1997-2008	• Hospitalisation for acute coronary syndrome (ACS)
Foppa et al. (2015)[13]	Any vaccines (n=40,127 over 65 years old from US National Respiratory and Enteric Virus Surveillance System)	Vaccinated (n=NA) Unvaccinated (n=NA)	2005-2014	• Death averted
Bonmarin et al. (2015)[14]	Any vaccines (n=85,411 above 65 years old France population)	Vaccinated (n=NA) Unvaccinated (n=NA)	NA	• All-cause deaths • Influenza-attributable deaths
Dominguez et al. (2017)[21]	Vaccine Type A (n=170,924, above 65 years old hospitalised in Spain)	Vaccinated (n=359) Unvaccinated (n=1053)	2013-2015	• Hospitalisation
Organisational and Societal studies (SR)				
Thomas et al. (2018)[19]	Any vaccines (n=1,055,337 above 60 years old in living community)	Vaccinated (n=NA) Unvaccinated (n=NA)	NA	• Methods to increase uptake of vaccines
Nagata et al. (2013)[24]	Any vaccines (n=58 studies above 65 years old in living community)	Vaccinated (n=NA) Unvaccinated (n=NA)	NA	• Barriers and Social determinants
Thompson et al. (2004)[23]	Any vaccines (n=270,000 US inpatient records)	Vaccinated (n=NA) Unvaccinated (n=NA)	NA	• Barriers and Social determinants

Table 1. Continued

Study	Types of vaccination (number of patients)	Intervention & Comparison (number of devices/patients)	Duration of follow-up	Outcome measures
Economic evaluation (SR)				
D'Angiolella et al. (2018)[27]	TIV and QIV (n=30 studies)	Vaccinated (n=NA) Unvaccinated (n=NA)	Annual and biannual	• Cost effectiveness analysis • Cosy-benefit analysis
Shields et al. (2017)[28]	Any vaccines (n=NA over 65 years old in EU)	Vaccinated (n=NA) Unvaccinated/antiviral (n=NA)	NA	• Cost effectiveness analysis
Yue et al. (2019)[29]	Any vaccines (n=10,000 over 65 years old in Singapore, Taipei, Tokyo)	Vaccinated (n=NA) Placebo (n=NA)	Annual and biannual	• Cost effectiveness analysis

5.1. QUALITY ASSESSMENT OF THE LITERATURES

Quality assessment of the studies

The tool used to assess the risk of bias or quality assessment for the included articles was the Critical Appraisal Skills Programme (CASP) checklist.[8] This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN (unclear risk of bias)
-	Indicates NO (high risk of bias)

Assessment for Systematic Review (SR) Studies Using Critical Appraisal Skills Programme (CASP) Checklist

The risk of bias or quality assessment for Systematic Review studies was assessed using CASP checklist. Five articles were included in this assessment. The risk of bias or quality assessment is shown in Figure 4. Vu et al. did not conduct the quality assessment of the included studies, thus was judged as 'No' in the parameter. On the other hand, Rondy et al. did not explain whether they did the quality assessment thus was judged as 'Unknown'. Three out of five articles were of good quality as all of the criteria assessed were judged as 'Yes'. The other two were of moderate quality.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Vu T et al. 2002[12]	+	+	-	+
Yin JK et al. 2011[15]	+	+	+	+
Remschmidt C et al. 2015[11]	+	+	+	+
Rondy M et al. 2017[10]	+	+	?	+
Demicheli V et al. 2018[9]	+	+	+	+

Figure 4. Quality assessment for Systematic Review study

Assessment for Cohort Study Using Critical Appraisal Skills Programme (CASP) Checklist

Figure 5 shows the risk of bias of one study based on the CASP checklist. The study was at low risk of bias for all six domains assessed.

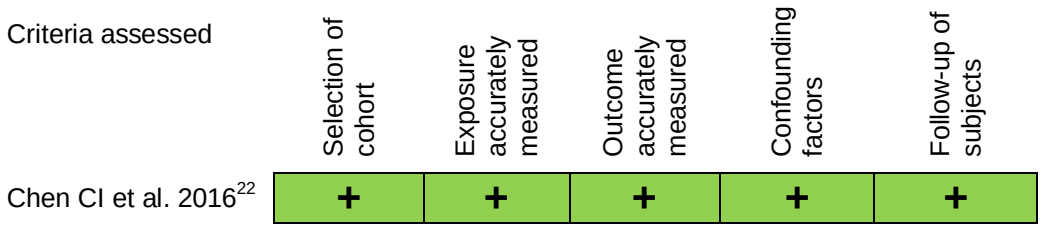

Figure 5: Quality assessment for Cohort study

Assessment for Case-control Study Using Critical Appraisal Skills Programme (CASP) Checklist

Figure 6 shows the risk of bias of one study based on the CASP checklist. The study was at low risk of bias for all six domains assessed

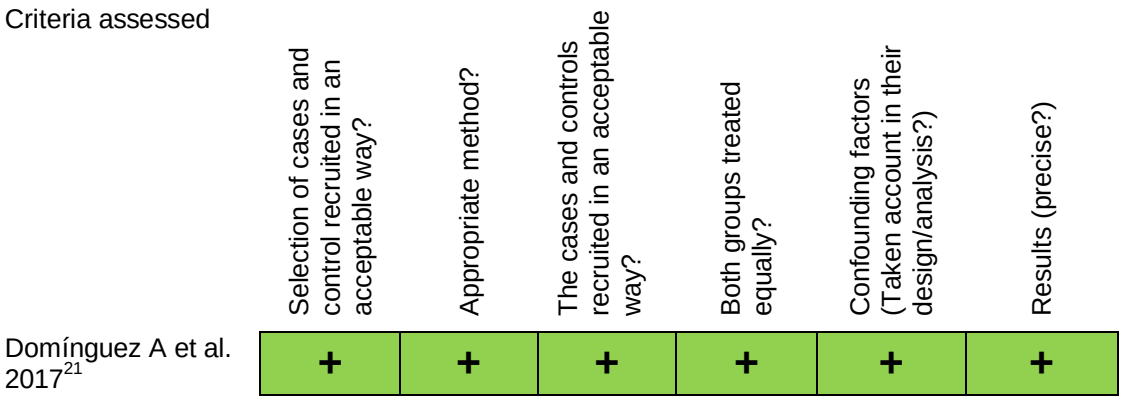

Figure 6: Quality assessment for Case-control study

5.2 EFFICACY / EFFECTIVENESS

There were nine studies retrieved on the effectiveness or safety of influenza vaccination for the elderly.[9-15,21-22] Three studies specifically reported on organisational and societal issues.[21,23-24] The outcome measures include influenza rate, influenza like-illness (ILI) incident, influenza-related mortality, influenza-related hospitalisation and immune response (immunogenicity).

5.2.1 INFLUENZA RATE

Demicheli et al. (2018) conducted a SR and MA to assess the effects (efficacy, effectiveness and safety) of vaccines against influenza in the elderly aged ≥65 years old. From eight included RCTs with over 5000 participants, they found the group that has been vaccinated experienced less influenza over a single season compared with placebo, from 6% to 2.4%, [risk ratio (RR) 0.42, 95% confidence interval (CI): 0.27, 0.66, influenza vaccination effectiveness/vaccine efficacy (IVE): 58%].[9, level I] Based on the data given in this article, it indicates that to prevent one person experiencing influenza, 30 people need to be vaccinated.

Another SR and MA conducted by Rondy et al. (2017) included 30 test-negative design case-control studies to report on IVE against laboratory-confirmed hospitalised influenza among adults. For adults aged ≥65 years old, the pooled IVE estimate against any type of influenza was statistically lower at 37% (95% CI: 30, 44), summary IVE for seasonal vaccine effectiveness against influenza A (H1N1)pdm09 viruses was 54% (95%CI: 26,82), summary IVE for seasonal vaccine effectiveness against influenza A(H3N2) viruses and B viruses were 33% (95% CI: 21; 45) and 31% (95% CI: 11, 51), respectively. The authors observed lower IVE among elderly participants (≥65 years old) compared to adults aged 18–64 years. However, the authors concluded that despite the lower effectiveness of influenza vaccines compared to other vaccines of the expanded programmes on immunization, seasonal vaccination remains the best and safest public health measure to reduce morbidity and mortality due to influenza, thus improving communication about IVE against severe influenza could increase influenza vaccine uptake and sustain investments in the vaccines.[10, level I]

5.2.2 INFLUENZA LIKE-ILLNESS (ILI)

Demicheli et al. reported that the group that was vaccinated experienced less ILI compared with the unvaccinated group over the course of a single influenza season (3.5% versus 6%; RR: 0.59, 95% CI: 0.47 to 0.73, IVE: 41%).[9, level I] Based on the data given in this article, it indicate that to prevent one person having an ILI, 42 people need to be vaccinated.

Remschmidt et al. (2015) conducted a SR and MA which included six cohort studies and five case-control studies with a total of 170,924 type 1 and type 2 diabetes participants to evaluate influenza IVE/effectiveness and safety in diabetic patients of all ages. They reported for elderly (aged ≥ 65 years old), the influenza vaccination prevented the ILI with IVE of 13% (adjusted odds ratio (OR): 0.87; 95% CI: 0.84, 0.90).[11, level I]

Another SR and MA was conducted by Vu et al. in 2002, included RCT, clinical trials, cohort and case-control studies to estimate the effectiveness of inactivated influenza vaccine in persons aged ≥ 65 years old living in the community. They found that influenza vaccine was effective in reducing ILI by 35% (95% CI: 19, 47), IVE ranged 19-45%. When there was a good match between influenza strains in the vaccine and those in circulation, vaccination would prevent approximately one in five cases of ILI.[12, level I]

5.2.3 MORTALITY

a. All-cause mortality

In the study by Demicheli et al., there were six deaths from each group during follow-up that was conducted over an influenza season (RR 1.02, 95% CI 0.11 to 9.72). [9, level I]

Based on study by Remschmidt et al., from the cohort studies among diabetic patients, the pooled analysis of adjusted point estimates showed protective effects of influenza vaccination against all-cause mortality with adjusted OR 0.62 (95% CI: 0.57, 0.68; IVE of 38%). The pooled analysis of case-control studies found that influenza vaccination prevented all-cause mortality with adjusted OR 0.44 (95% CI: 0.36, 0.53; IVE of 56%).[11, level I]

b. Influenza-related mortality

Demicheli et al. reported that there were three deaths from 522 participants (0.57%) in the vaccination group and one death from 177 participants (0.57%) in the placebo group. [9, level I]

Vaccination has been shown to reduce mortality following hospitalisation for pneumonia and influenza by 47% (95% CI: 25, 62; IVE 25-62%) and reduce the mortality from all causes by 50% (95% CI: 45, 56; IVE 45-56%) in study by Vu et al. 2002. When there was a good match between influenza strains in the vaccine and those in circulation, vaccination would prevent approximately one in four deaths following hospitalisation. [12, level I]

A retrospective cross-sectional study by Foppa et al. (2015) quantitatively estimate the benefit of United State annual vaccination programmes on influenza-associated mortality for the nine influenza seasons from 2005/06

through 2013/14. A total number of 40,127 participants were stratified into four age groups (group 1: 4 years, group 2: 5 to 19 years, group 3: 20 to 64 years and group 4: ≥65 years old). They found that of all studied seasons the most deaths were averted by influenza vaccination during the 2012/13 season (9398; 95% CI 2,386 to 19,897) and the fewest during the 2009/10 pandemic (222; 95% CI: 79, 347). Of all influenza-associated deaths averted, 88.9% (95% CI: 83, 92.5) were in group four, elderly ≥65 years old (35,673 patients).[13, level II-3]

Another retrospective cross-sectional study by Bonmarin et al. 2015 with a total of 85,411 participants involved was also to estimate the annual number of deaths avoided by vaccination among French people aged ≥65 years old from 2000 to 2009. The free-vaccination vouchers were given to all elderly population and the data of influenza vaccine coverage came from the Social Security Scheme database. They reported that, the average number of influenza-attributable deaths avoided by vaccination during the epidemic period was lower with a mean of 2485 (95% CI: 369, 4591) (range from 1809 to 3016 according to the season), compared to the unvaccinated with a mean of 11,510 (95% CI: 9394, 13 616). The calculated vaccine effectiveness to avoid an influenza-attributable death was 35% (95% CI: 6, 55).[14, level II-3]

By referring to background paper on Influenza Vaccines and Immunization SAGE Working Group, they found limited data suggested that influenza associated mortality among the elderly in low and middle income countries may be higher than in high income countries for person aged ≥ 65 years. Inactivated vaccines have been shown to reduce the risk of morbidity and mortality in the elderly, although effectiveness decreases with increasing age and in those with underlying medical conditions.[5]

5.2.4 IMMUNE RESPONSE (IMMUNOGENICITY)

Another SR and MA by Yin et al. conducted in 2011 included 728 cases and 1,826 matched controls to assess the effectiveness of influenza vaccination in preventing hospitalisation in individuals aged >60 years old in Spain.[15, level II-1] Based on the evidence of a strong relationship between haemagglutination inhibition (HI) titre and clinical effectiveness against influenza, the outcome measure was on the HI titre of the participants.[15, level II-1]

For the elderly aged >60 years old, the pre-injection seroprotection proportion among 2778 participants was estimated at 9.6% (95% CI: 4.3, 20.1) from 2778 participants. The first dose seroresponse among 2692 participants were 87.3% (95% CI: 82.3, 91.0) for non-adjuvanted vaccine, 68.1% (95% CI: 57.6, 77) for aluminium hydroxide-adjuvanted vaccine and 87.4% (95% CI: 80.1, 92.3) for AS03A-adjuvanted. However, after the second dose, all types of vaccine reported better immune responses; 91.2% (95% CI: 79.7, 96.5) for

non-adjuvanted, 91.5%, (95% CI: 85.5, 95.1) for aluminium hydroxide-adjuvanted and 97.0% (95% CI: 88.8, 99.3) for AS03A-adjuvanted. [15, level II-1]

5.3 ORGANISATIONAL ISSUES

5.3.1 Guidelines/ Recommendations

The World Health Organisation (WHO) recommended that the egg based quadrivalent vaccines for use in 2019-2020 for the northern hemisphere (including Malaysia) influenza season should contain the following:[16-18]

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A/Kansas/14/2017 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

It is recommended that the influenza B virus component of trivalent vaccines for use in the 2019-2020 northern hemisphere influenza season be a B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage.[16-18]

Vaccination Coverage Rate

The WHO's goal in 2010 and the European Council (2009) recommendation was to reach 75% vaccination coverage in older age groups by 2015.[16] However, there is still long way to achieve the target. One study conducted a survey on seasonal influenza vaccination programmes among European Region in 2018 reported that the high-income countries distributed considerably higher number of vaccines per capita (median; 139.2 per 1000 population) compared to lower-middle-income countries (median; 6.1 per 1000 population) and only one country (The Netherlands) reached 75% coverage in older persons (2014/2015), while 15 countries reported declining vaccination uptake.[18]

For population with Chronic Medical Conditions

The ECDC and WHO have recommended vaccination for those ≥65 years old. For those <65 years old, where several regions recommend vaccination for those ≥50 years old or ≥60 years old, they will look at the people with comorbidities. Recently, they are more countries recommending vaccination for those with morbid obesity, and chronic neurological and hepatic diseases.[16] Several chronic medical conditions have been highlighted in ECDC report (Table 8).

Table 8. Chronic Medical Conditions that are recommended to get vaccination[16]

Diseases (based on ECDC recommendation)
Respiratory (pulmonary) diseases (chronic obstructive pulmonary disease, cystic fibrosis, asthma)
Cardiovascular diseases (congenital heart disease, congestive heart failure and coronary artery disease, except Hypertension)
Renal diseases
Immunosuppression
Metabolic disorders
Haematological disorders
Hepatic diseases
HIV/AIDS
Chronic neurologic diseases (disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Morbid obesity (body mass index of 40kg/m² or more)

In Formulari Ubat KKM (FUKKM) page, other than front liners staff and essential services personnel, inactivated influenza vaccine was indicated to be given as prophylaxis in high risk groups particularly individuals who have chronic cardiovascular, pulmonary, metabolic or renal disease, immunocompromised and elderly patients.[19]

5.3.2 Implementation

One SR by Thomas RE et al. 2018 was conducted to assess access, provider, system, and societal interventions to increase the uptake of influenza vaccination in people aged ≥60 years old in the community in high-income countries (i.e. USA, Canada, Australia, UK, Spain, Denmark, Germany, Hong Kong, Israel, New Zealand, Puerto Rico and Switzerland).[20, level I]

The study included 61 RCTs with more than 1 million participants which were divided into three sub-groups of outcomes. The first outcome showed that there was an increased in community demand through the interventions of client reminders or recalls by letter plus leaflet or postcard compared to reminder alone (OR: 1.11). Other successful interventions were patient outreach by retired teachers (OR: 3.33), invitations by clinic receptionists (OR: 2.72), nurses or pharmacists educate patients and nurses vaccinating patients (OR: 152.95), medical students counselling patients (OR: 1.62) and multiple recall questionnaires (OR: 1.13). [20, level I]

The second outcome was improving vaccination access. The study showed that it was effective through interventions such as home visits (OR: 1.30),

client group clinic visits (OR: 2.72) and free vaccine offers compared with payment by patient (OR: 2.36). [20, level I]

The last outcome was improving provision by providers or the healthcare system. The study showed that effective interventions include physician payment (OR: 2.22), physician reminders to vaccinate patients (OR: 2.47), clinic posters presenting vaccination rates and encouraging competition between doctors (OR: 2.03) and chart reviews plus benchmarking to rates of the top 10% of physicians (OR: 3.43). [20, level I]

Interventions that were not effective included posters plus postcards versus posters alone, educational reminders to physicians compared with mailed educational materials, educational outreach plus feedback to teams versus written feedback and increasing staff vaccination rates. [20, level I]

5.3.3 Influenza Surveillance Programme in Malaysia

In the last few years, Disease Surveillance Sector has developed the Malaysian Influenza Surveillance Protocol (MISP) document. The development of this document was guided by the recent publication of the WHO Global Epidemiological Surveillance Standards for Influenza in 2013, which included revised global standards for a minimal basic respiratory disease surveillance system for the monitoring of influenza. The implementation of this improvised influenza surveillance in Malaysia began on Epid Week 1/2016.[21]

According to the Disease Control Division (DCD) report, in Malaysia, influenza did not show any seasonal variations whereby it occurred throughout the year. Based on their surveillance activity, both the National Public Health Laboratory (NPHL) Sungai Buloh and the Institute of Medical Research (IMR) received a total of 4,460 influenza samples for testing in 2018, out of which 493 (11.05%) samples tested positive for influenza. Influenza A virus was the most dominantly isolated virus with 291 (59.03%) positive isolates followed by influenza B with 202 (40.97%) isolates. However, data were not stratified according to age groups.[21]

Based on the latest report by DCD, Malaysia in 2019, for the 45th week of outpatient ILI surveillance data, the elderly (≥60 years old) accounted for 9.56% from the total outpatient visits for ILI.[21]

5.3.4 INFLUENZA-RELATED HOSPITALISATION

a. All-cause hospitalisation

According to Remschmidt et al., the pooled analysis of case–control studies among 102,575 diabetic patients indicated that influenza vaccination

prevented all-cause hospitalisation with adjusted OR 0.77 (95% CI: 0.60, 0.99; IVE of 23%). Only one study reported that the vaccination group was less likely to be hospitalised due to influenza or pneumonia with adjusted OR 0.55 (95% CI: 0.47, 0.66: IVE of 45%).[11, level I]

b. Influenza and pneumonia-related hospitalisation

Vu et al. reported that, vaccination has been shown to reduce hospitalisation for pneumonia and influenza by average of 33% (95% CI: 27, 38; IVE 28-37%). Vaccination would prevent approximately 25% hospitalisations for pneumonia when there was a good match between influenza strains in the vaccine and those in circulation. [12, level I]

Domínguez et al. (2017) conducted a multicentre case-control study in 20 major hospitals from 17 Spanish regions involving 2554 participants to assess the effectiveness of influenza vaccination in preventing hospitalisation in individuals aged ≥65 years old during two influenza seasons (2013/14 and 2014/15). The patients were hospitalised for at least 24 hours with laboratory-confirmed influenza virus infection (PCR, culture or immunofluorescence). [22, level II-2]

They reported the overall adjusted IVE against influenza hospitalisation was 36% (95% CI: 22, 47) without any differences between seasons (34% for 2013/14 and 37% for 2014/15). When the data was stratified according to the types of influenza, they found the IVE was 37% (95% CI: 32, 48) for all types of influenza A viruses, 49% (95% CI: 32, 62) for influenza A (H1n1) pdm09, 26% (95% CI: -3, 47) for influenza A (H3N2) and 18% (95% CI: -145, 73) for influenza B. There was no difference in adjusted IVE against hospitalisation among those vaccinated in the current season only (41%, 95% CI: 16, 59) and those vaccinated in both current and previous season (42%, 95% CI: 28, 54). However, IVE among those vaccinated in the previous season only was 24% (95% CI: -6, 45). [22, level II-2]

c. Acute coronary syndrome-related hospitalisation

One cohort study was conducted by Chen et al. in 2016 among 4406 Taiwan population (>55 years old) to observe the effects of influenza vaccination on the reduction of first hospitalisations for acute coronary syndrome (ACS) in the elderly patients with chronic kidney disease (CKD). The patients were followed up from 12 months to a maximum of ten years. They found the group receiving influenza vaccination exhibited a lower risk of hospitalisation for ACS in the elderly CKD patients without prior cardiovascular disease history (adjusted hazard ratio (HR): 0.25 (95% CI: 0.19, 0.32 for 65-74 years old and adjusted HR: 0.42, 95% CI: 0.31, 0.57 for ≥ 75 years old). They found consistent protective effects regardless of age groups (55–64, 65–74, and >75), gender, and seasonality of influenza. When the patients were stratified

according to the total number of vaccinations, the adjusted HRs for first ACS hospitalisation were 0.62 (95% CI: 0.52, 0.81) for one vaccination, 0.35 (95% CI: 0.28, 0.45) for two to three vaccinations, and 0.13 (95% CI: 0.09, 0.19) for four or more vaccinations for all seasons. Hence, there was a significant decrease risk of ACS hospitalisation with an increasing number of vaccinations. [23, level II-2]

d. Length of hospitalisation

One cross-sectional study by Thompson et al. (2004) estimated annual influenza-associated hospitalisations in the United States by hospital discharge category, discharge type, and age group that used data from National Hospital Discharge Survey (NHDS) and WHO Collaborating Laboratories influenza surveillance from the 1979-1980 through the 2000-2001 seasons using age-specific Poisson regression models.[24, level II-3]

Based on the study, they found the average hospital stay due to influenza increased from 5.8 days for those between the ages of five and 49 years, to over eight days for those ≥65 years old. Also, they found the median length of stay for primary pneumonia and influenza hospitalisations increased significantly with age for those older ≥65 years old ($p<0.5$ for each of age range). Another finding on the median length of stay for primary respiratory and circulatory hospitalisations was five to six days for those ≥65 years old ($p<0.5$ for each of age range). [24, level II-3]

5.4 SOCIETAL ISSUES

Nagata JM et al. (2013) conducted a systematic review of qualitative and quantitative studies on social determinants of health and seasonal influenza vaccination in adults ≥65 years living in the community or in nursing homes in high, middle and low income countries. The outcome measure of interest was vaccine coverage and the barriers (and their social determinants) that may affect vaccine uptake.[25, level I]

Based on the results from 58 studies, the common factors which influenced seasonal influenza vaccination as well as the barrier to immunization under structural social determinants and intermediary determinants aspects were concerns about the vaccine safety, effectiveness, side effects, fear of pain, injections and getting disease with the vaccine. While under the health system, most studies reported on affordability and cost where it is preferable if the vaccine is free of charge and advice from physician or professional health care provider may affect the vaccine acceptance. [25, level I]

5.4 SAFETY

Only one study (SR with MA) included information on adverse events.

The study reported no significant difference regarding the effect of vaccines in terms of fever and nausea harms in the elderly [fever: 1.6% with placebo compared with 2.5% after vaccination (RR: 1.57, 95% CI: 0.92, 2.71); nausea (2.4% with placebo compared with 4.2% after vaccination (RR: 1.75, 95% CI 0.74, 4.12)].[9, level 1]

Very recent report about influenza-related death that occurred in South Korea that involved 40 people with the used of QIV brand SKYCellflu Quadrivalent and Vaxigrip Tetra. However, those types of QIV have not been supplied in MOH facilities (refer to Appendix 3).

5.5 COST-EFFECTIVENESS

D' Angiolella et al. 2018 conducted a systematic review to estimate the costs and effectiveness of influenza vaccination.[26] Out of 30 studies, 11 studies were among elderly patients in Europe, US, China and Australia that compared Trivalent Inactivated Influenza Vaccine (TIV), Quadrivalent Inactivated Influenza Vaccine (QIV) with no vaccination. Based on the review, all types of vaccinations (high dose TIV, TIV and QIV) were cost-effective compared with no vaccination from the payer's perspective with incremental cost-effectiveness ratio (ICER) < €20 000 (three studies). Another two studies reported an ICER between €20 000 and €50 000. From the societal perspective, two studies found vaccination to be cost-effective compared to unvaccination with an ICER between €20 000 and €50 000. One study reported QIV as cost-saving option compared to TIV for elderly population in China and Germany. Another three studies reported QIV as cost-effective option but not cost-saving compared to TIV from societal and healthcare system perspective.[26] In elderly population, high-dose TIV was found to has the potential to be favoured over other vaccines (TIV standard dose and QIV). [26]

A systematic review by Shields GE et al. 2017 reported on the economic evaluations of seasonal influenza vaccination for the elderly population in the European Union.[27] All eight studies undertook either cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) with quality-adjusted life-year (QALY) as the measure of health benefit. One-year time horizon was used in seven out of eight studies for costs, consistent with an influenza season and the short term or immediate costs, therefore discounting costs were irrelevant. Studies applied country-specific guidelines for discounting outcomes that ranges from 1.5% to 5% annually, wherever relevant. The majority of studies considered direct costs only. Modelling approaches were relatively simple as they used static decision tree models while only one

study used a dynamic transmission model, hence able to capture the impact of transmission and herd immunity. [27]

The results varied widely. Five studies found that vaccination was cost-effective compared with no vaccination regardless of types of vaccines (adjuvanted, standard, opportunistic and reimbursed vaccine) among unknown risk and mixed risk of population with ICER ranging from €1065 to €11 790 per QALY gained. While in one study with low risk elderly population, influenza vaccine was judged not to be cost-effective with ICER €572 305 per QALY gained. [27]

Another study estimated that adjuvanted vaccine was over 90% likely to be cost-effective compared with standard vaccine, while one study showed that quadrivalent vaccine was estimated to be cost-effective when compared to trivalent vaccine among unknown risk and mixed risk elderly population. The vaccination of high-risk individuals was demonstrated to be more cost-effective compared with low-risk population. High risk in this study referred to the elderly population with another condition or circumstance that places them at a greater risk for complications for example respiratory conditions. [27]

One recent cost-effectiveness study by Yue et al. 2019 for Influenza Vaccination was conducted using an individual-based simulation model to quantify the incremental economic value of vaccination and to evaluate the optimal timing of influenza vaccination in tropical Singapore, in seasonality regimes based on the seasonality of Taipei and Tokyo, and with a no influenza seasonality baseline by measuring changes in ICER.[28] The time frame for the simulation model was 10 years. The simulation model was based on a population size of 10 000 with 1000 independent Monte Carlo simulations to obtain reliable comparisons between scenarios. By using no intervention as a baseline, they considered three alternative vaccination strategies; annual vaccination for a percentage of the elderly, biannual vaccination for a percentage of the elderly and annual vaccination for all elderly and a fraction (p) of the remaining population. Five vaccination coverage rate which were; p= 20%, 40%, 60%, 80% and 100% were considered for each strategy.[28]

With Singapore willingness-to-pay of USD $52 961/QALY, they found that the annual vaccination for a proportion of elderly was largely cost-effective. However, the partial biannual vaccination strategy for the elderly yields a higher ICER than partial annual vaccination for the elderly, resulted in a cost-ineffective ICER. However, by vaccinating all elderly and a proportion of other age groups, increasing the coverage rate makes the incremental cost more negative, which suggested there can be greater savings by vaccinating more people which was not in elderly group from a societal perspective. Thus, vaccinating all elderly and other age groups was

consistently cost saving, making this the most cost-effective strategy of the three immunization strategies. Their one-way sensitivity analysis conducted showed that vaccination cost and vaccine efficacy have an important effect on cost-effectiveness, whereas mortality costs, hospitalisation rate, and hospitalisation cost have the least effect on ICERs.[28]

5.6 ECONOMIC IMPLICATIONS (MALAYSIA)

Financial Implication

Annual influenza vaccination of the elderly has been recommended by WHO and the suggested vaccination coverage rate is 75%.[29] This analysis was undertaken to predict the potential cost implication of implementing annual influenza vaccination for the elderly in Malaysia. Table 2 shows the number of ILI based on 15 sentinel locations in Malaysia (primary healthcare and outpatient department) from year 2016 to 2019.[20]

Table 2. ILI among the elderly (≥60 years old) for year 2016 to 2019

Year	Total ILI from 15 sentinel locations	Percentage increase (%)
2016	56,372	NA
2017	61,263	8.68
2018	69,293	13.11
2019 (until 30th November 2019)	70,628	1.93

There was no local data retrieved with regards to the total population of ≥60 years old for the selected 15 sentinel location, percentage / proportion of patients with ILI in that population that require hospitalisation and rough estimation of the cost of treating ILI (drugs used, complications of drugs and the cost estimation, cost of hospitalisation for severe cases, death due to ILI). Data on the annual death stratified according to age was not available. Thus, we made the assumption that the percentage of annual population growth rate for elderly age 65 years old is similar with the elderly population age 60 years old. The population rate was taken from the Department of Statistics, Malaysia (DOSM). Hence, the estimated population for the next three years is shown in Table 3.[30] We calculated three years' budget with coverage rate of 25% in the first year with subsequent increase of 25% per year.

Table 3. Estimated elderly population (≥65 years old) in Malaysia

Year	Estimated Population	Estimated elderly population	Estimated percentage from total population (%)
2017	32.0 million	2.0 million	6.3%
2018	32.38 million	2.1 million	6.5%
2019	32.523 million	2.179 million	6.7%

2020	32.6573 million	2.286 million	7.0%
2021	33.53 million	2.38 million	7.1%
2022	33.9 million	2.48 million	7.3%
2023	34.3 million	2.57 million	7.5%

The price for Influenza Vaccine stated in CDC websites varies between $11.67 to $25.763.[31] According to the Formulari Ubat KKM (FUKKM), Malaysia, the available influenza vaccines as stated in Consumer Price Guide are the Type A (H1N1) 15mcg, Type A (H3N2) 15mcg and Type B 15mcg Haemagglutinin Injection. The price was between RM33.80 and RM48.75 (for year 2015-2016).[32]

Trivalent and Quadrivalent influenza vaccines were included in this analysis which is available in the Formulari Ubat KKM (FUKKM) page. The dosage of the vaccines for the elderly is based on the recommended by the drug company and FUKKM, which is 0.5ml per dose. The cost inputs for Trivalent and Quadrivalent were taken from the Pusat Perubatan UKM (PPUKM) and Hospital Queen Elizabeth, Sabah, MOH, Malaysia (Table 4).

Table 4. Cost parameters

Type of vaccine	Range of cost	Source
Trivalent 0.5 ml pre-filled syringe	RM 25-RM50	PPUKM & MOH
Quadrivalent 0.5ml pre-filled syringe	RM 35.50-RM 77	PPUKM & MOH

Results

Strategy 1: 100% elderly population immunised

We started with the coverage of 10% based on the economic evaluation assessment where many countries started the coverage rate of 10%. Based on the calculation, Trivalent Influenza Vaccine (lowest cost) as annual vaccination would incur a total cost of **RM 5.447 million** for vaccination **coverage of 10%** while a Quadrivalent Influenza Vaccine (lowest cost) would incur RM 7.735 million. If all elderly population are given TIV (100% vaccination coverage rate), the total financial implication per year is approximately RM 54.476 million. If QIV is to be given to the same population, the total financial implication per year is estimated to be RM 77.355 million (Table 5).

Table 5. Total cost (RM) for base-case (2019 elderly population)

Parameter	Value	Value
Assumption: coverage rate (%)	10%	100%
Number of elderly patient (in million)	217 904.1	2,179,041
TIV	**RM5,447,603**	RM54,476,025

QIV	**RM7,735,596**	RM77,355,956

Strategy 2: Achieving 75% of elderly population immunised in 3 years

The total cost for **TIV (lowest cost)** approximately between **RM13.619 million** to **RM 44.625 million** when influenza vaccination was given to elderly population for the next three years considering coverage rate increase by 25% for each year. Meanwhile, the use of QIV (lowest cost) as an alternative will increase the total cost of RM5.719 million to RM18.742 million for the next three years with 25% to 75% of coverage rate (Table 6). Additionally, analyses of the **highest cost** for both influenza vaccines were also performed and resulted an incremental cost of approximately between RM13 million to RM44 million for TIV and RM22 million to RM74 million for QIV. The results are summarised and illustrated as in Table 6 and Table 7.

Table 6. Total cost (RM) of influenza vaccination for three years (lowest price)

Scenario 1: With lowest cost TIV or QIV			
Vaccine	**Year 1 (coverage rate 25%)**	**Year 2 (coverage rate 50%)**	**Year 3 (coverage rate 75%)**
TIV	RM13,619,006	RM28,575,000	RM44,625,000
QIV	RM19,338,989	RM40,576,500	RM63,367,500
Total different cost	RM5,719,983	RM12,001,500	RM18,742,500

Table 7. Total cost (RM) of influenza vaccination for three years (highest price)

Scenario 2: With highest cost TIV or QIV			
Vaccine	**Year 1 (coverage rate 25%)**	**Year 2 (coverage rate 50%)**	**Year 3 (coverage rate 75%)**
TIV	RM27,238,013	RM57,150,000	RM89,250,000
QIV	RM41,946,539	RM88,011,000	RM137,445,000
Total different cost	RM14,708,527	RM30,861,000	RM48,195,000

Strategy 3: Elderly with one co-morbidity

High-risk group for elderly in Malaysia

Lack of data on the morbidity of several diseases in Malaysia has been the major limitation in this analysis. Only elderly (age 60 years old and above) with Ischaemic heart disease (IHD), diabetes mellitus (DM), obesity (BMI ≥ 40.0 kg/m^2) data in 2018 were available, therefore we could not estimate the budget impact for whole elderly with the chronic medical diseases.

Diabetes Mellitus is the most common co-morbidity among elderly in Malaysia. According to National Health Morbidity Survey (NHMS) 2019, the prevalence of diabetes among elderly (60 years old and above) in Malaysia was 41.5% from total elderly population. When we considered **elderly with diabetes mellitus** to be included in the coverage group, the estimated lowest cost based on the price given to implement annual influenza vaccination **was RM 22.61 million per year.**

There is uncertainty in the number of elderly population who may be eligible for the influenza vaccination due to the unavailability of local data for elderly mortality rate. However, the approximate financial implication may be useful as guidance for the decision makers on the requirement of the budget increment. Moreover, data for elderly with chronic medical conditions is needed to complete the estimation of budget impact analysis for those special group (if required) in order to provide additional information on the financial implication.

5.7 LIMITATIONS

Although there was no restriction in language during the search but only English full text articles were included in this report and the selection of studies was done by one reviewer. Lack of local data on population affected and cost implication were the major limitation to do the local economic evaluation.

6. CONCLUSION

6.1 Effectiveness

Influenza rate

There was good level of retrievable evidence to suggest that influenza vaccination was effective in reducing influenza rate in the elderly. The evidence showed vaccinated elderly experienced less influenza compared to placebo. The IVE ranged from 31% to 58% depending on the types of influenza viruses.

Influenza Like-Illness

There was good level of retrievable evidence to suggest that vaccinated elderly experienced less ILI compared with unvaccinated elderly with IVE ranged from 19% to 45% among older patients aged ≥65 years old. The influenza vaccination also prevented ILI in type 1 and type 2 diabetic patients with IVE of 13%.

Mortality

i. All-cause mortality

There was fair to good level of retrievable evidence to suggest that influenza vaccination reduced all-cause mortality with IVE of 38%-56% among diabetic patients.

ii. Influenza-related mortality

There was fair to good level of retrievable evidence to suggest vaccination reduce mortality following hospitalisation for pneumonia and influenza by 47% with IVE 25-62%. Study in US on seasonal-influenza, stated about 88.9% influenza-associated deaths averted among vaccinated group in the elderly while among French elderly population, showed that vaccination would avoid an influenza-attributable death with IVE of 35% compared to unvaccinated group.

Immune Response (Immunogenicity)

There was fair to good level of retrievable evidence to suggest better immune response (immunogenicity) for all types of vaccine which include non-adjuvanted vaccine, aluminium hydroxide-adjuvanted vaccine, and AS03A-adjuvanted vaccine.

6.2 Organisational issues

Guidelines

The WHO recommended that northern hemisphere (including Malaysia) influenza season should use both trivalent or quadrivalent vaccines that contain both influenza type A and influenza type B virus (B/Colorado/06/2017-like virus of the B/Victoria/2/87-lineage) with a 75% vaccination coverage. In Malaysia, healthcare workers (front liners) were included in annual immunization programme.

Implementation

One SR identified that among low intensity intervention, client reminder by letter or postcards showed significant positive effects to increase influenza vaccination rates for this elderly population (≥60 years old). While personalised phone calls (medium intensity intervention) and home visits, facilitators (high intensity intervention) showed significant positive effects that would increase community demand for vaccination, enhance access, and improve provider/system response.

Influenza Surveillance Programme in Malaysia

Both National Public Health Laboratory (NPHL) Sungai Buloh and the Institute of Medical Research (IMR) found that influenza A virus was the most dominantly isolated virus with 291 (59.03%) positive isolates followed by influenza B with 202 (40.97%) isolates. However, data were not stratified according to age groups.

Influenza-related hospitalisation

There was fair to good level of retrievable evidence to suggest that vaccination reduced influenza-related hospitalisation (also pneumonia) with IVE ranged from 18-49% depending on the types of influenza viruses. Vaccination also prevented all-cause hospitalisation in diabetic patients with IVE of 23% and reduced the first hospitalisation for ACS in elderly patients with CKD. Increased number of vaccination was associated with significant decreased risk of ACS hospitalisation.

The average hospital stays due to influenza for elderly (≥65 years old) was over eight days while the median length of stay for primary respiratory (influenza-related) and circulatory hospitalisations was five to six days.

6.3 Societal issues

One SR demonstrated that the ability of adults aged ≥65 years old to receive seasonal influenza vaccine was influenced by structural, intermediate, and healthcare-related social determinants which have an impact at the health system, provider and individual levels.

6.4 Safety

There was limited good level of retrievable evidence to suggest that the use of influenza vaccine was associated with non-significant adverse effects such as fever and nausea. The recent report regarding influenza-related death in South Korea was associated with the certain product brand for QIV.

6.5 Cost-effectiveness

SR on cost-effectiveness studies showing varying results ranging from being cost-effectiveness to not cost-effective in different population groups and countries. A cost-effectiveness study using societal perspective conducted in Singapore found the elderly plus some other age groups population to be the most cost-effective strategy.

6.6 Economic implication

Local economic evaluation cannot be conducted due to limitation of local data (epidemiological and costs data). Hence, the cost-effectiveness of

Influenza vaccination among elderly population in Malaysia cannot be determined. Based on the financial implication analysis, the use of TIV (lowest cost) as an annual influenza vaccination is estimated to have an economic implication of approximately RM 5.447 million for a starting coverage rate of 10% (strategy 1). While in strategy 2, the lowest cost estimated for a coverage rate of 25% was RM 13.619 million per year. For strategy 3, the estimated lowest cost of TIV for elderly with diabetes mellitus with a prevalence of 41.5% a year was RM 22.61 million per year.

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8. APPENDICES

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Database: Ovidsp: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 31, 2019>

Search Strategy:

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1 AGED/ (2932418)

2 aged.tw. (532280)

3 elderly.tw. (231475)

4 INFLUENZA A VIRUS/ (19798)

5 H1N1 SUBTYPE/ (14695)

6 h1n1 virus*.tw. (3268)

7 influenza a virus.tw. (10090)

8 h1n1 subtype.tw. (207)

9 ((swine origin or swine-origin) adj2 influenza a h1n1 virus*).tw. (136)

10 INFLUENZA A VIRUS, H1N1 SUBTYPE/ (14695)

11 INFLUENZA A VIRUS, H3N2 SUBTYPE/ (3833)

12 h3n2 virus*.tw. (1698)

13 influenza a virus, h3n2 subtype.tw. (7)

14 influenza virus, canine, h3n2 subtype.tw. (0)

15 INFLUENZA A VIRUS, H5N1 SUBTYPE/ (5874)

16 h5n1 virus*.tw. (2263)

17 influenza a virus, h5n1 subtype.tw. (6)

18 INFLUENZA, HUMAN/ (46849)

19 grippe.tw. (279)

20 (human adj2 (flu or influenza*)).tw. (3183)

21 influenza*.tw. (109259)

22 influenza in human*.tw. (116)

23 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (3447054)

24 INFLUENZA VACCINES/ (21757)

25 ((flu or laiv or influenza) adj2 vaccine*).tw. (13667)

26 ((high dose or high-dose) adj2 trivalent influenza vaccine*).tw. (14)

27 influenza virus vaccine*.tw. (1102)

28 influenzavirus vaccine*.tw. (3)

29 ((intranasal or trivalent) adj2 live attenuated influenza vaccine*).tw. (86)

30 ((monovalent or quadrivalent or universal or trivalent) adj2 influenza vaccine*).tw. (1613)

31 universal flu vaccine*.tw. (31)

32 flu vaccine*.tw. (715)

33 Annual immunization.tw. (65)

34 Annual vaccination.tw. (354)

35 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (25099)

36 23 and 35 (23982)

37 limit 36 to (english language and full text and humans) (4316)

38 limit 37 to "systematic review" (81)

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Database: Virtual Library: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily - without Revisions <2015 to August 02, 2019>

Search Strategy:

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1 AGED/ (468860)

2 aged.tw. (160710)

3 elderly.tw. (59643)

4 INFLUENZA A VIRUS, H1N1 SUBTYPE/ (2557)

5 h1n1 virus*.tw. (705)

6 influenza a virus, h1n1 subtype.tw. (0)

7 ((swine origin or swine-origin) adj2 influenza a h1n1 virus*).tw. (28)

8 INFLUENZA A VIRUS, H3N2 SUBTYPE/ (1022)

9 h3n2 virus*.tw. (423)

10 influenza a virus, h3n2 subtype.tw. (0)

11 influenza virus, canine, h3n2 subtype.tw. (0)

12 INFLUENZA A VIRUS, H5N1 SUBTYPE/ (894)

13 h5n1 virus*.tw. (507)

14 influenza a virus, h5n1 subtype.tw. (1)

15 INFLUENZA, HUMAN/ (6907)

16 grippe.tw. (56)

17 (human adj2 (flu or influenza*)).tw. (702)

18 influenza*.tw. (23670)

19 influenza in human*.tw. (16)

20 INFLUENZA VACCINES/ (3831)

21 ((flu or laiv or influenza) adj2 vaccine*).tw. (3988)

22 ((high dose or high-dose) adj2 trivalent influenza vaccine*).tw. (12)

23 influenza virus vaccine*.tw. (213)

24 influenzavirus vaccine*.tw. (0)

25 ((intranasal or trivalent) adj2 live attenuated influenza vaccine*).tw. (36)

26 ((monovalent or quadrivalent or universal or trivalent) adj2 influenza vaccine*).tw. (643)

27 universal flu vaccine*.tw. (16)

28 flu vaccine*.tw. (223)

29 Annual immunization.tw. (10)

30 Annual vaccination.tw. (101)

31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (643284)

32 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (5671)

33 31 and 32 (5450)

34 limit 33 to (english language and full text and humans and "systematic review") (13)

****

Database: Virtual Library: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 31, 2019>

Search Strategy:

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1 [AGED/] (0)

2 aged.tw. (3595)

3 elderly.tw. (1149)

4 [INFLUENZA A VIRUS, H1N1 SUBTYPE/] (0)

5 h1n1 virus*.tw. (6)

6 influenza a virus, h1n1 subtype.tw. (3)

7 ((swine origin or swine-origin) adj2 influenza a h1n1 virus*).tw. (0)

8 [INFLUENZA A VIRUS, H3N2 SUBTYPE/] (0)

9 h3n2 virus*.tw. (4)

10 influenza a virus, h3n2 subtype.tw. (1)

11 influenza virus, canine, h3n2 subtype.tw. (0)

12 [INFLUENZA A VIRUS, H5N1 SUBTYPE/] (0)

13 h5n1 virus*.tw. (1)

14 influenza a virus, h5n1 subtype.tw. (1)

15 [INFLUENZA, HUMAN/] (0)

16 grippe.tw. (8)

17 (human adj2 (flu or influenza*)).tw. (42)

18 influenza*.tw. (329)

19 influenza in human*.tw. (4)

20 [INFLUENZA VACCINES/] (0)

21 ((flu or laiv or influenza) adj2 vaccine*).tw. (51)

22 ((high dose or high-dose) adj2 trivalent influenza vaccine*).tw. (0)

23 influenza virus vaccine*.tw. (2)

24 influenzavirus vaccine*.tw. (0)

25 ((intranasal or trivalent) adj2 live attenuated influenza vaccine*).tw. (3)

26 ((monovalent or quadrivalent or universal or trivalent) adj2 influenza vaccine*).tw. (9)

27 universal flu vaccine*.tw. (0)

28 flu vaccine*.tw. (7)

29 Annual immunization.tw. (0)

30 Annual vaccination.tw. (4)

31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (4232)

32 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (53)

33 31 and 32 (52)

34 limit 33 to (full text and yr="2015 - 2019" and english language) [Limit not valid; records were retained] (0)

35 limit 34 to randomized controlled trial [Limit not valid; records were retained] (0)

****

OTHER DATABASES	
EBM Reviews - Cochrane database of systematic reviews	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane Central Register of Controlled Trials	
EBM Reviews - Health Technology Assessment	
EBM Reviews – NHS Economic Evaluation Database	

8.2. Appendix 2:

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

8.3. Appendix 3:

KENYATAAN AKHBAR
KEMENTERIAN KESIHATAN MALAYSIA

ISU PEMBERHENTIAN SEMENTARA PENGGUNAAN DUA PRODUK VAKSIN INFLUENZA RENTETAN DARIPADA LAPORAN KES KEMATIAN DI KOREA SELATAN

Kementerian Kesihatan Malaysia (KKM) mengambil maklum akan *MOH Circular No. 214/2020* yang dikeluarkan oleh Health Science Authority (HSA), Singapura pada 25 Oktober 2020 bertajuk "*Temporary Cessation on The Use of Two Influenza Vaccines*" mengenai pemberhentian sementara penggunaan 2 produk vaksin influenza, iaitu SKYCellflu Quadrivalent dan VaxigripTetra sebagai langkah berjaga-jaga berikutan terdapat laporan kes kematian dikaitkan dengan kedua-dua produk tersebut di Korea Selatan.

KKM ingin memaklumkan terdapat 9 produk vaksin influenza yang berdaftar dengan Pihak Berkuasa Kawalan Dadah (PBKD) Malaysia, termasuk 2 produk vaksin influenza yang dikaitkan dengan kes kematian di Korea Selatan iaitu SKYCellflu Quadrivalent dan Vaxigrip Tetra (rujuk Jadual). Sebagai makluman, **hanya Vaxigrip Tetra, Suspension for Injection in Pre-filled Syringe sahaja yang dibekalkan di fasiliti kesihatan KKM.**

Syarikat Sanofi Pasteur (pengeluar produk Vaxigrip Tetra) memaklumkan bahawa nombor kelompok produk Vaxigrip Tetra yang digunakan di Korea Selatan, **tidak terdapat** di pasaran negara lain, termasuk

Malaysia. Setakat ini juga, **tiada kes kematian** yang dilaporkan susulan imunisasi vaksin influenza (quadrivalen) di negara ini.

Namun demikian, sebagai langkah berjaga-jaga, KKM menasihatkan agar **pengamal perubatan menghentikan sementara penggunaan produk vaksin SKYCellflu Quadrivalent dan VaxigripTetra**. KKM akan memaklumkan perkembangan berkenaan situasi ini setelah maklumat lanjut diperolehi.

KKM juga menjalankan pemantauan secara berterusan melalui program pemantauan mutu produk berdaftar dan farmakovigilans bagi memastikan kualiti, keselamatan dan keberkesanan ubat-ubatan sentiasa terjamin. Pihak KKM akan memaklumkan perkembangan terkini kepada orang ramai dari semasa ke semasa.

Sekian, terima kasih.

DATIN DR. FARIDAH ARYANI BINTI MD YUSOF
PENGARAH KANAN PERKHIDMATAN FARMASI

28 OKTOBER 2020

Senarai produk-produk vaksin influenza yang berdaftar di Malaysia

Bil.	No. Pendaftaran Produk	Nama Produk (Jenis)	Pemegang Pendaftaran Produk	Pengilang
1	MAL18086125ARZ	*__VAXIGRIP TETRA, SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE__ (quadrivalen)	SANOFI-AVENTIS (MALAYSIA) SDN. BHD.	SANOFI PASTEUR (FRANCE)
2	MAL18026177ARZ	*__SKYCELLFLU QUADRIVALENT PREFILLED SYRINGE 0.5ML__ (quadrivalen)	AJ BIOLOGICS SDN. BHD.	SK Bioscience Co., Ltd. (KOREA, SOUTH)
3	MAL20076005AZ	SKYCELLFLU TRIVALENT SOLUTION FOR INJECTION IN PREFILLED SYRINGE 0.5ML (trivalen)	AJ BIOLOGICS SDN. BHD.	SK Bioscience Co., Ltd. (KOREA, SOUTH)
4	MAL20076004AZ	SKYCELLFLU TRIVALENT SOLUTION FOR INJECTION IN PREFILLED SYRINGE 0.25ML (trivalen)	AJ BIOLOGICS SDN. BHD.	SK Bioscience Co., Ltd. (KOREA, SOUTH)
5	MAL14075039ARZ	FLUQUADRI QUADRIVALENT INFLUENZA VACCINE, 0.5 ML (quadrivalen)	SANOFI-AVENTIS (MALAYSIA) SDN. BHD.	SANOFI PASTEUR INC (UNITED STATES)
6	MAL14075040ARZ	FLUQUADRI QUADRIVALENT INFLUENZA VACCINE, 0.25 ML (quadrivalen)	SANOFI-AVENTIS (MALAYSIA) SDN. BHD.	SANOFI PASTEUR INC (UNITED STATES)
7	MAL15085081ARZ	FLUARIX TETRA INFLUENZA VACCINE (quadrivalen)	GLAXOSMITH KLINE PHARMACEUTICAL SDN. BHD.	GlaxoSmithKline Biologicals, Branch of SmithKline Beecham Pharma GmbH & Co. KG (GERMANY)

Bil.	No. Pendaftaran Produk	Nama Produk (Jenis)	Pemegang Pendaftaran Produk	Pengilang
8	MAL20061585ARZ	INFLUVAC SUSPENSION FOR INJECTION (trivalen)	ABBOTT LABORATORIES (M) SDN. BHD.	Abbott Biologicals B.V. (NETHERLANDS)
9	MAL20016220AZ	INFLUVAC TETRA, SUSPENSION FOR INJECTION IN PRE-FILLED SYRINGE (quadrivalen)	ABBOTT LABORATORIES (M) SDN. BHD.	Abbott Biologicals B.V (NETHERLANDS

**Dua (2) produk vaksin influenza yang berkaitan dengan nama SKYCellflu Quadrivalent dan Vaxigrip Tetra berdasarkan laporan MOH Circular oleh HSA.*

8.4. Appendix 4: Evidence table

INFLUENZA VACCINATION FOR THE ELDERLY

Evidence Table : Effectiveness and safety
Question : Is Influenza vaccination for the elderly effective and safe?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Demicheli V, Jefferson T, Di Pietrantonj C, Ferroni E, Thorning S, Thomas RE, Rivetti A. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2018. In: Ovid MEDLINE(R) The studies were conducted in community and residential care settings in Europe and the USA between 1965 and 2000	**Systematic Review & meta-analysis** included **75 studies** in previous versions of the review: 68 studies were used to assess efficacy/effectiveness, and 8 were included in the safety assessment (one RCT was included in both assessments). **Aim** To assess the effects (efficacy, effectiveness, and harm) of vaccines against influenza in the elderly. **Methods** Database searched: Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2016, Issue 11), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to 31 December 2016); Embase (1974 to 31 December 2016); Web of Science (1974 to 31 December 2016); CINAHL (1981 to 31 December 2016); LILACS (1982 to 31 December 2016); WHO	II-1	8 RCTs (over 5000 participants), Elderly participants aged 65 years or older	1. Vaccination with any influenza vaccine given independently, in any dose, preparation, or time schedule, 2. We also considered new, as yet unlicensed vaccine types (e.g. live attenuated and DNA vaccines).	Placebo		**<u>Influenza assessed</u>** Older adults **receiving the influenza vaccine** may **experience less influenza** over a single season compared with placebo, from **6% to 2.4%, IVE 58%,** (risk ratio **(RR) 0.42, 95% confidence interval (CI) 0.27 to 0.66**). **<u>Influenza-like Illness</u>** Older adults probably **experience less influenza-like illness (ILI) compared** with those who do not receive a vaccination over the course of a single influenza season **(3.5% versus 6%; RR 0.59, 95% CI 0.47 to 0.73**; moderate-certainty evidence). **IVE 41%.** These results indicate that **30 people would need to be vaccinated** to prevent one person experiencing influenza, and **42 would need to be vaccinated** to prevent one person having an ILI. **<u>Pneumonia & Hospitalisation (influenza-related)</u>** The study providing data for **mortality and pneumonia was underpowered to detect differences** in these outcomes. There were **3 deaths from 522 participants in the vaccination arm** and **1 death from 177 participants in the placebo arm**, providing very low-certainty evidence for the effect on mortality **(RR 1.02, 95% CI 0.11 to 9.72). No cases of pneumonia occurred in one study** of **699 people** that reported this outcome (very low-	Quality was assessed using GRADE. Evidence were of low to moderate quality

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	International Clinical Trials Registry Platform (ICTRP; 1 July 2017); and ClinicalTrials.gov (1 July 2017). Randomised controlled trials (RCTs) and quasi-RCTs assessing efficacy against influenza (laboratory-confirmed cases) or effectiveness against influenza-like illness (ILI) or safety. Considered any influenza vaccine given independently, in any dose, preparation, or time schedule, compared with placebo or with no intervention. **Exclusion** Excluded studies: assessing efficacy in selected groups affected by a specific chronic pathology (i.e. diabetes or cardiac disease), as we were interested in the whole population. The question of whether these vaccines are effective in specific at-risk populations is the topic of other reviews. Excluded studies in which a vaccine was administered after the beginning of the epidemic period. Excluded old oil adjuvant vaccine or vaccines with a content greater than 15 µg of haemagglutinin/strain/dose from the safety assessment.						certainty evidence). **No data on hospitalisations were reported.** **<u>Safety</u>** Confidence intervals around the effect of vaccines on fever and nausea were wide, and we do not have enough information about these harms in older people (small increases) (fever: 1.6% with placebo compared with 2.5% after vaccination (RR 1.57, 0.92 to 2.71; moderate-certainty evidence)); nausea (2.4% with placebo compared with 4.2% after vaccination (RR 1.75, 95% CI 0.74 to 4.12; low-certainty evidence)). **Conclusion** We are uncertain how big a difference these vaccines will make across different seasons. We do not have enough information to assess harms relating to fever and nausea in this population. The evidence for a lower risk of influenza and ILI with vaccination is limited by biases in the design or conduct of the studies. Lack of detail regarding the methods used to confirm the diagnosis of influenza limits the applicability of this result. The available evidence relating to complications is of poor quality, insufficient, or old and provides no clear guidance for public health regarding the safety, efficacy, or effectiveness of influenza vaccines for people aged 65 years or older.	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Rondy M, El Omeiri N, Thompson MG, et al. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. The Journal of infection. 2017;75(5):381-394.	**Systematic Review & meta-analysis of 30 studies (test-negative design case-control studies)** **Aim** Summary evidence of influenza vaccine effectiveness (IVE) against hospitalized influenza is lacking. We conducted a meta-analysis of studies reporting IVE against laboratory-confirmed hospitalized influenza among adults. **Methods** Database searched: Pubmed (January 2009 to November 2016) for studies that used test-negative design (TND) to enrol patients hospitalized with influenza-associated conditions. Two independent authors selected relevant articles. Calculated pooled IVE against any and (sub) type specific influenza among all adults, and stratified by age group (18–64 and 65 years and above) using random-effects models. All 27 studies reporting seasonal IVE presented estimates adjusted for age and presence of comorbidities and 13/27 further adjusted for calendar time. The	I	18- above 65 years old. used test-negative design (TND) to enrol patients hospitalized with influenza-associated conditions.	1. Vaccination with any influenza vaccine given independently, in any dose, preparation, or time schedule, 2. Also considered new, as yet unlicensed vaccine types (e.g. live attenuated and DNA vaccines).	1. placebo	-	Overall, we compiled **116 IVE estimates,** including **59 estimates against any influenza**, 18 against influenza A(H1N1)pdm09, 28 against A(H3N2) and 11 against B viruses Summarized IVE estimates by adult age groups (18–64 years, ≥ 65 years of age), influenza subtype/lineage and influenza season. **<u>Influenza vaccination effectiveness (IVE)</u>** **<u>Estimates against any type of influenza</u>** The pooled seasonal IVE was 41% (95% CI: 34; 48) for any influenza (51% (95% CI: 44; 58) among people aged 18–64y**. For adults aged ≥65 years,** IVE ranged from −25% to 58%, I^2 was 26% and the **pooled IVE estimate was statistically lower at 37% (95% CI: 30; 44).** **<u>Seasonal vaccine effectiveness against influenza A(H1N1)pdm09 viruses</u>** IVE was 48% (95%CI:37; 59), 37% (95%CI:24; 50) and 38% (95%CI:23;53) against influenza A(H1N1)pdm09. **For adults ≥ 65 years of age, summary IVE was 54% (95%CI: 26;82) with I^2 = 64%** **<u>Seasonal vaccine effectiveness against influenza A(H3N2) viruses and B viruses</u>** **Among persons aged ≥65 year, IVE against A (H3N2) was 33% (95% CI: 21; 45)** Among persons aged ≥65 year, IVE against B was 31% (95% CI: 11; 51) **Conclusion**	Quality of case-control and cohort studies (prospective and retrospective) was evaluated using the appropriate Newcastle-Ottawa Scales (NOS)

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	three studies reporting pandemic IVE adjusted for calendar time and 2/3 further adjusted for age; none of them adjusted for comorbidities.						Lower IVE among persons 65 years and older compared to adults aged 18–64 years. They noted poor performance of the seasonal influenza vaccines against influenza A(H3N2) viruses among the elderly in seasons characterized by a mismatch between vaccine and circulating strains. Real-time monitoring of antigenic drift during influenza A(H3N2) epidemics may facilitate the early implementation of alternative prevention measures, such as prophylactic use of antivirals, among the elderly. Despite the lower effectiveness of influenza vaccines compared to other vaccines of the expanded programs on immunization, seasonal vaccination remains the best and safest public health measure to reduce morbidity and mortality due to influenza. Improving communication about IVE against severe influenza could increase influenza vaccine uptake and sustain investments in the vaccines.	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up	Outcome Measures/Effect Size	General Comments
3. Remschmidt C, Wichmann O, Harder T. Vaccines for the prevention of seasonal influenza in patients with diabetes: systematic review and meta-analysis. BMC Medicine. 2015;13(1):53. Germany	**Systematic review & meta-analysis of Observational studies 6 cohort & 5 case-control** **Aim** Knowledge of the benefits and harms is important to inform decision-making for vaccination and crucial for public health authorities when defining vaccination target groups. Performed a systematic review and meta-analysis on influenza IVE/effectiveness (VE) and safety in diabetic patients of all ages. **Methods** Conducted a systematic review and meta-analysis by searching Medline, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception until November 2014. We included all types of studies reporting on the efficacy, effectiveness, and/or safety of influenza vaccination in patients with type 1 and type 2 diabetes of all ages. Residual confounding was addressed by comparing estimates of vaccine effectiveness (VE) during influenza seasons to those obtained during off-seasons. Quality of the evidence for each outcome was assessed using the GRADE methodology.	I	11 observational studies with a total of 170,924 participants were included. Patients with type 1 and type 2 diabetes Mean age 55 above	Vaccinated with any types of vaccine	Placebo/ unvaccinated	-	**<u>All-cause mortality</u>** In the elderly (65+), influenza vaccination prevented all-cause mortality (VE 38%; 95% CI, 32–43%). In cohort studies, pooled analysis of adjusted point estimates showed protective effects of influenza vaccination against all-cause mortality (adjusted VE 38%, 95% CI, 32–43%, I^2 = 0%, n = 2). Pooled analysis of case–control studies indicated that influenza vaccination prevented all-cause mortality (adjusted VE 56%, 95% CI, 47–64%, I^2 = 0%, n = 2) **<u>All-cause hospitalisation</u>** Case control study: all-cause hospitalisation (VE 23%; 95% CI, 1–40%) **<u>hospitalisation due to influenza or pneumonia (based on hospital discharge diagnosis codes)</u>** Only one study reported data on VE against hospitalisation due to influenza or pneumonia (VE 45%; 95% CI, 34–53%) **<u>influenza-like illness (ILI)</u>** ILI (VE 13%; 95% CI, 10–16%), OR: 0.87; 95% CI, 0.84-0.90. None of the studies reported data on vaccine safety and none of the studies gave data on laboratory confirmed influenza infections. However, significant off-season estimates for several outcomes indicated residual confounding, particularly in elderly patients. **Conclusion** Due to strong residual confounding in most of the identified studies, the available evidence is insufficient to determine the magnitude of benefit that diabetic people derive from seasonal influenza vaccination.	GRADE: For elderly patients (≥65), evidence on effectiveness was rated as being of very low quality due to serious risk of bias.

Evidence Table : Effectiveness and safety
Question : Is Influenza vaccination for the elderly effective and safe?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
4. Yin JK, Khandaker G, Rashid H, Heron L, Ridda I, Booy R. Immunogenicity and safety of pandemic influenza A (H1N1) 2009 vaccine: systematic review and meta-analysis. Influenza Other Respir Viruses. 2011;5(5):299–305.doi:10.1111/j.1750-2659.2011.00229.x	**Systematic review and meta-analysis (17 studies included)** **A total of 728 cases and 1,826 matched controls.** **Aim** To assess the effectiveness of influenza vaccination in preventing hospitalisation in individuals aged ≥ 60 years in Spain. **Methods** Database searched: Medline, EMBASE, the Cochrane Library and other online databases up to 1st October 2010 for studies in any language comparing different pandemic H1N1vaccines, with or without placebo, in healthy populations aged at least 6 months.	II-1	**Healthy populations** **Children aged 6-35 months** **Children 3-8 years** **Adolescents 9-17 yrs** **Adults 18-60 years** **Adult ≥ 60 years**	Influenza Vaccine Type A (H1N1) Adjuvanted vaccines	Placebo/ no vaccine Non-adjuvanted vaccines	-	**<u>The elderly (aged >60 years)</u>** The pre-injection seroprotection proportion was estimated as 9.6% (4.3–20.1%, I2 = 48.8%) based on the data of 2778 subjects. The seroresponse results were obtained for 2692 participants from six trials. After 1st / one dose of non-adjuvanted vaccine, the overall seroprotection estimate was 87.3% (82.3–91.0%, I2 = 45.4%;); a lower response was shown in those that received aluminium hydroxide-adjuvanted vaccine, 68.1% (57.6–77.0%, I2 = 43.6%). With a low antigen dose (3.75 µg) of AS03A-adjuvanted vaccine, a high proportion, 87.4% (80.1–92.3%), achieved seroprotection. After 2nd dose, all types of vaccine reported better immune responses (non-adjuvanted: 91.2%, 79.7–96.5%, I2 = 48.4%; aluminium hydroxide-adjuvanted: 91.5%, 85.5–95.1%, I2 = 33.4%; AS03A-adjuvanted: 97.0%, 88.8–99.3%). **Safety** It concluded that the benefit–risk profile of pandemic H1N1 vaccine, with or without adjuvant, continued to be positive, and the majority of post-vaccination adverse events were considered to be non-severe. **Conclusion** The pandemic influenza (H1N1) 2009 vaccine, with or without adjuvant, appears generally to be seroprotective after just one dose and safe among healthy populations aged ‡36 months; very young children (6–35 months) may need to receive two doses of non-adjuvanted vaccine or one dose of AS03A / B-adjuvanted product to achieve seroprotection.	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
5. Vu T, Farish S, Jenkins M, et al. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. Vaccine. 2002;20(13-14):1831-1836. North America and Europe	**Systematic Review and Meta-analysis (15 studies RCT, trial, cohort, case-control)** **Aim** To estimate the effectiveness of inactivated influenza vaccine in persons aged 65 years and over living in the community. **Methods** Biomedical databases used in the search included Medline, Biosis, FirstSearch, Bandolier, Cochrane Library, Current Contents, Effectiveness Matters, Derwent Drug File, American College of Physicians Journal Club and Database of Abstracts of Reviews of Effectiveness (DARE). Influenza-dedicated databases, including FluNet (the World Health Organization), the CDC Influenza Home Page (Center for Disease Control and Prevention) and the Influenza Bibliography (National Institute for Medical Research, London) were also included in the search, as were several government Internet sites. Articles selected for inclusion were searched manually to identify further publications. Two prominent researchers in the field were asked to assist in identifying unpublished studies and to review our bibliograph	I	**300-80,000 participants in the living community**	Inactivated Influenza vaccine	unvaccinated	-	**Influenza like-illness (ILI) incident (3 studies)** Influenza vaccine was effective in reducing influenza-like illness by 35% (95% confidence interval (CI) 19–47%), **hospitalisation for pneumonia and influenza** by 33% (CI 27–38%), **mortality following hospitalisation for pneumonia and influenza** by 47% (CI 25–62%); and mortality from all causes by 50% (CI 45–56%). When there is a good match between influenza strains in the vaccine and those in circulation, vaccination would prevent approximately **one in five cases of influenza-like illness, one in four hospitalisations for pneumonia and influenza and one in four deaths following hospitalisation for these conditions**. **Outpatient visits for pneumonia and influenza (2 studies)** The smallest reduction (6–26%) was found for the outcome outpatient visits for pneumonia and influenza Hospitalisation for all respiratory conditions 4: 23-36 Hospitalisation for pneumonia and influenza 9; 24-38 **Mortality following hospitalisation for pneumonia and influenza (3 studies)** The largest reduction (25–62%) was associated with the outcome mortality following hospitalisation for pneumonia and influenza. **Mortality from all causes (4 studies)** The summary estimate of reduction in all-cause mortality with and without this study was 43–55 and 45–56%, respectively. **Conclusion** Results of this meta-analysis confirm that the influenza vaccine is effective in reducing influenza-related illness and death among persons 65 years and over living in the community.	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
6. Chen CI, Kao PF, Wu MY, et al. Influenza Vaccination is Associated with Lower Risk of Acute Coronary Syndrome in Elderly Patients with Chronic Kidney Disease. Medicine. 2016;95(5):e2588.	**Retrospective Cohort** **Aim** To observe the effects of influenza vaccination on the reduction of first hospitalisations for acute coronary syndrome (ACS) in elderly patients with CKD. **Methods** Conducted a cohort study using data from the Taiwan Longitudinal Health Insurance Database 1997 to 2008. This cohort study comprised elderly patients (ages >55 years) with a recorded diagnosis of CKD (n¼4406) between January 1, 1999, and December 31, 2007. Each patient was followed up until the end of 2008. To minimize the selection bias of vaccine therapy, a propensity score adjustment was applied. The hazard ratio (HR) and 95% confidence interval (CI) for the association between the influenza vaccination and the occurrence of first hospitalisation for ACS was evaluated by Cox proportional hazards regression. We further categorized the patients into 4 groups according to their vaccination status (unvaccinated, and total number of vaccinations: 1, 2–3, and >4).	II-1	**Elderly patients with CKD (ages > 55 years). 4406 individual with CKD** From the Taiwan Longitudinal Health Insurance Database 1977-2008	2206 patients in the vaccinated group	2200 patients in the unvaccinated group	1997-2008	**<u>The rate of hospitalisation for ACS</u>** After adjusting potential confounders was significantly lower in the vaccination group (adjusted HR = 0.35, 95% CI 0.30–0.42; P<0.001) than in the unvaccinated group. Observed similar protective effects in both genders and all elderly-age groups (55–64, 65–74, and >75 years). Found that elderly CKD patients without prior CVD history receiving influenza vaccination exhibited a lower risk of hospitalisation for ACS (adjusted HR=0.35, 95% CI 0.30–0.42; P<0.001). **Observed consistent protective effects regardless of age groups (55– 64, 65–74, and >75), gender, and seasonality of influenza.** When the patients were stratified according to the total number of vaccinations**, the adjusted HRs for first ACS hospitalisation were 0.62 (95% CI 0.52–0.81), 0.35 (95% CI 0.28–0.45), and 0.13 (95% CI 0.09–0.19) for patients who received 1, 2 to 3, and >4 vaccinations.** There was a significant trend of decreasing risk of ACS hospitalisation with an increasing number of vaccinations. **<u>Risk of Acute Coronary Syndrome</u>** Influenza vaccination significantly reduced the risk of ACS hospitalisations in elderly patients with CKD irrespective of influenza seasonality. (Adjusted HR 0.25 (0.19-0.32). The Kaplan–Meier estimates of cumulative ACS event rates in the unvaccinated control were significantly higher as compared to the vaccinated group. (log-rank test, P<0.001) **Conclusion** Clinically important evidence suggesting that annual influenza vaccination is associated with a lower risk of hospitalisation for ACS in elderly patients with CKD.	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
7. Foppa IM, Cheng P-Y, Reynolds SB, et al. Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14. Vaccine. 2015;33(26):3003-3009.	**Retrospective cross-sectional study** **Aim** Excess mortality due to seasonal influenza is substantial, yet quantitative estimates of the benefit of annual vaccination programs on influenza-associated mortality are lacking. **Methods** Estimated the numbers of deaths averted by vaccination in four age groups (0.5 to 4, 5 to 19, 20 to 64 and ≥65 yrs.) for the nine influenza seasons from 2005/6 through 2013/14. These estimates were obtained using a Monte Carlo approach applied to weekly U.S. age group-specific estimates of influenza-associated excess mortality, monthly vaccination coverage estimates and summary seasonal influenza vaccine effectiveness estimates to obtain estimates of the number of deaths averted by vaccination. The estimates are conservative as they do not include indirect vaccination effects.	II-3	Number of patients with all groups : 40,127 US WHO COLLABORATING LABORATORIES AND the National Respiratory and Enteric Virus Surveillance System (NREVSS)	Vaccination with any type of vaccine	No vaccination	-	**Deaths averted by influenza vaccination** 9 years, we estimated that 40,127 (95% confidence interval [CI] 25,694 to 59,210) deaths were averted by influenza vaccination. We found that of all studied seasons the most deaths were averted by influenza vaccination during the 2012/13 season (9398; 95% CI 2,386 to 19,897) and the fewest during the 2009/10 pandemic (222; 95% CI 79 to 347). Of all influenza-associated deaths averted, **88.9% (95% CI 83 to 92.5%) were in people ≥65 yrs. Old (35, 673 patients)** **Conclusion** The estimated number of deaths averted by the US annual influenza vaccination program is considerable, especially among elderly adults and even when vaccine effectiveness is modest, such as in the 2012/13 season. **As indirect effects ("herd immunity") of vaccination are ignored, these estimates represent lower bound estimates and are thus conservative given valid excess mortality estimates**	

Evidence Table : Organizational
Question : Is annual number of death avoided by vaccination is good?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
8. Bonmarin I, Belchior E, Levy-Bruhl D. Impact of influenza vaccination on mortality in the French elderly population during the 2000-2009 period. Vaccine. 2015;33(9):1099-1101. France	**Retrospective cross-sectional study** **Aim** To estimate the annual number of deaths avoided by vaccination in the people aged 65 years or more. **Methods** Three elements: an estimate of vaccine effectiveness against all-cause mortality (based on the "difference-in-differences" approach which reduces the usual bias seen in observational studies), French mortality data and vaccine coverage data.	II-3	> 65 years old Coverage 60- 65% of population 85,411	Annual vaccinated patients	Unvaccinated patients		**Number of observed all-cause deaths= 85,411** **Number of influenza-attributable deaths=9025 (11%)** The number of influenza-attributable deaths avoided by vaccination (DAV-S) during the epidemic period varied from 1809 to 3016 according to the season, with a mean of 2485 [95%CI: 369–4591] The average number of influenza-attributable deaths expected in the absence of vaccination (DFluNv) was 11,510 [95%CI:9394–13,616] Vaccine effectiveness to avoid an influenza-attributable death (VEFlu) was estimated at 35% [95%CI: 6–55%]. To avoid a death, an average of 2647 vaccinations [95%CI: 1722–14,204] were needed. **Conclusion** We estimated an annual average of 2000 deaths currently avoided through vaccination and a vaccine effectiveness of 35% against influenza-attributable deaths. Around 2650 vaccinations are needed to prevent a death among the elderly. Communicating these results should help restoring at-risk populations' confidence in influenza vaccination	

Evidence Table : Effectiveness
Question : Is Influenza vaccination for the elderly effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
9. Dominguez A, Soldevila N, Toledo D, et al. The effectiveness of influenza vaccination in preventing hospitalisations of elderly individuals in two influenza seasons: a multicentre case-control study, Spain, 2013/14 and 2014/15. Euro surveill. 2017;22(34).	**Case-control study (A total of 728 cases and 1,826 matched controls).** **Aim** to assess the effectiveness of influenza vaccination in preventing hospitalisation in individuals aged ≥ 65 years in Spain. **Methods** A multicentre case–control study was conducted in 20 Spanish hospitals of 17 Spanish regions (Andalusia, the Basque Country, Catalonia, Castile and Leon, Madrid, Navarra and Valencian Community), covering 1,444,688 individuals aged ≥ 65 years and representing 16.8% of the Spanish population in this age group. Cases and corresponding controls admitted to participating hospitals between December 2013 and March 2015 were recruited. Patients aged ≥ 65 years who were hospitalised with laboratory-confirmed influenza were matched with controls according to sex, age and date of hospitalisation. Adjusted vaccine effectiveness (VE) was calculated by multivariate conditional logistic regression.	II-3	Patients aged ≥ 65 years who were hospitalised with laboratory-confirmed influenza Cases were considered vaccinated with the current influenza vaccine or pneumococcal vaccine if they had received a dose of the vaccine ≥ 14 days before symptom onset. Controls were considered vaccinated if they had received a dose of the influenza vaccine ≥ 14 days before the onset of symptoms of the matched case. Influenza vaccination in the previous season in cases and controls was defined as administration of the seasonal influenza vaccine during the preceding influenza season.	Cases and controls who received vaccination	Cases and controls who did not received vaccination	-	A total of 359 cases (49.3%) and 1,053 controls (57.7%) had received influenza vaccination. 433 were from the 2013/14 season and 295 were from the 2014/15 season. Overall VE was 36% (95% confidence interval (CI): 22–47). VE was 51% (95% CI: 15–71) in patients without high-risk medical conditions and 30% (95% CI: 14–44) in patients with them. VE was 39% (95% CI: 20–53) in patients aged 65–79 years and 34% (95% CI: 11–51) in patients aged ≥ 80 years, and was greater against the influenza A (H1N1) pdm09 subtype than the A (H3N2) subtype. Adjusted VE against hospitalisation was 41% (95% CI: 16–59) among those only vaccinated in the current season and 42% (95% CI: 28–54) among those vaccinated in both the current and previous season. VE among those only vaccinated in the previous season only was 24% (95% CI: −6 to 45) **Conclusion** Influenza vaccination was effective in preventing hospitalisations of elderly individuals.	

Evidence Table : Organisational
Question : Is access, provider, system and societal interventions to increase the uptake of influenza good?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. Thomas RE and Lorenzetti DL. Interventions to increase influenza vaccination rates of those 60 years and older in the community. Cochrane Database Syst Rev. 2018; In: Ovid MEDLINE	**Systematic Review** **Aim** To assess access, provider, system, and societal interventions to increase the uptake of influenza vaccination in people aged 60 years and older in the community. **Methods** We searched CENTRAL, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE, Embase, CINAHL, and ERIC for this update, as well as WHO ICTRP and ClinicalTrials.gov for ongoing studies to 7 December 2017. We also searched the reference lists of included studies. Quality of the evidence: Overall, we assessed the included studies as at moderate risk of bias. The overall GRADE assessment of the evidence was high to moderate quality.	I	Total 61 RCTs; 1,055,337 participants. Trials involved people aged 60 years and older living in the community in high-income countries	Trivalent Inactivated Influenza Vaccine, Quadrivalent Inactivated Influenza Vaccine, Live Attenuated Influenza Vaccine, Quadrivalent Live Attenuated Vaccine, Inactivated Vaccine	No vaccination		One successful intervention that could be meta-analysed was **client reminders or recalls by letter plus leaflet or postcard compared to reminder** (odds ratio (OR) 1.11, 95% confidence interval (CI) 1.07 to 1.15; 3 studies; 64,200 participants). Successful interventions tested by single studies were **patient outreach by retired teachers** (OR 3.33, 95% CI 1.79 to 6.22); **invitations by clinic receptionists** (OR 2.72, 95% CI 1.55 to 4.76**); nurses or pharmacists educating and nurses vaccinating patients** (OR 152.95, 95% CI 9.39 to 2490.67); **medical students counselling patients** (OR 1.62, 95% CI 1.11 to 2.35); and **multiple recall questionnaires** (OR 1.13, 95% CI 1.03 to 1.24). **Enhancing vaccination access (6 strategies, 8 trials, 10 arms, 9353 participants)** We meta-analysed results from two studies of home visits (OR 1.30, 95% CI 1.05 to 1.61) and two studies that tested free vaccine compared to patient payment for vaccine (OR 2.36, 95% CI 1.98 to 2.82). We were unable to conduct meta-analyses of two studies of home visits by nurses plus a physician care plan (both with 95% CI above unity) and two studies of free vaccine compared to no intervention (both with 95% CI above unity). One study of group visits (OR 27.2, 95% CI 1.60 to 463.3) was effective, and one study of home visits compared to safety interventions was not. **Provider- or system-based interventions (11 strategies, 15 trials, 17 arms, 278,524 participants)** One successful intervention that could be meta-analysed focused on payments to physicians (OR 2.22, 95%CI 1.77 to 2.77). Successful interventions tested by individual studies were: reminding	Cochrane Tools for Risk of Bias

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
							physicians to vaccinate all patients (OR 2.47, 95% CI 1.53 to 3.99); posters in clinics presenting vaccination rates and encouraging competition between doctors (OR 2.03, 95% CI 1.86 to 2.22); and chart reviews and benchmarking to the rates achieved by the top 10% of physicians (OR 3.43, 95% CI 2.37 to 4.97). We were unable to meta-analyse four studies that looked at physician reminders (three studies with 95% CI above unity) and three studies of facilitator encouragement of vaccination (two studies with 95% CI above unity). Interventions that were not effective were: comparing letters on discharge from hospital to letters to general practitioners; posters plus postcards versus posters alone; educational reminders, academic detailing, and peer comparisons compared to mailed educational materials; educational outreach plus feedback to teams versus written feedback; and an intervention to increase staff vaccination rates. **Conclusions** We identified interventions that demonstrated significant positive effects of low (postcards), medium (personalised phone calls), and high (home visits, facilitators) intensity that increase community demand for vaccination, enhance access, and improve provider/system response. The overall GRADE assessment of the evidence was moderate quality. Conclusions are unchanged from the 2014 review.	

Evidence Table : Societal
Question : Is there any barrier that may affect vaccine uptake among elderly > 65 years?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
2. Nagata JM, Hernandez-Ramos I, Kurup AS, et al. Social determinants of health and seasonal influenza vaccination in adults >=65 years: a systematic review of qualitative and quantitative data. BMC Public Health. 2013;13:388. Asia, Europe, Latin America, Middle-east. More than half were done in developed countries.	**Systematic Review (58 studies)** **13 qualitative methods, 3 mixed, 42 quantitative methods** **Aim** The objective of this study was to Explore barriers and assess the social determinants of health preventing adults ≥ 65 years old from accessing and accepting seasonal influenza vaccination. **Methods** A systematic search was performed in January 2011 using MEDLINE, ISI – Web of Science, PsycINFO, and CINAHL (1980–2011). Reference lists of articles were also examined. Selection criteria included qualitative and quantitative studies written in English that examined social determinants of and barriers against seasonal influenza vaccination among adults ≥ 65 years. Two authors performed the quality assessment and data extraction. Thematic analysis was the main approach for joint synthesis, using identification and juxtaposition of themes associated with vaccination. Qualitative data collection techniques included one-on-one interviewing,	I		-	-		Overall, 58 studies were analyzed. **1. Structural determinants** **Structural social determinants** such as age, gender, marital status, education, ethnicity, socio-economic status, social and cultural values, **2. Intermediate determinants** as well as **intermediary determinants** including housing-place of residence, behavioral beliefs, social influences, previous vaccine experiences, perceived susceptibility, sources of information, and perceived health status influenced seasonal influenza vaccination. **3. Health system** Healthcare system related factors including accessibility, affordability, knowledge and attitudes about vaccination, and physicians' advice were also important determinants of vaccination. **Conclusion** Our results demonstrate that the ability of adults ≥65 years to receive seasonal influenza vaccine is influenced by structural, intermediate, and healthcare-related social determinants which have an impact at the health system, provider, and individual levels.	

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
	questionnaires, key informant selection, focus groups, participant observation, participatory action research, and community mobilization techniques. Quantitative studies encompassed mainly descriptive studies and cross sectional surveys, two ecologic studies, and one controlled trial							

Evidence Table : Organisational
Question : Is access, provider, system and societal interventions to increase the uptake of influenza good?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
3. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalisations in the United States. Jama. 2004;292(11):1333-1340.	**Systematic Review (15 studies)** **Aim** To estimate annual influenza-associated hospitalisations in the United States by hospital discharge category, discharge type, and age group. **Methods** National Hospital Discharge Survey (NHDS) data and World Health Organization Collaborating Laboratories influenza surveillance data were used to estimate annual average numbers of hospitalisations associated with the circulation of influenza viruses from the 1979-1980 through the 2000-2001 seasons in the United States using age-specific Poisson regression models.	II-3	approximately 270000 inpatient records sampled from approximately 500 hospitals Annual averages of 94735 (range, 18 908-193 561) primary and 133900 (range, 30 757-271 529) any listed pneumonia and influenza hospitalisations were associated with influenza virus infections. Annual averages of 226 054 (range, 54 523- 430 960) primary and 294128 (range, 86 494-544 909) any listed respiratory and circulatory hospitalisations were associated with influenza virus infections.	-	-		Persons 85 years or older had the highest rates of influenza-associated primary respiratory and circulatory hospitalisations (1194.9 per 100 000 persons). Children younger than 5 years (107.9 primary respiratory and circulatory hospitalisations per 100 000 persons) had rates similar to persons aged 50 through 64 years. Estimated rates of influenza associated hospitalisations were highest during seasons in which A(H3N2) viruses predominated, followed by B and A(H1N1) seasons. After adjusting for the length of each influenza season, influenza-associated primary pneumonia and influenza hospitalisations increased over time among the elderly. There were no significant increases in influenza-associated primary respiratory and circulatory hospitalisations after adjusting for the length of the influenza season. **Conclusions** Significant numbers of influenza-associated hospitalisations in the United States occur among the elderly, and the numbers of these hospitalisations have increased substantially over the last 2 decades due in part to the aging of the population. Children younger than 5 years had rates of influenza-associated hospitalisations similar to those among individuals aged 50 through 64 years. These findings highlight the need for improved influenza prevention efforts for both young and older US residents.	Cochrane Tools for Risk of Bias

Evidence Table : Economic evaluation
Question : Is Influenza vaccination for the elderly cost-effective?

Bibliographic Citation	Study Type/Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/Effect Size	General Comments
1. D'Angiolella LS, Lafranconi A, Cortesi PA, Rota S, Cesana G, Mantovani LG. Costs and effectiveness of influenza vaccination: a systematic review. Ann Ist Super Sanita. 2018;54(1):49-57. In: Ovid MEDLINE 12 Europe, 9 USA, 3 Canada, 3 China, 1 Turkey, 1 Thailand, 1Australia and 1 Israel	**Systematic Review** **29 studies CEA, 1 study CBA** **Aim** The aim of this review is to estimate the efficiency of influenza vaccination. **Methods** The bibliographic search was performed in PubMed, Web of Science and Scopus, using "cost effectiveness" OR "cost utility" OR "cost benefit" OR "cost consequence" AND "influenza vaccination" as keywords research terms. To maximise retrieval of all pertinent papers, we applied medical subject headings (MeSH terms), or keyword searches when appropriate. Original articles that estimated cost-effectiveness, cost-utility or cost-benefit of influenza vaccination, for the entire population or specific subgroups (e.g. children, elderly), were included. Furthermore, the other inclusion criteria used to select the articles were: articles that summarize findings in English; articles not related to pandemic influenza; original studies and analyses published between January 2012 and January 2017	I	7 assessed the vaccine program in the whole population, 7 among children (0-18 years), **11 among elderly**, 3 among pregnant women, 1 among adult healthcare workers and 5 among high risk populations	**Trivalent Inactivated Influenza Vaccine (TIV), Quadrivalent Inactivated Influenza Vaccine (QIV)** Live Attenuated Influenza Vaccine, Quadrivalent Live Attenuated Vaccine, Inactivated Vaccine High-dose & Standard-dose	No vaccination		**Studies information (elderly)** Twelve out of 30 studies were performed in Europe, 9 in USA, 3 in China, 1 in Australia. All CEA papers reported the results in terms of ICER's, presented as cost per Quality Adjusted Life Year (QALY) or LY (Life Year) gained, except 1 cost per life saved. **Perspective of the analyses (elderly)** The **payer-only perspective** was adopted in 6 studies while the **societal-only perspective** was adopted in 2 studies and **both perspectives** were used in 3 studies. **Time Horizon** - **Discounting** - **Key findings** **Cost** In elderly patients, the cost associated with vaccination and no vaccination scenarios **were comparable among studies.** The majority of the costs of the vaccination program were associated with the cost of vaccine. However, the incremental cost of the vaccination program was partially counterbalanced by costs averted from additional cases of influenza and prevented hospitalisations. **Effectiveness** In elderly patients high-dose **TIV has the potential to be favoured over other vaccines (TIV SD, QIV).** QIV seemed to be effective as TIV, however several analyses indicated that QIV would deliver substantial health benefits in terms of reduced number of symptomatic influenza cases and deaths and consequent gains in QALYs and Lys.	

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							Cost-Effectiveness From the payer's perspective, eight studies had an ICER below €20,000 (2 in general population, 1 in children, **3 in elderly**, 1 in pregnant women and 1 in patients at risk). Five studies reported an ICER between €20,000 and €50,000: such studies were carried out in children (n =2), **in elderly (n=2)** and in pregnant women (n = 1) Two studies **reported QIV as a cost-saving option**, compared to TIV, for the Chinese and the German society, and in elderly and whole population, respectively. From the healthcare provider's perspective, QIV was cost-effective in young children (6 months-9 years) and elderly (≥ 80 years), but not cost-effective in other age groups (10-79 years). On the other hand, vaccinating elderly is also associated with a reduction in hospitalisations. Cost-effectiveness of QIV was reported in different subgroups and countries, showing that QIV could be a cost-effective option compared to TIV in the elderly and at high risk individuals. **Conclusion** When vaccines with different method of administration were considered, the cost-effectiveness results were highly dependent on vaccine effectiveness and population type. Some recent studies estimated that the cost-effectiveness results of LAIV in children aged 2-8 years were highly sensitive to effectiveness variation. At last, concerning the methods used, the cost-effectiveness of vaccination was assessed using a wide range of models, including decision tree models, dynamic models, Markov models, etc., and some models did not include impact of herd immunity generated by vaccine coverage. Therefore, some studies could have underestimated the benefits of influenza vaccination programs.	

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2. Shields GE, Elvidge J, Davies LM. A systematic review of economic evaluations of seasonal influenza vaccination for the elderly population in the European Union. BMJ Open. 2017;7(6):e014847.	**Systematic Review** **8 studies** **Aim** The aims were to systematically review and critically appraise economic evaluations for influenza vaccination in the elderly population in the EU. **Methods** Electronic searches of the NHS Economic Evaluation, Health Technology Assessment, MEDLINE and Embase databases were run to identify full economic evaluations. Two levels of screening were used, with explicit inclusion criteria applied by two independent reviewers at each stage. Pre-specified data extraction and critical appraisal were performed on identified studies. Results were summarised qualitatively. **Studies information** CEA, CUA-model-based EE Observational study from GP databases, National data sources, **Perspective of the analyses (elderly)** Healthcare provider and societal **Time Horizon**	I		seasonal influenza vaccination intervention	an alternative form of vaccination or antiviral treatments or usual care/no intervention		**Key findings** Results varied widely, with the incremental cost-effectiveness ratio ranging from being both more effective and cheaper than no intervention to costing €4 59 350 per life-year gained. Cost-effectiveness was most sensitive to variations in influenza strain, vaccination type and strategy, population and modelling characteristics. **Quadrivalent vaccination was cost-effective when compared with trivalent vaccination** in the base case scenario Baio et al estimated that **adjuvanted vaccination was over 90% likely to be cost-effective compared with standard vaccination.** Quadrivalent vaccination was estimated to be cost-effective in between 68% and 87% of scenarios compared with trivalent across the total modelled population. However, this was not restricted to the elderly population subgroup; thus, it is impossible to draw conclusions from this study about the uncertainty around estimates that are specific to the elderly population. One study **compared results between the low- and high-risk population.** As expected, the vaccination of high-risk individuals was demonstrated to be more cost-effective than vaccinating low-risk individuals, as this population is more susceptible to complications, which are costly and negatively impact quality of life. **A passive vaccination strategy was found to be more cost-effective compared with no intervention than a comprehensive/targeted strategy.** Comprehensive strategies are associated with greater health benefits, but the passive strategy has reduced costs as they avoid	

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	Lifetime, short-term and long-term **Discounting** Seven out of eight studies used a 1-year time horizon for costs, consistent with an influenza season and the short term/ immediate associated costs						the additional consultation costs, only vaccinating when people present at the general practitioner (GP) for other reasons. The inclusion of **herd immunity has important implications for the vaccination coverage** in the intervention and comparator arm. Herd immunity means that the impact of increasing vaccination levels is not linear, for example, an equal change in the coverage rate between studies could have very different results depending on what the comparator/usual care coverage rate is, as the scope for benefits from herd immunity will be different. While this does not affect this review because only one study included herd immunity, it is an important point for future researchers looking to compare study results as more studies including herd immunity become available in the future. **One study which compared vaccination to no intervention included probabilistic sensitivity analysis and determined that vaccination was 79.93% likely to be cost-effective (below the threshold of 3 GDP percapita).** **Conclusion** Most studies suggest that vaccination is cost-effective (seven of eight studies identified at least one cost-effective scenario). All but one study used economic models to synthesise data from different sources. The results are uncertain due to the methods used and the relevance and robustness of the data used. Sensitivity analysis to explore these aspects was limited. Integrated, controlled prospective clinical and economic evaluations and surveillance data are needed to improve the evidence base. This would allow more advanced modelling techniques to characterise the epidemiology of influenza more accurately and improve the robustness of cost-effectiveness estimates.	

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Author	Population	Study	Key results	Conclusion	Comment
3. Yue M, Dickens BL, Yoong JS-y, et al. Cost-Effectiveness Analysis for Influenza Vaccination Coverage and Timing in Tropical and Subtropical Climate Settings: A Modeling Study. Value in Health. 2019;22(12):1345-1354.	**A modelling study** The simulation model was based on a population size of 10 000 with 1000 independent Monte Carlo simulations to obtain reliable comparisons between scenarios.	**Aim** To study optimal vaccination scheduling and assess cost-effectiveness of these vaccination schedules in scenarios of no influenza seasonality and the seasonality regimes of Singapore, Taipei, and Tokyo. **Methods** The simulation models heterogeneities in human contact networks, levels of protective antibodies following infection, the effectiveness of the influenza vaccine, and seasonality. Using a **no intervention baseline,** we consider 3 alternative vaccination strategies: (1) annual vaccination for a percentage of the elderly, (2)biannual vaccination for a percentage of the elderly, (3) annual vaccination for all elderly and a fraction of the remaining population. 5 vaccination uptake rates: 20, 40, 60, 80, 100 were considered for each strategy. One-way sensitivity analysis was conducted to account for the uncertainty in the data owing to a lack of unambiguous reference values. By increasing (decreasing) **mortality rate**, **mortality cost**, **hospital rate**, **hospital cost, outpatient rate, outpatient cos**t, and **vaccination cost** by 25% at each time	**Key findings** **-Incremental cost are reported in USD** **-Singapore willingness-to-pay of $52 961/QALY** **-Fixed uptake rate: 20, 40, 60, 80, 100%** **-From societal perspective** **<u>3 Different strategies</u>** -Therefore, in Singapore, **annual vaccination** for a proportion of elderly **is largely cost-effective**. -However, with fixed uptake rates, **partial biannual vaccination for the elderly yields a higher ICER than partial annual vaccination** for the elderly, resulting in a cost-ineffective ICER. -The most optimal strategy is the total **vaccination of all the elderly and a proportion of individuals from other age groups**, which **results in a cost-saving ICER.** This finding is consistent across different seasonality regimes. From a societal perspective there can be greater savings by vaccinating more nonelderly people. **<u>Sensitivity analysis</u>** -The tornado diagram showed that **vaccination cost and vaccine efficacy** have an important effect on cost-effectiveness, whereas mortality costs, hospitalization rate, and hospitalization cost have the least effect on ICERs.	**Conclusion** Tropical countries like Singapore can have comparably cost-effective vaccination strategies as found in countries with winter epidemics. The **vaccination of all the elderly and a proportion of other age groups is the most cost-effective strategy,** supporting the need for an extensive national influenza vaccination program	