FINAL ANNEXES

Vaccines against influenza: WHO position paper – May 2022

Contents

Annex 1. Target group: Health workers – evidence-to-recommendations framework

Question: Should health workers be a target group for seasonal influenza vaccination?
Population: Health workers
Intervention: Seasonal influenza vaccination
Comparison(s): No seasonal influenza vaccination
Outcome: Seasonal influenza

Background: Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Influenza occurs globally; in temperate climates, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza may occur throughout the year, causing outbreaks more irregularly.
Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to escape control by strain-specific immunity in the population. Compared to the general population, health workers are at increased risk of exposure to respiratory pathogens, including influenza, with potential threat for their own health and for the safety of their patients.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Compared to adults working in non-health-care settings, health workers (HWs) are at significantly higher risk of contracting influenza. A 2011 review and meta-analysis evaluated the annual incidence of influenza among HWs. Pooled influenza incidence rates (IRs) per 100 HWs per season, and corresponding incidence rate ratios (IRRs) as compared to those for healthy adults, were as follows. For symptomatic infections in unvaccinated HWs, the IR was 7.5 (95%CI: 4.9–11.7) and the IRR, 1.5 (95%CI: 0.4–2.5); in vaccinated HWs the IR was 4.8	–

					(95%CI: 3.2–7.2) and IRR, 1.6 (95%CI: 0.5–2.7) *(1)*. A 2016 meta-analysis on the occupational risk of pandemic H1N1 in HWs compared to the general population, or across occupations, showed a significantly increased odds ratio (OR) in unvaccinated HWs of 2.08 (95%CI: 1.73–2.51), with a higher risk in physicians (OR=6.03; 95%CI: 2.11–17.8) *(2)*.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A 2018 paper reported the findings of several studies showing evidence of the benefits of influenza vaccination for HWs *(3)*: i) A 2011 meta-analysis of 29 studies covering 97 influenza seasons with 58 245 study participants found that influenza vaccination is effective in protecting HWs and reducing infection, both symptomatic and asymptomatic *(1)*. ii) A randomized controlled trial in 1999, found that vaccine efficacy in HWs was 88% for influenza A, and 89% for influenza B. Moreover, vaccination contributed to a decrease in cumulative days of febrile respiratory illness in HWs and days of absence *(4)*. iii) A 2011 systematic review concluded that there was limited evidence to suggest that vaccination reduces laboratory-confirmed influenza infection in HWs. No evidence was found of vaccination significantly reducing incidence of influenza; number of	–

					episodes of influenza-like illness (ILI); days with ILI symptoms, or amount of sick leave taken among vaccinated HWs. There are insufficient data from these studies to assess the adverse effects after vaccination, although the vaccine safety profile in HWs is assumed to correspond to that in healthy adults *(5)*. A 2016 Cochrane review suggests that evidence around vaccinating HWs to protect the populations they are caring for (i.e. individuals aged ≥60 years in long-term care institutions (LTCIs)) is often limited and of poor quality. Vaccination of HWs may have little or no effect for residents of LTCIs in terms of reduction of laboratory-proven infections (pooled risk difference (RD)= 0). Vaccinating HWs probably reduces lower respiratory tract infection in residents from 6% to 4% (RD= -0.02), but has very little or no effect in reducing upper respiratory illness (RD= 0) *(6)*. No evidence is available from hospitals and other health-care settings, including from low- and middle-income countries (LMICs).	
	<u>Harms of the intervention</u> Are the undesirable	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A 2018 Cochrane review on vaccines for preventing influenza in healthy adults *(7)* found no evidence of an association between seasonal inactivated vaccines and Guillain-Barré syndrome; between H1N1 pandemic vaccine and Guillain-Barré	–

	anticipated effects small?		syndrome; or between seasonal inactivated influenza vaccine and other serious adverse events such as multiple sclerosis, optic neuritis, or immune thrombocytopenic purpura *(7)*. Despite a higher reactogenicity with some newer and enhanced influenza vaccines, a large body of evidence suggests an acceptable safety profile *(8)*.	
	Balance between benefits and harms	*Favours inter-vention* ☒ | *Favours com-parison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Balancing benefits and harms, the intervention is favoured.	–
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☐ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☐	For risk of bias assessments and grading of evidence on specific vaccines, and for various outcomes in healthy adults (which health workers are assumed to be in the majority of cases), please refer to the 2018 Cochrane review *(7)* and the 2020 European Centre for Disease Prevention and Control systematic review *(8).*	–
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☒ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	The relative importance of the desirable and undesirable outcomes related to the intervention and the comparison varies. There is possible uncertainty and variability in the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine/natural immunity) and the undesirable outcomes (i.e. reactogenicity of the vaccine/disease). Different population groups may have different opinions regarding the weights	–

			assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☒	The weight that the target population assigns to the desirable and undesirable effects of influenza vaccination varies.	–
RESOURCE USE	Are the resources required small?	*No* ☒ | *Uncertain* ☐ | *Yes* ☐ | *Varies* ☐	Considerable resources will be needed to ensure implementation of an influenza vaccination programme in HWs; however resources may be smaller than for other population groups which may be more difficult to identify and target.	–
	Cost–effectiveness	*No* ☐ | *Uncertain* ☐ | *Yes* ☐ | *Varies* ☒	A 2018 systematic review and meta-analysis concluded that all published economic evaluations consistently found that vaccination of HWs was cost-saving based on crude estimates of avoided absenteeism from vaccination. However, no studies comprehensively evaluated both health outcomes and costs of vaccination programmes to examine cost–effectiveness *(9)*. Additional studies, not included in the review, suggest that influenza vaccination of HWs is likely to be cost–effective under specific assumptions *(10, 11)*.	Limited data are available from LMICs.

EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	Influenza vaccines administered to HWs in different settings, particularly LMICs, may have considerable impact on reducing health inequities by minimizing the risk of disease in this group, and safeguarding health systems by ensuring a healthy workforce.	–
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-ventio n* ☐	*Com paris on* ☐	*Both* ☒	*Neith er* ☐	*Un-clear* ☐	Public health priorities differ by setting and may vary considerably, based on different parameters such as disease burden, demographics, the need for competing intervention, etc.	–
	Which option is acceptable to target group?	*Inter-ventio n* ☐	*Com paris on* ☐	*Both* ☐	*Neith er* ☐	*Un-clear* ☒	The main determinants of vaccine acceptance among HWs have been largely investigated *(3)*; they include the desire to protect self and family above concerns about absolute risk of disease or desire to protect patients. Concerns regarding vaccine safety is a reason for decreased vaccine uptake. Vaccine hesitancy is associated with several issues such as low perception of risk of disease; denial of the social benefits of influenza vaccination; low social pressure to be vaccinated; lack of perceived behavioural control; a negative attitude toward vaccines; no previous vaccination against influenza; no previous	–

			influenza disease; lack of adequate influenza-specific knowledge; lack of access to vaccination facilities; and sociodemographic variables *(3)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	Given that this target group is easy to identify and to target, implementation of programmes to vaccinate HWs, including in LMICs, is assumed to be feasible (e.g. via vaccination at the workplace which should have the necessary infrastructure).	–

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

	☐ Only in specific contexts or specific (sub)populations
Recommendation (text)	Please see WHO Influenza vaccine position paper: https://apps.who.int/iris/bitstream/handle/10665/354264/WER9719-eng-fre.pdf
Implementation considerations	As above
Monitoring and evaluation	As above
Research priorities	As above

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Annex 2. Target group: Individuals with underlying conditions and comorbidities – evidence-to-recommendations framework

Question: Should individuals with comorbidities be a target group for seasonal influenza vaccination?
Population: Individuals with certain underlying conditions and comorbidities.
Intervention: Seasonal influenza vaccination
Comparison(s): No seasonal influenza vaccination
Outcome: Seasonal influenza

Background: Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Influenza occurs globally; in temperate climates, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza may occur throughout the year, causing outbreaks more irregularly.

Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to escape control by strain-specific immunity in the population. Risk groups include those at increased risk of exposure to influenza virus as well as those at particular risk of developing severe disease (i.e. disease resulting in hospitalization or death). Certain underlying conditions, comorbidities and risk factors (e.g. chronic lung disease, cardiovascular disease, neuromuscular disorders, HIV) are associated with an increased risk of severe influenza.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	A 2011 systematic review and meta-analysis *(1)* showed that individuals with influenza who had any underlying condition or comorbidity, had a significantly higher risk of death (OR=2.04; 95%CI: 1.74–2.39); pneumonia (OR=1.53; 95%CI: 1.04–2.24); hospital admission (OR=3.39; 95%CI: 2.60–4.42); or admission to an intensive care unit (ICU) (OR=1.74; 95%CI: 1.32–2.29). Immunocompromised individuals with influenza likewise had a significantly higher	–

				risk of death (OR=3.81; 95%CI: 1.28–11.35). Limited evidence from one study suggests a non-significant increased risk of death in persons living with HIV (OR=3.87; 95%CI: 0.52–28.96).	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐ *Un-certain* ☐ *Yes* ☒	*Varies* ☐	Systematic reviews have shown that influenza vaccination has a protective effect in persons living with asthma *(2)*; in immunosuppressed adults with cancer *(3)*; in patients with chronic obstructive pulmonary disease (COPD) *(4)*; and people with cystic fibrosis *(5)*. Adjuvanted and high-dose influenza vaccines result in high vaccine immunogenicity responses in HIV infected and immunocompromised persons *(6, 7)*.	–
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Un-certain* ☐ *Yes* ☒	*Varies* ☐	Traditional influenza vaccines are well tolerated in people with underlying conditions and comorbidities *(2–5)*. Adjuvanted-influenza vaccination showed good tolerability in persons infected with HIV, the only adverse effect being a significant increase in the rate of local pain at injection site (RR=2.03; 95%CI: 1.06-3.86) *(7)*. A recent study showed that high-dose influenza vaccine is more effective than a standard dose seasonal influenza vaccine *(8)*.	–

			Restrictions apply to the administration of live-attenuated influenza vaccines (LAIVs) in certain (age-) groups with comorbidities or underlying conditions.	
	Balance between benefits and harms	*Favours intervention* ☒ | *Favours comparison* ☐ | *Favours both* ☐ | *Favours neither* ☐ | Unclear ☐	Balancing benefits and harms, the intervention is favoured	–
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☐ Safety of the intervention: *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☐ | *High* ☐	For risk of bias assessments and grading of evidence on specific vaccines, and for various outcomes in people with underlying conditions and comorbidities, please refer to the Cochrane systematic reviews of evidence *(2–5)*.	–
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☒ | *Probably no important uncertainty or variability* ☐ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	The relative importance of the desirable and undesirable outcomes related to the intervention and the comparison varies. There is possible uncertainty and variability to the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine/natural immunity) and the undesirable outcomes (i.e. reactogenicity of the vaccine/disease). Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	–

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	The target population probably assigns more weight to the desirable effects than to the undesirable effects related to influenza vaccination.	–
RESOURCE USE	Are the resources required small?	*No* ☒		*Un-certain* ☐	*Yes* ☐		*Varies* ☐	Considerable resources will be needed to ensure the implementation of an influenza vaccination programme in people with certain underlying conditions and comorbidities.	–
	Cost–effectiveness	*No* ☐		*Un-certain* ☒	*Yes* ☐		*Varies* ☐	Formal global cost–effectiveness analyses have been conducted on vaccination of people with underlying conditions and comorbidities. Individual studies are inconclusive, particularly on the cost–effectiveness in low-resource settings. A cost–effectiveness analysis from Belgium suggests that vaccinating people with underlying illnesses is probably highly cost–effective for the age group >50 years, and borderline cost–effective for younger age groups, depending on relative life expectancy and vaccine efficacy in this risk group compared to the general population *(9)*. A study in the Netherlands found that if, as current evidence suggests, inactivated	–

						influenza vaccine reduces only severe disease outcomes, annual immunization of medically high-risk children is unlikely to be cost–effective *(10)*.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Influenza vaccines administered to people with underlying illnesses in different settings, particularly LMICs, may have considerable impact on reducing health inequities by minimizing the risk of severe disease in this vulnerable group.	–
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-vention* ☐	*Com parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☒	Public health priorities differ by setting and may vary considerably, based on different parameters such as disease burden, demographics, the need for competing intervention, etc.	–
	Which option is acceptable to target group?	*Inter-vention* ☐	*Com parison* ☐	*Both* ☐	*Neither* ☐	*Un-clear* ☒	Acceptability of seasonal influenza vaccination may vary between (sub)population groups and is correlated with social determinants such as age, sex, marital status, education, ethnicity, socioeconomic status, social and cultural values, as well as intermediary determinants including housing/place of residence, behavioural beliefs, social influences, previous vaccine experiences, perceived susceptibility to infection,	–

			sources of information, and perceived health status *(11)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒	Vaccination platforms for those with underlying conditions and comorbidities may not be currently available in many LMICs, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities.	–

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

		☐ Only in specific contexts or specific (sub)populations		
Recommendation (text)	Please see WHO Influenza vaccine position paper: https://apps.who.int/iris/bitstream/handle/10665/354264/WER9719-eng-fre.pdf			
Implementation considerations	As above			
Monitoring and evaluation	As above			
Research priorities	As above			

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Annex 3. Target group: Older adults – evidence-to-recommendations framework

Question: Should older adults be a target group for seasonal influenza vaccination?
Population: Older adults
Intervention: Seasonal influenza vaccination
Comparison(s): No seasonal influenza vaccination
Outcome: Seasonal influenza

Background: Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Influenza occurs globally; in temperate climates, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza may occur throughout the year, causing outbreaks more irregularly.
Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to escape control by strain-specific immunity in the population. Risk groups for influenza include those at increased risk of exposure to influenza virus as well as those at particular risk of developing severe disease (i.e. disease resulting in hospitalization or death). Older age (aged 60 years and older) is associated with an increased risk of severe influenza.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Influenza is an important contributor to mortality in older people. People aged >60 years are at the highest risk of influenza-associated mortality and account for a disproportionately high percentage of influenza-associated deaths in countries of all income groups, in both temperate and subtropical areas. The 2017 Global Burden of Disease Study modelled the incidence, hospitalizations, and mortality of lower respiratory tract infections (LRTIs) attributable to influenza for all countries	–

					studied, and selected subnational locations by age and year from 1990 to 2017. The influenza LRTI mortality rate was highest among adults aged >70 years (16.4 deaths per 100 000 [95%CI: 11.6–21.9]) *(1)*. Further, a systematic review of people aged ≥65 years found a significant increase both in risk of death (OR=2.95; 95%CI: 1.53–5.70) and in hospital admission (OR=4.65; 95%CI: 1.74–12.41) compared with non-elderly people *(2)*. A modelling study estimated influenza-related excess mortality rates of 2.9–44.0 per 100 000 individuals for people aged 65–74 years; and of 17.9–223.5 per 100 000 for people aged >75 years *(3)*.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A 2017 systematic review estimated a pooled vaccine effectiveness (VE) of 37% (95%CI: 30–44) against any type of influenza in older adults (≥65 years) *(4)*. A 2018 Cochrane review concluded that older adults receiving the influenza vaccine may experience less influenza during a single season compared with placebo or no intervention (6% vs 2.4%; RR=0.42; 95%CI: 0.27‑0.66), and probably less ILI compared with those who receive no vaccination (3.5% vs 6%; RR=0.59; 95%CI 0.47–0.73) *(5)*. During the course of 5 seasons, in adults aged ≥65 years in the United States of America, VE was 14% (95%CI: -14–36) against A(H3N2) viruses; 49% (95%CI: 22–	While there is a paucity of randomized controlled trials of inactivated influenza vaccine among adults aged ≥60 years, many observational studies of the effectiveness of these vaccines in this age group have been conducted. Further, influenza vaccine efficacy and VE may vary by year. This is based on the degree of antigenic match between strains selected for inclusion in the vaccine and circulating strains *(8, 9)*.

				66) against A(H1N1)pdm09; and 62% (95%CI 44–74) against B viruses *(6)*. Enhanced and newer influenza vaccines, including adjuvanted and high-dose vaccines, provide better efficacy and/or effectiveness for older adults than traditional influenza vaccines *(7)*.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Serious adverse events following vaccination are rare, although influenza vaccines are reactogenic in older adults. While few studies assess safety of seasonal influenza vaccination in older adults, the safety profile of the vaccines is acceptable *(5)*. Enhanced and newer vaccines have been associated with increased reactogenicity compared with standard-dose, but not with increased risk of serious adverse events *(7)*.	–
	Balance between benefits and harms	*Favours inter-vention* ☒	*Favours com-parison* ☐	*Favours both* ☐	*Favours neither* ☐	Unclear ☐	Balancing benefits and harms, the intervention is favoured.	–
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Mod-erate* ☐	*High* ☐	For risk of bias assessments and grading of evidence on specific vaccines, and for various outcomes in older adults, please refer to the 2020 European Centre for Disease Prevention and Control systematic review *(7)*, and the 2018 Cochrane review *(10)*.	–
		Safety of the intervention *No included studies* ☐	*Very low* ☐	*Low* ☐	*Mod-erate* ☐	*High* ☐		
VALUES		*Importa nt uncertai*	*Possibly importa nt*	*Probabl y no importa*	*No importa nt*	*No known undesira*		–

	How certain is the relative importance of the desirable and undesirable outcomes?	*nty or variability* ☒ / *uncertainty or variability* ☐ / *nt uncertainty or variability* ☐ / *uncertainty or variability* ☐ / *ble outcomes* ☐	The relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine) and the undesirable outcomes (i.e. reactogenicity of the vaccine), varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☒ / *Yes* ☐ / *Varies* ☐	The target population probably assigns more weight to the desirable effects than to the undesirable effects related of influenza vaccination.	–
RESOURCE USE	Are the resources required small?	*No* ☒ / *Uncertain* ☐ / *Yes* ☐ / *Varies* ☐	Considerable resources will be needed to ensure the implementation of an influenza vaccination programme in older adults. However, most published studies show that use of influenza vaccination results in an overall reduction in expenditures, although data from LMICs are limited *(11, 12)*.	A substantial number of economic evaluations of influenza vaccine and vaccination programmes have been conducted, mainly in high-income countries.
		No / *Uncertain* / *Yes* / *Varies*		–

	Cost–effectiveness	☐	☐	☒	☐					Formal global cost–effectiveness analyses have been conducted, but the emerging evidence stems mainly from high-income settings. Data suggest that vaccination of older adults is cost–effective *(12)*.	
EQUITY	What would be the impact on health inequities?	*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*					Influenza vaccines administered to older adults in different settings, particularly LMICs, may have considerable impact on reducing health inequities by minimizing the risk of severe disease in this vulnerable group.	–
		☐	☐	☒	☐						
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-ventio n*	*Com paris on*	*Both*	*Neith er*	*Un-clear*				Public health priorities differ by setting and may vary considerably, based on different parameters such as disease burden, demographics, the need for competing intervention, etc.	–
		☐	☐	☐	☐	☒					
	Which option is acceptable to target group?	*Inter-ventio n*	*Com paris on*	*Both*	*Neith er*	*Un-clear*				Acceptability of seasonal influenza vaccination may vary between (sub)population groups and is correlated with social determinants such as age, sex, marital status, education, ethnicity, socioeconomic status, social and cultural values, as well as intermediary determinants including housing/place of residence, behavioural beliefs, social	–
		☐	☐	☐	☐	☒					

			influences, previous vaccine experiences, perceived susceptibility to infection, sources of information, and perceived health status *(13)*.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | *Varies* ☒	Vaccination platforms for older adults may not be currently available in many LMICs, and in some regions of high-income countries, particularly in hard-to-reach or otherwise already disadvantaged communities. COVID-19 vaccination efforts may be leveraged for administration of vaccines to new target populations.	–

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

	☐ Only in specific contexts or specific (sub)populations
Recommendation (text)	Please see WHO Influenza vaccine position paper: https://apps.who.int/iris/bitstream/handle/10665/354264/WER9719-eng-fre.pdf
Implementation considerations	As above
Monitoring and evaluation	As above
Research priorities	As above

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Annex 4. Target group – Pregnant women: evidence-to-recommendations framework

Question: Should pregnant women be a target group for seasonal influenza vaccination?
Population: Pregnant women
Intervention: Seasonal influenza vaccination
Comparison(s): No seasonal influenza vaccination
Outcome: Seasonal influenza

Background: Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Influenza occurs globally; in temperate climates, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza may occur throughout the year, causing outbreaks more irregularly.
Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to escape control by strain-specific immunity in the population. Pregnant women are increasingly being targeted for immunization using inactivated seasonal influenza vaccines, both to protect them and to provide their newborn infants with passive protection via transplacentally-transferred maternal antibodies up to the time infants can receive the vaccine themselves (i.e. at age 6 months).

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	A 2017 systematic review and 2019 meta-analysis showed that pregnant women with influenza have a 7 times higher risk of hospital admission (OR=6.80; 95%CI: 6.02–7.68), a lower risk of ICU admission (OR=0.57; 95%CI: 0.48–0.69), and no significant association with death (OR=1.00; 95%CI 0.75–1.34) *(1, 2)*.	–
BENEFITS	Benefits of the intervention	*No*	*Un-certain*	*Yes*	*Varies*	Data show that vaccination provides effective protection against influenza for	–

	Are the desirable anticipated effects large?	☐ ☐ ☒ ☐	pregnant women *(3)* and their offspring through transfer of maternal antibodies *(4)* against influenza.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* *Un-certain* *Yes* *Varies* ☐ ☐ ☒ ☐	Clinical trials and observational studies have found no evidence that receipt of inactivated influenza vaccine is associated with any adverse effects in pregnant women (either HIV-uninfected or HIV-infected) or their newborn infant; this includes studies of fetal death, spontaneous abortion, and congenital malformations *(5–7)*.	–
	Balance between benefits and harms	*Favours inter-vention* *Favours com-parison* *Favours both* *Favours neither* Unclear ☒ ☐ ☐ ☐ ☐	Balancing benefits and harms, the intervention is favoured.	–
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* *Very low* *Low* *Mod-erate* *High* ☐ ☐ ☐ ☐ ☐ Safety of the intervention *No included studies* *Very low* *Low* *Mod-erate* *High* ☐ ☐ ☐ ☐ ☐	For risk of bias assessments and grading of evidence on specific vaccines, and for various outcomes in pregnant women, please refer to systematic reviews in the References section *(3)(4).*	–
VALUES & PREFERENC	How certain is the relative importance of the desirable and	*Importa nt uncertai nty or variabilit y* *Possibly importa nt uncertai nty or variabilit y* *Probabl y no importa nt uncertai nty or variabilit y* *No importa nt uncertai nty or variabilit y* *No known undesira ble outcome s*	The relative importance of the intervention, as well as the relative weights that the target population attributes to the desirable outcomes (i.e. protection conferred by the vaccine) and the	–

	undesirable outcomes?	☐ ☒ ☐ ☐ ☐	undesirable outcomes (i.e. reactogenicity of the vaccine), varies. Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies* ☐ ☐ ☐ ☐ ☐ ☒	The weight that the target population assigns to the desirable effects and the undesirable effects related to influenza vaccination varies.	–
RESOURCE USE	Are the resources required small?	*No* *Uncertain* *Yes* *Varies* ☒ ☐ ☐ ☐	Considerable resources will be needed to ensure the implementation of an influenza vaccination programme in pregnant women; however resources may be smaller than for other population groups which may be more difficult to identify and target.	–
	Cost–effectiveness	*No* *Uncertain* *Yes* *Varies* ☐ ☐ ☐ ☒	Data from various settings (Belgium, Japan, Mali, and the USA) suggest that vaccination during pregnancy can be cost–effective under specific assumptions *(8–11)*.	–
EQ		*Increased* *Uncertain* *Reduced* *Varies*		–

	What would be the impact on health inequities?	☐ ☐ ☒ ☐	Influenza vaccines administered to pregnant women in different settings, particularly LMICs, may have considerable impact on reducing health inequities, by protecting women and their newborn infants, particularly in resource-constrained settings with limited access to health care.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Public health priorities differ by setting and may vary considerably, based on different parameters such as disease burden, demographics, the need for competing intervention, etc.	–
	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☒	Acceptance and uptake of influenza vaccine during pregnancy may vary by setting and (sub)population *(12–16)*.	–
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Given that antenatal contacts could be used to administer vaccination during pregnancy, vaccination of pregnant women is assumed to be feasible to implement, including in LMICs.	–

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	Please see WHO Influenza vaccine position paper: https://apps.who.int/iris/bitstream/handle/10665/354264/WER9719-eng-fre.pdf				
Implementation considerations	As above				

Monitoring and evaluation	As above
Research priorities	As above

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Annex 5. Target group: Children – evidence-to-recommendations framework

Question: Should children (<5 years) be a target group for seasonal influenza vaccination?
Population: Children (<5 years)
Intervention: Seasonal influenza vaccination
Comparison(s): No seasonal influenza vaccination
Outcome: Seasonal influenza

Background: Influenza A and B viruses are important human respiratory pathogens which are transmitted mainly by droplets and aerosols originating from the respiratory secretions of infected people, but occasionally also through contact with virus contaminated fomites. Both A and B viruses cause seasonal influenza epidemics and out-of-season sporadic cases and outbreaks. Influenza occurs globally; in temperate climates, seasonal epidemics are experienced mainly during the winter, while in tropical regions influenza may occur throughout the year, causing outbreaks more irregularly.
Influenza A viruses may also cause worldwide pandemics characterized by rapid dissemination of new influenza A subtypes (or strains of subtypes) that have the capacity for human-to-human transmission and are sufficiently different antigenically from recently circulating influenza viruses to escape control by strain-specific immunity in the population. Children aged under 5 years, in particular under 2 years, have a high burden of influenza. Two types of vaccines are available: live-attenuated influenza vaccines (LAIVs) for children aged 24 months and older; and inactivated vaccines which can be given to children as young as 6 months of age.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The 2017 Global Burden of Disease Study concludes that incidences of non-hospitalized and hospitalized influenza LRTIs are high in children aged <5 years, with the greatest number of LRTI episodes of all age-groups *(1)*. A 2020 systematic review and modelling study found that in 2018, among children aged <5 years globally, influenza accounted for 4% of deaths due to acute lower respiratory infection (ALRI), with an estimated 34 800 overall influenza-virus-associated ALRI	–

					deaths *(2)*. Nonetheless, evidence on the burden of severe disease and deaths are limited and vary by setting. While some data, mainly from high-income countries, show a high burden of hospitalization and death in the youngest children (<5 years of age), other studies have not found the same burden in low-income countries *(3)*.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A 2018 Cochrane review *(4)* concludes that compared with placebo or no intervention, LAIVs probably reduce the risk of influenza infection in children aged 3–16 years from 18% to 4% (RR=0.22; 95%CI: 0.11–0.41; 7718 children; moderate-certainty evidence); and may reduce ILI by a smaller degree, from 17% to 12% (RR=0.69; 95%CI: 0.60–0.80; 124 606 children; low-certainty evidence). Compared with placebo or no vaccination, inactivated vaccines reduce the risk of influenza in children aged 2–16 years from 30% to 11% (RR=0.36; 95%CI: 0.28–0.48; 1628 children; high-certainty evidence), and probably reduce ILI from 28% to 20% (RR=0.72; 95%CI: 0.65–0.79; 19 044 children; moderate-certainty evidence).	–
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Data from 4 studies on live attenuated vaccines measuring fever following vaccination vary considerably, with a range of 0.16–15% in children who had received live vaccines, to 0.71–22% in the placebo groups (very low-certainty evidence).	–

			Limited data of inactivated vaccines in children are available. Generally LAIV is very well-tolerated in healthy children *(4)*.	
	Balance between benefits and harms	*Favours inter-vention*: ☒ / *Favours com-parison*: ☐ / *Favours both*: ☐ / *Favours neither*: ☐ / Unclear: ☐	Balancing benefits and harms, the intervention is favoured.	–
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention: *No included studies*: ☐ / *Very low*: ☐ / *Low*: ☐ / *Mod-erate*: ☒ / *High*: ☐ Safety of the intervention: *No included studies*: ☐ / *Very low*: ☐ / *Low*: ☐ / *Mod-erate*: ☒ / *High*: ☐	For risk of bias assessments and grading of evidence on specific vaccines and for various outcomes in healthy children, please see the 2018 Cochrane review *(4)*.	–
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability*: ☐ / *Possibly important uncertainty or variability*: ☒ / *Probably no important uncertainty or variability*: ☐ / *No important uncertainty or variability*: ☐ / *No known undesirable outcomes*: ☐	The relative importance of the desirable and undesirable outcomes related to the intervention and the comparison varies. There is possible uncertainty and variability in the relative weights that the target population attributes to these desirable outcomes (i.e. protection conferred by the vaccine/natural immunity), and the undesirable outcomes (i.e. reactogenicity of the vaccine/disease). Different population groups may have different opinions regarding the weights assigned to desirable and undesirable outcomes.	–

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒	The weight that the target population assigns to the desirable effects and the undesirable effects related to influenza vaccination varies.	–
RESOURCE USE	Are the resources required small?	*No* ☐ *Un-certain* ☐ *Yes* ☐ *Varies* ☒	Considerable resources will be needed for implementation of an influenza vaccination programme in children. However, given the possibility of co-administration with other vaccines in routine childhood immunization programmes, resources may be smaller than for other population groups which may be more difficult to identify and target.	–
	Cost–effectiveness	*No* ☐ *Un-certain* ☒ *Yes* ☐ *Varies* ☐	A systematic review of economic evaluations on influenza vaccines in LMICs concluded that seasonal influenza vaccination in children aged <2 years, and in children with high-risk conditions is cost–effective *(5)*. Global systematic reviews confirm that most studies on influenza vaccination of children are cost-saving or cost–effective *(6, 7)*.	–

						Given the very high incidence rates of influenza virus infection and illness in young children, along with the sustained shedding of high levels of virus in their respiratory secretions and very effective mixing, especially in schools, it is plausible that achieving high levels of vaccine-induced immunity in school children can reduce the rates of influenza virus infection and illness in other age groups in the community, in the absence of vaccination of those individuals.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	Influenza vaccines administered to children in different settings, particularly LMICs, may have considerable impact on reducing health inequities by minimizing the risk of severe influenza disease in this group and potentially reducing the risk of transmission to other vulnerable groups.	–
ACCEPTABILITY	Which option is acceptable to key stakeholders (e.g. ministries of health, immunization managers)?	*Inter-ventio n* ☐	*Com paris on* ☐	*Both* ☒	*Neith er* ☐	*Un-clear* ☐	Public health priorities differ by setting and may vary considerably, based on different parameters such as disease burden, demographics, the need for competing intervention, etc.	–
	Which option is acceptable to target group?	*Inter-ventio n*	*Com paris on*	*Both*	*Neith er*	*Un-clear*	Several studies address the issue of (parental) acceptance of influenza vaccination in children. Acceptance levels vary by setting and population group.	–

		☐	☐	☐	☐	☒				
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Un-certain* ☒	*Probably Yes* ☐	*Yes* ☐	*Varies* ☐	LAIV is very easy to implement without skilled vaccinators. In certain settings, implementation may be feasible by leveraging existing childhood immunization programmes and/or school setting.		–
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐		The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐		Desirable consequences *probably outweigh* undesirable consequences in most settings ☒	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐		
Type of recommendation		We recommend the intervention ☐	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific (sub)populations				We recommend the comparison ☐	We recommend against the intervention and the comparison ☐		

Recommendation (text)	Please see WHO Influenza vaccine position paper: https://apps.who.int/iris/bitstream/handle/10665/354264/WER9719-eng-fre.pdf
Implementation considerations	As above
Monitoring and evaluation	As above
Research priorities	As above

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