SEASONAL INFLUENZA VACCINES: An overview for decision-makers
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CONTENTS

1. Executive Summary ......................................................... iv

2. Introduction ........................................................................ 1
   2.1 Seasonal influenza ......................................................... 1
   2.2 Why is having a seasonal influenza vaccination programme important? ......................................................... 1

3. Burden of disease .................................................................. 2
   3.1 Monitoring influenza ......................................................... 2
   3.2 The burden of seasonal influenza ......................................... 3
   3.3 Vaccine cost effectiveness .................................................. 4

4. About seasonal influenza vaccines ........................................ 5
   4.1. Vaccine types .............................................................. 5
   4.2. Vaccine composition ....................................................... 6
   4.3. Vaccine production ......................................................... 7
   4.4. Vaccine storage ............................................................ 7
   4.5. Vaccine costs .............................................................. 7
   4.6. Vaccine effectiveness, safety and uptake .................................. 8

5. Seasonal influenza vaccine coverage ...................................... 11
   5.1. Estimates of global coverage ........................................... 11
   5.2. Estimates of regional coverage ........................................ 13

6. Other prevention and control measures ................................... 14
   6.1. Antivirals ................................................................. 14
   6.2. Public Health Measures (PHMs) ....................................... 15

7. Seasonal influenza vaccines for preparedness ......................... 16

8. Introducing seasonal influenza vaccines ................................. 18
   8.1. Is seasonal influenza vaccination a public health priority? ................................................................. 18
   8.2. How to Develop a Seasonal Influenza Vaccination Programme ................................................................. 18

References .............................................................................. 19

Annex 1. Example costs for different influenza vaccines ................. 24

LIST OF FIGURES, TABLES AND BOXES

Figure 1. The benefits of having a seasonal influenza vaccination programme ................................................................. 1
Table 1. WHO case definitions for ILI and SARI .............................................. 2
Box 1. Vulnerable populations .......................................................... 3
Figure 2. Global estimates for the burden of seasonal influenza ................................................................. 3
Box 2. Value of Seasonal Influenza Vaccination ......................................... 4
Box 3. Trivalent and quadrivalent vaccines ........................................... 5
Box 4. What makes influenza vaccines unique? ........................................ 6
Figure 3. Range of cost per dose (in US$) for seasonal influenza vaccines ................................................................. 8
Box 5. Adverse events .................................................................. 8
Box 6. Coverage challenges ........................................................... 11
Figure 4. Proportion of countries with national influenza immunization policies, as reported through the 2018 JRF.* ........................................... 12
Table 2. Influenza antiviral treatments ................................................ 14
Figure 5. Recommended PHMs for use during influenza outbreaks ................................................................. 15
Table. Examples of seasonal influenza vaccine costs ................................................................. 24
1. EXECUTIVE SUMMARY

Influenza causes 3-5 million cases of severe illness and up to 650,000 respiratory deaths a year globally.
Lower respiratory infections are the leading cause of death in low income countries annually.1 Influenza vaccine are the leading public health tool for prevention and control of influenza.

This document presents a summary of the evidence and know-how on seasonal influenza vaccines; where relevant, it includes links to the latest WHO guidance. It has been written to support Ministries of Health and other key stakeholders in their decision-making around designing and implementing seasonal influenza interventions.

Key points include:

- Seasonal influenza vaccines are safe, effective, and cost-effective.
- WHO recommends annual seasonal influenza vaccination for five target groups (health workers, pregnant women, children, elderly, and people living with chronic conditions) to protect these vulnerable populations.
- Vaccination against seasonal influenza has been shown to reduce the substantial national, regional, and global health and economic burden of influenza.
- Seasonal influenza programmes contribute to pandemic preparedness by annually using global and national systems that would be needed during a response. These include: sustaining manufacturing facilities, developing delivery capacities, increasing acceptance of vaccine, training health workers, strengthening decision making, and exercising systems annually.

Throughout this document, additional information can be found on seasonal influenza vaccine types, costs, and target groups. This Seasonal influenza vaccines: An overview for decision-makers also includes resources, guidance, and key questions for Ministries to review as they consider how to introduce a seasonal influenza vaccination programme.
2. INTRODUCTION

2.1 Seasonal influenza

Seasonal influenza is an acute respiratory infection that is caused by two types of influenza virus (types A and B), which circulate in all parts of the world. In recognition of the significant health threat posed by this disease, public health authorities in high- and low-income countries alike are increasingly prioritizing influenza prevention and control.

WHO advises that the best way for people to avoid getting seasonal influenza is to get vaccinated once a year.

**Influenza vaccines:**
- are safe and generally well tolerated;
- are key to reducing the health and economic burden of influenza;
- can prevent illness and death, and reduce disease transmission and severity;
- do not cause influenza disease and very rarely have serious side effects.

2.2 Why is having a seasonal influenza vaccination programme important?

- Seasonal influenza can be deadly. To protect against influenza, WHO recommends annual vaccination of the five target groups (health workers, pregnant women, children, elderly, and people living with chronic conditions).
- The burden of seasonal influenza is likely to be higher than you think because current estimates tend not to include influenza-related deaths from other diseases such as cardiovascular diseases.
- Vaccination reduces the need for antiviral treatments, which can lose effectiveness when over-prescribed (because of drug resistance).
- Having a seasonal influenza vaccination programme could help strengthen health systems by adding capacities (such as cold chain storage and health worker skills).
- It could also save money: several studies show that vaccinating against seasonal influenza reduces costs for the health system.
- Having a seasonal influenza vaccination programme also helps prepare health systems for public health emergencies by building the systems for timely delivery of vaccines.
- Seasonal influenza vaccination campaigns can build on, and build up, other ongoing immunization programmes such as adult, health worker, and other non-traditional target group vaccination programmes.

Figure 1. The benefits of having a seasonal influenza vaccination programme.
3. BURDEN OF DISEASE

3.1 Monitoring influenza

Seasonal influenza is characterized by the sudden onset of fever and cough. Other symptoms can include headache, muscle and joint pain, sore throat and a runny nose. In many cases, it is not clinically easy to distinguish seasonal influenza from other respiratory infections; and a definitive diagnosis requires a diagnostic test.

In this context, WHO has developed two standard case definitions for use in national influenza surveillance programmes: one for influenza-like illness (ILI) and one for severe acute respiratory infection (SARI) (see Table 1). All countries are encouraged to use these case definitions; and to support their use with laboratory testing of samples obtained from all, or a systematic proportion of, case patients.

Table 1. WHO case definitions for ILI and SARI.

<table>
<thead>
<tr>
<th>ILI case definition</th>
<th>SARI case definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>An acute respiratory infection with:</strong></td>
<td><strong>An acute respiratory infection with:</strong></td>
</tr>
<tr>
<td>• measured fever of ≥ 38°C;</td>
<td>• history of fever or measured fever of ≥ 38°C;</td>
</tr>
<tr>
<td>• and cough;</td>
<td>• and cough;</td>
</tr>
<tr>
<td>• with onset within the last ten days.</td>
<td>• with onset within the last ten days;</td>
</tr>
<tr>
<td></td>
<td>• and requires hospitalization.</td>
</tr>
</tbody>
</table>


Data from influenza surveillance programmes are essential to inform local, national and global burden of disease estimates. At all levels, they are useful for driving action and decision making.

At a local level, surveillance data can help alert healthcare providers of emerging outbreaks and inform and improve clinical management in high-risk patients.

At a national level, surveillance data can help allocate resources for response; and be used to develop and revise influenza prevention and treatment policies. These policies include deciding whether and when to use pharmaceutical and/or non-pharmaceutical interventions to control spread as well as choosing when and who to vaccinate.

At a global level, influenza surveillance is conducted by the WHO-coordinated Global Influenza Surveillance and Response System (GISRS), through country collaboration and sharing of viruses, data and benefits. GISRS data provide the basis for:

- identifying and tracking the constant changes in influenza epidemiology and disease;
- alerting countries to novel influenza viruses;
- recommending the composition of seasonal influenza vaccines twice a year;
- supplying virus samples and potency reagents for vaccine production; and
- researching and developing new diagnostic tools, vaccines and other treatments.

WHO GUIDANCE

WHO has developed Global epidemiological surveillance standards for influenza and encourages all countries to conduct their own national epidemiological surveillance in line with these international standards; and to report their data to global surveillance systems.
3.2 The burden of seasonal influenza

Developing reliable national and global estimates of the burden of disease (BoD) for seasonal influenza can inform activities to mitigate influenza’s public health and economic consequences. Governments, health systems, donors, partners and pharmaceutical manufacturers can all use BoD estimates to inform their decision-making.6

In 2018, WHO estimated that up to 650,000 people may die from respiratory-related effects of seasonal influenza each year (see Figure 2).7

These global figures reflect illness and death in the general population. But some groups are known to be more vulnerable to severe health outcomes than others (see Box 1. Vulnerable populations). Reporting BoD for high-risk groups can drive appropriate targeted interventions and provide cost-effective options to reduce the influenza disease burden.

In all cases, global estimates of influenza BoD currently only include respiratory deaths (not influenza derived cardiovascular or diabetes deaths) and as such are likely to be an underestimate. Recent advances in estimation methods and national efforts to calculate BoD have yielded significant insights into the burden of seasonal influenza in several LMICs.8 But disease burden information is still sparse in regions such as Africa, Asia and South America. There is also a relative lack of data from the tropics. Many LMICs do not have any seasonal influenza surveillance system in place, making burden estimation difficult. And in other LMICs, healthcare access and use are low, so surveillance systems can miss large numbers of cases.

Box 1. Vulnerable populations

Some populations are at higher risk of severe health outcomes from influenza than others.

Since 2012, the WHO has identified five groups that are particularly vulnerable to seasonal influenza, either because they have a greater risk of exposure or because they have a greater risk of developing severe disease:9

- pregnant women;
- health workers;
- people with chronic health conditions (such as diabetes, HIV, asthma, heart or lung disease);
- people over the age of 65 years; and
- children from 6 months to 5 years.

The WHO recommends annual vaccination for these groups.

There is some additional evidence to suggest that:

- children with neurological conditions are at higher risk of severe outcomes, especially in LMICs;
- adults are more likely than children to suffer severe outcomes if they have certain comorbidities, including diabetes, obesity and liver disease; and
- asthma is a risk factor for hospitalization but not for severe influenza outcomes.10

Figure 2. Global estimates for the burden of seasonal influenza.

WHO GUIDANCE

WHO has several resources designed to support countries to calculate the burden of seasonal influenza in their countries and to continue strengthening the evidence base for seasonal influenza vaccination and other interventions.

The WHO Manual for estimating disease burden associated with influenza provides guidance and standardized approaches for estimating influenza BoD. It is particularly aimed at supporting BoD estimates in LMICs using ILI and SARI data.

WHO’s Global epidemiological surveillance standards for influenza is also useful for estimating BoD, in that it recommends how to stratify BoD analysis by age. Importantly, the standards suggest including an age grouping of under-two-year-olds if feasible. The WHO guidance suggests that BoD estimates should ideally be based on data covering three to five years; but even a single year’s worth of data can serve as a valuable starting point.

Box 2. Value of Seasonal Influenza Vaccination

- Influenza vaccination was cost saving in two-thirds (12/18) of studies for children, one-third (8/27) of studies for elderly and one-third (2/6) of studies for pregnant women.
- A 2017 study found vaccinating children was cost-saving for the health system.
- Influenza vaccination in South Africa found that vaccinating people with active tuberculosis, adults living with HIV and pregnant women was the most cost effective.
- About US$500 per DALY saved.

General consensus

Given the available evidence, influenza vaccinations for children and other vulnerable populations are likely to be cost effective. Vaccinating children is often cost saving in HICs, and may be cost saving in LMICs, especially if it is integrated into existing immunization programmes. Such integration requires evidence-based decision making on the appropriate vaccine type and timing, and can be facilitated by SAGE recommendations.

It is important that influenza vaccination does not divert money, time, attention or other resources away from routine immunization or vaccination programmes for diseases like measles, yellow fever, meningitis A, Haemophilus influenzae b (Hib), hepatitis B, Streptococcus pneumoniae, Japanese encephalitis, or human papillomavirus, which have all been demonstrated to be both cost-effective and life-saving.

More research and analysis are needed to inform cost effectiveness analyses of influenza vaccine campaigns in LMICs. Still, it is likely that LMICs with a sufficiently robust and well-funded childhood vaccination programme will find a targeted influenza vaccination programme to be a good use of resources.

Across all income settings, cost effectiveness studies of seasonal influenza vaccination programmes have not considered the benefits of preparing countries for pandemic response.

WHO GUIDANCE

The WHO Guidance on the economic evaluation of influenza vaccination is a helpful resource for countries conducting cost effectiveness analyses.

3.3 Vaccine cost effectiveness

Given BoD estimates, vaccine costs and vaccine effectiveness, it is possible to analyse the cost effectiveness of implementing a seasonal influenza vaccination programme. Such analyses also enable decision-makers to compare the value of influenza vaccination with other public health interventions, and to consider how and why an influenza vaccination campaign should fit into a national budget (see Box 2. Value of Seasonal Influenza Vaccination).

Influenza vaccination cost effectiveness has been demonstrated in LMICs and HICs.
4. ABOUT SEASONAL INFLUENZA VACCINES

4.1. Vaccine types

Seasonal influenza vaccines are available and have been used for more than 60 years, although they remain largely underused in many LMICs. They target the three or four influenza virus strains that are likely to be the most circulating for the season (see Box 3. Trivalent and quadrivalent vaccines).

WHO convenes the Vaccine Composition Meeting (VCM) twice a year to review the latest influenza surveillance data, predict which strains of the virus are most likely to be circulating during the next influenza season, and recommend the composition of both trivalent and quadrivalent vaccines (see Section 3.2 Vaccine composition).

Trivalent influenza vaccines (TIVs) protect against two influenza A viruses and one influenza B virus. WHO notes that there are three main types of TIV: whole virus vaccines, split virus vaccines, and subunit vaccines.

Quadrivalent influenza vaccines (QIVs) target two influenza A viruses and both influenza B viruses. Originally licensed in the United States of America (USA) in 2012, QIVs have since been increasingly incorporated into other countries’ national immunization programmes. They provide wider protection against influenza B disease.

There is considerable debate about the pros and cons of using trivalent versus quadrivalent vaccines to combat influenza. Some scholars favour the use of QIVs because it can be difficult to predict which influenza B strain will circulate during a season. QIVs reduce the risk of a mismatch in the vaccine and seasonal strains which can increase the vaccine effectiveness and boost public confidence in influenza vaccination.

WHO notes that TIVs appear to be less efficacious among people living in tropical regions. However, TIVs tend to be cheaper. Countries can procure more TIV doses with smaller budgets, protecting more people from seasonal influenza. The cost effectiveness of TIVs or QIVs depends on the influenza B burden as well as on patient comorbidities and contraindications. WHO does not provide a preferential recommendation. Countries can review the respective costs, benefits, and context-specific evidence to inform their decisions about which type of vaccine to choose.

Inactivated versus live attenuated influenza vaccines

Both TIVs and QIVs can be made using a weakened form of the virus (live attenuated vaccines) or using a protein or other small piece of the dead virus (inactivated vaccines).

Inactivated vaccines are recommended for pregnant women, the elderly, health workers, and immuno compromised people. Older adults may require the use of more antigen, multiple doses, or adjuvants to achieve the efficacy comparable to younger adults.
Live attenuated influenza vaccines (LAIVs) can be delivered through a nasal spray and can induce a more protective and longer-lasting immune response in naive populations (i.e. children) because they are more similar to the real virus. Studies have shown that LAIVs are particularly effective in children above two years of age. However, for seasonal influenza vaccines, LAIV have lower efficacy in adolescents and adults. Because they contain a small amount of live virus, they are not recommended for people with weakened immune systems or long-term health problems.

Most influenza vaccines (both TIVs and QIVs) that are licensed for use are inactivated vaccines; although some LAIVs are available. The efficacy and effectiveness of both LAIV and inactivated vaccines vary considerably with season and age group. For example, LAIV is recommended for children in Germany and the United Kingdom. Universal vaccines: Research is underway to develop vaccines that do not need to be changed every year to match the circulating strains. Numerous clinical trials are ongoing but no vaccine has yet been approved that achieves this goal.

4.2. Vaccine composition

Circulating influenza virus strains change and evolve rapidly so seasonal influenza vaccines must be regularly reformulated to ensure they cover the strains with the highest probability of circulation (see Box 4. What makes influenza vaccines unique?). Twice a year, the VCM reviews the latest surveillance data so that WHO can be confident in its recommendation for which virus strains to include in the seasonal influenza northern and southern hemisphere vaccines. These data are generated by the GISRS network of WHO Collaborating Centres, National Influenza Centres, WHO Essential Regulatory Laboratories and WHO HS Reference Laboratories. They include information on:

- the antigenic and genetic characteristics of circulating viruses; and
- vaccine effectiveness and antiviral resistant strains.

At the VCM, experts use the data to forecast the strains likely to circulate and make recommendations on how to optimize the next vaccine. The recommendations inform the development of candidate vaccine viruses, for use in manufacturing the vaccine.

Box 4. What makes influenza vaccines unique?

Two things in particular differentiate seasonal influenza vaccines from most other vaccines:

1. **Annual re-vaccination.** Unlike most other vaccines, seasonal influenza vaccines must be re-formulated and re-administered every year to account for the constant changes in circulating strains and rapid evolution of the virus. Vaccine formulations can also differ between northern and southern hemispheres, which may have different circulating strains.

2. **Variable effectiveness.** Because influenza viruses change so quickly, the effectiveness of seasonal vaccines depends, in part, on the match between the circulating viral strains and the strains included in the vaccine. If the match is poor, then the vaccine is less effective. Individual immune response to influenza vaccination also influences effectiveness of the vaccine and differs by target group. Past exposure to influenza may also influence individuals’ immune response to the vaccine and so impact vaccine effectiveness.

Because there can be different influenza strains circulating in northern and southern hemispheres, and because peak influenza seasons occur at different times of the year, the VCM is convened twice a year: in February and September. The timing of the meeting is designed to provide at least 6–8 months for the vaccine to be produced and distributed before the next peak influenza season.

Tropical and subtropical regions may experience multiple peaks of influenza, or year-round activity. This means that regional and national surveillance data should be reviewed to identify which seasonal influenza vaccine to use and when to vaccinate.

WHO GUIDANCE

To support public health authorities in these regions in deciding whether to use northern or southern hemisphere seasonal influenza vaccine, WHO has developed a series of maps and tables that identify, for each country, whether the primary influenza activity starts in April or October. This information can be used by countries to decide which type of vaccine to use and when to vaccinate against seasonal influenza.

In addition, WHO recommends countries in the tropics and subtropics use local surveillance data to establish seasonality patterns and influenza transmission levels.
4.3. Vaccine production

In 2015, the global production capacity for seasonal influenza vaccines was estimated to be 1.5 billion doses with the ability to expand, in a best-case scenario, to 6.4 billion doses in the event of an influenza pandemic. Seasonal influenza vaccination programmes maintain seasonal influenza and pandemic vaccine production capacity. Without sufficient seasonal influenza vaccination, vaccine production capacity would be drastically reduced, impacting accessibility of the pandemic vaccine (see Section 6).

The full timeline for moving a vaccine from bench to bedside—including strain selection, production, testing, formulation, packaging, shipping and vaccination—can take as long as a full calendar year. Most seasonal influenza vaccines licensed for use are produced using egg-based methods, which rely on supplies of eggs and candidate vaccine viruses (CVVs). Egg-based vaccines can take as long as 5 to 8 months to produce, may be prone to changes in antigenicity, and can pose health risks to people with egg allergies.

Other ways of producing influenza vaccines that do not rely on using eggs tend to be faster but have limited production capacity. Increasing availability of other production technologies could enable quicker scale-up and expansion of manufacturing during a pandemic.

Cell-culture is one example of a new technology that could be used for influenza manufacturing. The advantage of cell-culture vaccines could be to reduce dependence on egg supply (a key concern in particular for influenza strains that impact poultry) and to potentially avoid egg-derived changes in the virus strain. But, cell-based technologies still rely on CVVs and are particularly vulnerable to contamination. In most cases switching to cell-based or other vaccine production technologies would require an overhaul of existing manufacturing facilities.

Another type of vaccine production uses recombinant technology. Recombinant vaccines could potentially be produced more quickly than vaccines from traditional technologies. These vaccines do not need CVVs. They are produced synthetically by taking a small piece of DNA made from the virus sequence and inserting it into other cells to produce large quantities of active ingredient for the vaccine.

Other next-generation vaccines—based on the use of virus-like particles or viral vectors—remain in relatively early stages of development but show considerable promise for further reducing production times.

4.4. Vaccine storage

Influenza vaccines are typically not heat stable and require cold chain storage from the time they are manufactured until the time they are administered. Specific storage requirements for different seasonal influenza vaccines are included in the vaccine package inserts.

WHO GUIDANCE

WHO’s training module on vaccine cold chain provides guidance for workers in health facilities on how to use cold chain and temperature monitoring equipment to safely transport and store vaccines that require cold chain.

WHO’s Guidelines for establishing or improving primary and intermediate vaccine stores, which apply to all vaccines, provide guidance on vaccine storage locations and refrigeration equipment, site and building selection, space planning and equipment procurement for cold chain.

4.5. Vaccine costs

The cost of influenza vaccines varies considerably depending on a broad range of factors, which include but are not limited to:

- how the vaccine is being procured (self-procurement vs. UNICEF or group purchasing);
- who is buying the vaccine (government agency vs. private sector entity);
- what type of vaccine is being sought (trivalent vs. quadrivalent);
- how the vaccine is presented (pre-filled syringe vs. injector vs. vials or ampoules); and
- how many doses are being purchased.

It is cheaper to procure vaccines through UNICEF than to self-procure them. For example, in 2017, the same adult influenza vaccine that was sold to an LMIC in Europe for US$1.51 per dose through UNICEF was sold to an upper middle-income country in Africa for US$11.44 per dose through self-procurement. That same vaccine was also self-procured by a high-income country (HIC) in the Eastern Mediterranean for US$2.90 per dose and by another HIC in the Western Pacific for US$5.82 per dose.
Trivalent vaccines also tend to be cheaper than quadrivalent ones. For example, the 2019 weighted average price per dose for the southern hemisphere trivalent vaccine was US$3.29, compared with US$5.40 for the quadrivalent one.\textsuperscript{41} From available data, replacing TIV with QIV could result in a more than 25% budget increase for seasonal influenza vaccination in low- and middle-income countries.\textsuperscript{43}

The more doses a country procures, the cheaper the vaccine tends to be. For example, countries tend to receive better prices when they procure through multi-year contracts or as part of a group (i.e. the Gulf Cooperation Council). But this requires demand forecasting and coordination, which can be difficult because demand for seasonal influenza vaccine can vary by year.

Overall, the cost of seasonal influenza vaccines in recent years has ranged from US$1.08–24.05, with a median cost of $4.56 (see Figure 3; and Annex 1 for more information).

\textbf{Figure 3. Range of cost per dose (in US$) for seasonal influenza vaccines.}

<table>
<thead>
<tr>
<th>Cost (US$)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>1.08</td>
</tr>
<tr>
<td>First quartile</td>
<td>2.90</td>
</tr>
<tr>
<td>Second quartile</td>
<td>4.56</td>
</tr>
<tr>
<td>Median</td>
<td>4.56</td>
</tr>
<tr>
<td>Third quartile</td>
<td>8.08</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>15.77</td>
</tr>
<tr>
<td>Maximum</td>
<td>24.05</td>
</tr>
</tbody>
</table>

4.6. Vaccine effectiveness, safety and uptake

Seasonal influenza vaccines are considered globally to be safe and well tolerated, with few serious side effects or complications (see Box 5. Adverse events).\textsuperscript{44}

\textbf{Box 5. Adverse events}

Common side effects from seasonal influenza vaccination include soreness, tenderness, redness and swelling; as well as systemic effects such as general malaise, fever, headache, nausea, and muscle aches. These side effects are generally mild and go away on their own within a few days.

Serious complications from seasonal influenza vaccination are rare. In particular, concerns about Guillain-Barr Syndrome (GBS) are not supported by the latest research. Evidence indicates that a person is more likely to get GBS from influenza than from the vaccine.\textsuperscript{45}

The effectiveness of seasonal influenza vaccines, however, varies depending on the age and immune status of the person receiving it (as well as the match between vaccine composition and circulating strains).

Vaccine uptake is similarly variable, shaped by a mix of:

- structural social determinants, such as age, gender, marital status, education, ethnicity, socio-economic status and cultural values;
- intermediary determinants, including place of residence, behavioral beliefs, social influences, previous vaccine experiences, perceived susceptibility and health status and sources of information;\textsuperscript{46} and
- factors related to the healthcare system, including accessibility, affordability and health workers’ knowledge, attitudes and advice.\textsuperscript{47}

Importantly, effectiveness and uptake can vary across target groups. The rest of this section looks at the effectiveness, safety and uptake of seasonal influenza vaccines in each of the WHO-recommended priority groups.

Historically, many estimates of influenza vaccine efficacy came from randomized controlled trials (RCTs) held in wealthier countries with temperate climates, leaving LMICs to rely on their own local epidemiological data—or data from neighbouring or epidemiologically similar countries—to develop their vaccine policy. But efforts to include LMICs in influenza vaccine RCTs are rising and are anticipated to diversify and strengthen the evidence base for vaccine policy-making in these countries (and elsewhere).
Pregnant women

In 2012, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) identified pregnant women as the highest priority group for vaccination against seasonal influenza. Influenza infection during pregnancy can also cause negative outcomes in fetal development.

Pregnant women should receive inactivated vaccines. Both TIVs and QIVs are considered safe and effective, and neither are associated with adverse effects in mothers or infants. In addition to protecting mothers against severe disease, vaccination during pregnancy also protects fetuses via transplacental transfer of antibodies.

There is no evidence of negative pregnancy outcomes with inactivated influenza vaccines. Studies show that vaccine acceptance and uptake in pregnant women is driven by recommendations from healthcare providers. The biggest barriers to uptake by pregnant women include lack of knowledge about the vaccine and its safety profile.

Health workers

WHO recommends health workers receive seasonal influenza vaccinations and are prioritized for pandemic vaccination to protect health workers, maintain healthcare services during influenza epidemics, and reduce the spread of influenza to vulnerable patient groups (nosocomial infection).

There is evidence that health workers are at risk of contracting influenza and that many health workers continue to work while infected. Influenza vaccines are shown to be as effective in HWs as in other adults of similar age. Data on whether vaccinating HWs protects patients is of mixed quality and does not universally indicate a protective outcome. However, there are strong signals from studies in long term care facilities that HW vaccination protects patients, especially with regard to mortality.

Health workers represent an attractive option for building influenza vaccination capacity in LMICs as they are typically the smallest of the five SAGE-recommended target groups. Health worker infections in Ebola, MERS, SARS and COVID-19 outbreaks provide reminders of the importance of protecting health workers, our first line of defense for responding to disease outbreaks. Annual health worker vaccination programmes for seasonal influenza build capacity for efficient and timely delivery of epidemic/pandemic vaccines.

Finally, health workers serve as educators and trusted advisors for the population. Vaccinated health workers who receive a vaccine are more likely to recommend vaccination to other high-risk groups.

Uptake of influenza vaccines by health workers is low. Mandatory influenza vaccination programmes exist in some healthcare settings and have shown to be effective at increasing vaccine uptake. But there are legal and ethical issues to be considered, and the decision to use mandatory vaccination is highly context dependent.

Children

All over the world, children under five years of age have a high burden of influenza and a high risk of hospitalization. Vaccinating children against influenza is important to:

- prevent severe illness and deaths;
- reduce transmission of influenza (because children shed more virus, for longer periods of time, compared with adults).

Building seasonal influenza vaccination into existing schedules for expanded programmes on immunization (EPI) can increase coverage among children and reduce the disease burden in this high-risk population.

Infants younger than six months of age should not receive influenza vaccines. But vaccinating mothers during or shortly after pregnancy can protect these infants by transferring antibodies through breast milk. Vaccination of close contacts can also help protect infants by preventing transmission.
WHO recommends that children aged two years to five years receive influenza vaccines, which can be either live attenuated or inactivated. Evidence suggests that LAIVs may be more effective for this group. Children being vaccinated against influenza for the first time should receive two doses of vaccine.

Influenza vaccines can cause localized side effects in children that are usually mild. Safety concerns about influenza vaccines in children are extremely rare. In 2010, an inactivated TIV (Fluvax) was associated with increased risk of febrile seizures in under-five-year-olds. But further investigation found this to be an isolated occurrence and confirmed that no other TIVs carry a greater risk of febrile seizure.

Influenza vaccine effectiveness in children varies by season and, as in adults, is influenced by the match between vaccine and circulating strains of the virus. Evidence suggests that the overall vaccine efficacy in preventing laboratory-confirmed influenza in healthy children ranges from 67–74%. Wider variation in vaccine efficacy (from 20–77%) has been reported in LMICs.

The elderly (65 years of age and older)

The elderly have a greater risk of hospitalization and death if they contract influenza. Data suggest that influenza-related deaths in over-65-year-olds may be higher in LMICs than in HICs. One study estimates these deaths at 545 per 100,000 in South Africa compared with 133 per 100,000 in the United States.

WHO recommends that anyone over the age of 65 receive inactivated TIVs.

Influenza vaccination is considered to be safe for the elderly and effective in reducing illness and death. Vaccine efficacy may decrease with increasing age. Efficacy is also lower in elderly people with underlying medical conditions.

High-dose and adjuvanted influenza vaccines have been shown to prompt a stronger immune response in the elderly and be more effective in preventing influenza.

People with chronic health conditions, such as asthma, chronic heart or lung disease, HIV or diabetes, have a higher risk of infection, severe illness, hospitalization and death if they get influenza. This risk varies with demographic characteristics and severity of the underlying condition but holds true for both children and adults.

Immunocompromised people (including, for example, chemotherapy and transplant patients) also have a higher risk of influenza infection.

Chronic lung diseases are the conditions most often associated with a severe health outcome. A meta-analysis of 2009 A (H1N1) pandemic influenza cases found that individuals with chronic conditions (most often chronic lung disease) accounted for 31% of hospitalized cases, 52% of ICU admissions, and 62% of fatal cases. Among children in the USA, those with asthma are hospitalized two to four times more often than those without medical conditions.

Overall, there is limited evidence available on the effectiveness of influenza vaccination among patients with underlying health conditions. Nevertheless, influenza vaccination has been associated with health benefits in patients with cardiovascular or lung disease, including fewer outpatient visits, fewer hospitalizations, and fewer deaths; so, influenza vaccines are recommended for these patients.

Similarly, influenza vaccination has been found to be beneficial for people living with HIV. For example, a meta-analysis of influenza vaccine effectiveness found that vaccinated people living with HIV were 66% less likely to contract influenza compared to non-vaccinated people living with HIV. In some cases, vaccine effectiveness may be influenced by higher viral HIV loads and anti-retroviral treatment.
5. SEASONAL INFLUENZA VACCINE COVERAGE

Vaccine coverage data are critical to understand vaccine uptake and population immunity. They enable health authorities to assess coverage gaps and to measure trends over time, both of which are key components of a successful influenza prevention and control programme.

Monitoring vaccine coverage among vulnerable populations is particularly important. In 2003, the 56th World Health Assembly called on all countries to achieve 75% vaccination coverage among the elderly by 2010.83 Years later, many countries still do not monitor or measure influenza vaccine coverage among the elderly, or any other vulnerable population. Without data, countries cannot know if they are achieving their vaccination targets (estimates suggest that vaccination rates remain well below recommended targets).84

In many cases, the lack of data is due to practical challenges in estimating vaccine coverage, particularly for high-risk groups in LMICs (see Box 6. Coverage challenges).

5.1. Estimates of global coverage

WHO/UNICEF joint reporting form

Global information on influenza vaccination programmes comes from the WHO/UNICEF Joint Reporting Form on Immunization (JRF), a standard questionnaire sent to all Member States each year to collect information on immunization, vaccines, and biologicals.86 It includes a section on seasonal influenza vaccination, with questions on policy, vaccine type and distribution.

A look at 2018 JRF data shows that around half the countries that reported data have a national influenza immunization policy, with policies most prevalent in the region of the Americas (AMR), the Eastern Mediterranean region (EMR) and European region (EUR) (see Figure 4).87

Box 6. Coverage challenges

Common challenges associated with estimating vaccine coverage for high-risk groups include:86

- **Denominator data.** Coverage estimates for subgroups require reliable estimates of the group size (the ‘denominator’). But such detailed demographic data are unavailable in many LMICs: up to 88% of WHO Member States in the Eastern Mediterranean and African regions do not have reliable estimates of the size of influenza high-risk groups.

- **Overestimates.** The coverage estimates for high-risk groups in LMICs that do exist are often based on the proportion of vaccine doses that have been distributed or administered, rather than the proportion of the target population that was vaccinated. In many cases, these estimates also fail to account for unused or otherwise wasted doses, which results in an overestimation of vaccine coverage.
By comparison, in the 2014 JRF, 115 Member States (59%) reported having a national influenza immunization policy, with AMR, EUR, and the Western Pacific Region (WPR) having the highest proportions of countries with national policies. The difference between the 2018 and 2014 data may be at least partially explained by data quality and/or lack of reporting in 2018 rather than a drop in the number of countries with national influenza immunization policies.

Other key features of the 2018 JRF data include:

- **Limited coverage data.** Few countries answered the 2018 JRF questions on how many vaccine doses were distributed, how many were administered to target groups, and what coverage was achieved for target groups.

- **Few recommendations for priority groups.** Only 29 out of 187 countries that responded to the JRF reported recommending influenza vaccination for all priority groups (children over 6 months of age, adults with chronic conditions, the elderly, travelers, health workers and pregnant women).

- **Limited progress in meeting coverage targets.** Only 10 countries provided coverage data for all priority groups, with just three countries seeming to meet the WHA target of 75% coverage among the elderly. A total of 41 countries reported coverage of pregnant women, but this varied significantly, from 0–90%.

- **Poor coverage data quality.** In several cases, reported coverage among some priority groups exceeded 100%, pointing to problems with data quality.

*This data does not include countries that did not provide data to the 2018 JRF. As such, the true proportion of countries with an influenza policy may be higher.
Influenza vaccine distribution
In the absence of more robust data, global influenza vaccine distribution can be used as a proxy measure for vaccine coverage. According to one study in 2015, influenza vaccine distribution (and presumably use) increased 87% from 2004–2013; but only 12% from 2008–2013. The study found that all over the world, seasonal influenza vaccination coverage was well below recommended targets. It also found that vaccine distribution varied significantly from region to region:

- AMR had the highest levels of vaccine distribution.
- EUR distribution was mostly flat.
- WPR had sharp growth in vaccine distribution.
- AFR, EMR and the South East Asia Region (SEAR) had limited distribution.

Influenza vaccine is an underutilized public health tool in LMICs for prevention and control of this disease.

Seasonal influenza vaccine coverage in the tropics
In 2015, WHO published a review of seasonal influenza vaccine use and effectiveness in LMICs in the tropics. The review, which covered more than 200 articles and four global databases, found that only 46% of LMICs in the tropics had a national policy for seasonal influenza vaccination. Furthermore, vaccine coverage among all priority groups in most of these countries was low, less than 5 per 1,000 population.

WHO GUIDANCE
WHO's Methods for assessing influenza vaccination coverage in target groups are designed to support countries estimate vaccine coverage. Not all methods described will work for all countries and multiple methods may be used simultaneously to achieve accurate estimates. The following are all reasonable approaches to estimating coverage in high-risk populations:

- Analysis of data from health care facilities or healthcare providers.
- Analysis of data from national health insurance records.
- Analysis of administrative data from well-documented national or private vaccination programmes targeting specific groups.
- Evaluation of national vaccination registries.
- National surveys of individuals.

The WHO manual on How to implement seasonal influenza vaccination of health workers provides guidance on monitoring vaccine coverage among health workers, with a focus on data from health facility registries, national vaccination programmes and surveys. Similarly, the WHO manual on How to implement seasonal influenza vaccination of pregnant women provides guidance on monitoring coverage among pregnant women. The PAHO Maternal and Neonatal Immunization Field Guide includes a tool for establishing the denominator to calculate vaccine coverage among pregnant women (i.e. the number of pregnant women in a population).
6. OTHER PREVENTION AND CONTROL MEASURES

6.1. Antivirals

Influenza antivirals are essential components in countries’ clinical management of influenza since they play an important part in treating and reducing disease severity in people infected with influenza. Antivirals complement vaccination in both seasonal influenza programmes and pandemic preparedness planning, and thus, serve as an additional tool for countries to protect vulnerable risk groups and health systems.

Table 2. Influenza antiviral treatments.

<table>
<thead>
<tr>
<th>Antiviral Name</th>
<th>Mechanism of Action</th>
<th>Mode of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>Neuraminidase inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Neuraminidase inhibitor</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Peramivir</td>
<td>Neuraminidase inhibitor</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>Neuraminidase inhibitor</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Polymerase inhibitor</td>
<td>Oral</td>
</tr>
<tr>
<td>Baloxavir marboxil</td>
<td>Polymerase inhibitor</td>
<td>Oral</td>
</tr>
</tbody>
</table>

Table sources:


How an antiviral is given can help or hinder its use for specific target groups. For example, antivirals that have to be given intravenously are of limited use in non-hospital settings.

Some antivirals are not suitable for specific groups: favipiravir, for example, cannot be administered to pregnant women due to the risk of birth defects or other serious complications during pregnancy.

Across nearly all antiviral treatments, resistance is a rising concern. One class of influenza antivirals called adamantanes have already been withdrawn from use because of high levels of resistance. Antiviral resistance against oseltamivir and other neuraminidase inhibitors has also been reported.

Concerns about rising levels of resistance means that antivirals are generally only given to high-risk patients. These concerns have also prompted research into drug repurposing and therapeutics with new mechanisms of action, such as immunotherapies or immunomodulators; most remain in early stages of development.
WHO GUIDANCE

WHO is developing guidance on antivirals for patients with severe seasonal influenza in clinical settings.

6.2. Public Health Measures (PHMs)

PHMs are public health measures that can be used by governments and the public to reduce transmission and limit geographic spread of infectious diseases like influenza. They can be used alongside pharmaceutical interventions like vaccines and antivirals; PHMs can also be used when vaccines and treatments are unavailable, for example during the early stages of a pandemic.\(^{107}\)

WHO recommends using a range of PHMs, depending on the severity of the influenza outbreak (see Figure 5).\(^{108}\)

The social and economic consequence of using any extreme PHM, for example during an extraordinary outbreak of influenza, should be weighed carefully against the public health benefits they may provide.

In all cases, there are some measures that are not recommended because there is not enough evidence to suggest that they are effective against influenza. These include:

- border closures or screening at borders,
- contact tracing,
- environmental humidity modification,
- use of UV light, and
- quarantine of exposed individuals.\(^{109}\)

WHO GUIDANCE

WHO has issued guidance on Non-pharmaceutical public health measures for mitigating the risk and impact of epidemic and pandemic influenza, summarizing the evidence on a range of PHMs and making recommendations on their use.

PAHO has a practical tool on PHMs, which gives governments a checklist of PHM options, explaining why each is important, how it can be implemented and requirements for success.
Implementing a seasonal influenza vaccination programme can have benefits beyond fewer illnesses and deaths. In particular, it can increase preparedness for pandemics and other disease epidemics by helping to sustain manufacturing facilities, develop deployment capacities, increase vaccine acceptance, train health workers, familiarize regulatory systems, strengthen decision-making processes, practice risk communication and community engagement and exercise response systems.

**Sustaining manufacturing facilities**

Increasing the demand for seasonal vaccine from LMICs can help sustain vaccine production capacity that has been built since 2006, that can be leveraged during a pandemic. The WHO Global Action Plan for Influenza Vaccines (GAP) was a catalyst for developing influenza vaccine manufacturing capacity across the globe, including in LMICs. By the end of the GAP in 2016, the potential influenza vaccine production capacity had quadrupled from 1.5 billion doses to 6.4 billion doses, with substantial capacity improvements in LMICs. But without continued demand through seasonal influenza programmes, these gains could be lost.

**Developing delivery capacities**

Seasonal influenza vaccination programmes help build the regulatory, operational and legal capacities needed for a pandemic response. In 2009, countries with seasonal influenza vaccination programmes in place were two times more likely to be able to meet the requirements to receive WHO donated pandemic vaccines than those without. Reviews after the pandemic showed that those countries that did not manage to deploy the vaccine lacked critical capacities such as regulatory pathways for rapid licensing and vaccine deployment plans.

**Increasing acceptance of vaccine**

Seasonal influenza vaccination programmes can help ensure vaccine acceptance during a pandemic. For example, studies of vaccine uptake during the 2009 pandemic suggest that people who had experience in being vaccinated against seasonal influenza were more likely to get vaccinated against pandemic influenza.

**Training and targeting health workers**

Having a seasonal influenza vaccination policy—especially one that prioritizes health workers—lays the foundations for strengthening health workers skills. Seasonal influenza vaccination of health works can support systems for vaccine deployment to this high-risk group quickly in the event of other disease outbreaks, such as Ebola. Implementing an annual influenza vaccination programme should include health worker training and empowerment. Health workers responsible for annual seasonal vaccination should be trained how to administer and track vaccines. Through annual seasonal influenza vaccination programmes, countries can regularly update their health worker registries and practice communication for vaccine advocacy. These systems and processes can support rapid delivery and uptake during pandemics or other disease epidemics.

**Strengthen decision-making**

In some cases, introducing a seasonal influenza vaccination programme can also drive the establishment of a National Immunization Technical Advisory Group (NITAG), or if one already exists, can strengthen its technical expertise. A new or stronger NITAG can help governments with decision-making on policy issues around influenza vaccination—seasonal or pandemic— that is informed by the evidence base.
Exercising systems regularly

Finally, because seasonal influenza vaccination campaigns are repeated every year, countries with a seasonal influenza vaccination programme exercise their systems for procuring and deploying these vaccines regularly. This repeated practice strengthens a country’s preparedness to fulfil these functions during a pandemic.117

WHO GUIDANCE

The WHO Pandemic Influenza Preparedness (PIP) Framework encourages countries that are seeking new vaccine technologies to consider implementing a seasonal influenza programme as a way of sustaining manufacturing facilities.

The WHO Global Influenza Strategy (2019-2030) includes a specific objective to “support countries to develop and implement national seasonal immunization policies for health workers and other target groups, as recommended by SAGE.”

The WHO’s Checklist for pandemic influenza risk and impact management highlights the links between seasonal influenza vaccination programmes and pandemic preparedness, and lists a number of essential and desirable actions for countries that already have, are considering or do not have a programme in place. In all cases, the checklist includes establishing regulatory pathways to expedite the import and licensing of pandemic vaccine as an essential action point.
8. INTRODUCING SEASONAL INFLUENZA VACCINES

A country interested in establishing a seasonal influenza vaccination programme can begin by determining whether introducing seasonal influenza vaccines is a public health priority, and assessing its existing readiness to start.

In all cases, countries should consider the potential impact of introducing seasonal influenza vaccines on the financing, planning and operation of the broader immunization programme and on the overall health system.

8.1. Is seasonal influenza vaccination a public health priority?

Each country should evaluate whether a seasonal influenza vaccination programme is a public health priority. Influenza vaccine programmes have been shown to reduce illness, death and economic burden on a healthcare system. But they require financial, logistical and political commitments to be successful.

Key questions for the Ministry of Health to consider include:

- Does preventing seasonal influenza align with, and/or contribute significantly to, the goals and priorities in our national health and development plans?
- Will preventing seasonal influenza help improve health equity within our population?

8.2. How to Develop a Seasonal Influenza Vaccination Programme

Before introducing a seasonal influenza vaccination programme, countries should consider if they have the necessary capacities. The health system must, for example, be capable of properly handling, storing and administering the vaccine. The health system and public’s acceptance and demand of vaccines is also important to consider as part of a country’s readiness. Introduction of seasonal influenza vaccination involves evidence-based decisions about the type of vaccine to use and when to deploy it, which can be facilitated by the SAGE recommendations.

Key questions for the Ministry of Health to consider include:

- What are our priority target groups for seasonal influenza vaccination?
- Do we know what the costs, benefits, risks, and trade-offs associated with manufacturing, procuring, and distributing seasonal influenza vaccines are?
- Can our cold chain system support the introduction of a seasonal influenza vaccine?
- Can our supply chains and health system distribute seasonal influenza vaccines?
- Does our health workforce have the capacity to handle the addition of a seasonal influenza vaccine?
- Do we have the capacity to train health workers to manage and administer the vaccine?
- What information systems will we have to update to include seasonal influenza vaccine?

Incorporating seasonal influenza vaccination into existing EPI schedules builds from existing capacities and systems.

WHO GUIDANCE

WHO’s Principles and considerations for adding a vaccine to a national immunization programme is designed to support countries make informed decisions about adding a vaccine to their national immunization programme. It provides comprehensive guidance on deciding whether or not to introduce a vaccine, planning and managing the vaccine introduction and monitoring and evaluating vaccine coverage and safety after it has been introduced.
REFERENCES


SEASONAL INFLUENZA VACCINES: AN OVERVIEW FOR DECISION-MAKERS


ANNEX 1.

Example costs for different influenza vaccines

The table below provides examples of seasonal influenza vaccines and their cost per dose.

**Table. Examples of seasonal influenza vaccine costs.**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Presentation</th>
<th>Cost per Dose (USD)</th>
<th>Prequalified by WHO?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern Hemisphere 2019 - Pediatric - Korea Origin</td>
<td>Trivalent, seasonal vaccine</td>
<td>20 dose vial</td>
<td>$1.095 (via PAHO Revolving Fund)</td>
</tr>
<tr>
<td>Northern Hemisphere 2019-2020 - Adult - France Origin</td>
<td>Trivalent, seasonal vaccine</td>
<td>Pre-filled syringe (1 dose)</td>
<td>$4.50 via PAHO Revolving Fund</td>
</tr>
<tr>
<td>Southern Hemisphere 2019 - Adult - Korea Origin</td>
<td>Quadrivalent, seasonal vaccine</td>
<td>10 dose vial</td>
<td>$4.40 (via PAHO Revolving Fund)</td>
</tr>
<tr>
<td>Northern Hemisphere 2019-2020 - Adult - France Origin</td>
<td>Quadrivalent, seasonal vaccine</td>
<td>Pre-filled syringe (1 dose)</td>
<td>$6.00 (via PAHO Revolving Fund)</td>
</tr>
<tr>
<td>Hualanii</td>
<td>Trivalent, seasonal, split virion, inactivated vaccine</td>
<td>1 dose vial</td>
<td>$1.19 (LMIC) - $4.50 (UMIC) (EURO Region)</td>
</tr>
<tr>
<td>IL-Yangi</td>
<td>Trivalent, seasonal, inactivated vaccine</td>
<td>1 dose vial</td>
<td>$7.67-$8.08 (HIC, WPRO Region)</td>
</tr>
<tr>
<td>Fluzone® Quadrivalentii</td>
<td>Quadrivalent, seasonal vaccine</td>
<td>10 dose vial, 1-dose vial, or syringes</td>
<td>$13.832 (U.S. CDC) - $18.314 (private sector)</td>
</tr>
</tbody>
</table>

Table sources:

Estimates of the current cost per dose for pandemic influenza vaccines are not available. The 2009 H1N1 influenza pandemic vaccine cost countries between US$2.50–20 per dose, with HICs paying between US$10–20 per dose, MICs paying approximately half that amount, and LICs paying roughly a quarter that amount. WHO reported that after accounting for local funding and financial support provided by the WHO Vaccine Deployment Initiative, the average cost per dose for vaccine deployment and administration ranged from US$0.16 in SEARO to US$0.66 in AFRO. For more detailed information on influenza vaccine types and pricing, see:

- WHO’s database of prequalified vaccines,
- the Expanded Program of Immunization’s 2019 vaccine price list for AMR, the US Centers for Disease Control & Prevention’s price lists for pediatric and adult seasonal influenza vaccines, and
- WHO Market information for access to vaccines resource gateway (including its most recent market report on vaccine purchase data).

Notes
Working together for better global tools & stronger country capacities

- **Promote** research & innovation to address public health needs
- **Expand** seasonal prevention & control policies and programmes to protect the vulnerable
- **Strengthen** global influenza surveillance, monitoring & data utilization
- **Strengthen** pandemic preparedness & response for influenza to make the world safer