

Global Influenza Strategy
2019–2030



Global influenza strategy 2019-2030

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Contents

Abbreviations and acronyms.....	4
Introduction.....	5
The investment case for influenza prevention, control and preparedness	7
Vision.....	9
Mission.....	9
Goals	9
High-level outcomes for 2030	9
Strategic objectives and actions	10
Strategic objective 1: Promote research and innovation to address unmet public health needs...	11
Strategic objective 2: Strengthen global influenza surveillance, monitoring and data utilization	13
Strategic objective 3: Expand seasonal influenza prevention and control policies and programmes to protect the vulnerable.....	15
Strategic objective 4: Strengthen pandemic preparedness and response for influenza to make the world safer	17
Implementation of the strategy	19
Annex 1: Achievements in influenza prevention, control and preparedness since 2002.....	22
Annex 2: Ongoing challenges in influenza prevention, control and preparedness.....	26
References.....	29

Abbreviations and acronyms

AMR	antimicrobial resistance
FAO	Food and Agriculture Organization of the United Nations
GAP	WHO Global Action Plan for Influenza Vaccines
GISRS	WHO Global Influenza Surveillance and Response System
GPW	WHO General Programme of Work
HICs	high-income countries
HLIP	High-Level Implementation Plan
IHR (2005)	International Health Regulations (2005)
ILI	influenza-like illness
JEE	Joint External Evaluation
LMICs	low- and middle-income countries
NAPHS	national action plans for health security
NCD	noncommunicable disease
NPI	nonpharmaceutical intervention
NRA	national regulatory authority
OIE	World Organisation for Animal Health
PC	Partnership Contribution
PIP	Pandemic Influenza Preparedness
SAGE	WHO Strategic Advisory Group of Experts
SDG	Sustainable Development Goal
SMTA	standard material transfer agreement
UHC	universal health coverage
WHE	WHO Health Emergencies Programme
WHO	World Health Organization

Introduction

Influenza is a viral respiratory disease of global importance; indeed, many experts believe that an influenza pandemic is the greatest threat to global public health. In 2018, the world observed the centenary of the start of the 1918–1919 influenza pandemic. Its estimated toll of up to 50 million deaths (1,2) exceeded that of the First World War, resulting in a dramatic decline in life expectancy in many countries at the time of the pandemic. Its impact led to fundamental changes in public health and health care systems, including centralized and consolidated health care, greater recognition of the role of socioeconomic factors in health, and the coordination of public health at national and global levels. Since the 1918–1919 pandemic, there has been significant progress in medical science, including the development of influenza vaccines, antiviral drugs and better diagnostics. Subsequent pandemics occurred in 1957–1958, 1968–1969 and 2009–2010, resulting in 1–4 million, 1–4 million and 100 000–400 000 deaths, respectively (3). Pandemic (H1N1) 2009 caused significant deaths, particularly in those aged under 65 years; it also tested national health response systems (in particular, the pandemic vaccine response capacity) and exposed weaknesses in those systems. It reiterated that influenza viruses of both avian and swine origin can cause a pandemic, and it underscored the importance of intersectoral collaboration for pandemic preparedness. Although it is impossible to predict when the next pandemic might occur, its occurrence is considered inevitable, and it could well occur during the time frame of this strategy. Given increased economic globalization, urbanization and mobility, the next pandemic will spread further and faster, and could lead to significant disruptions. Despite significant medical advances over the past 100 years, there will still be populations that have limited access to care and will be likely to experience high mortality rates during a pandemic.

The substantial morbidity and mortality due to influenza – well-recognized during a pandemic – is often underappreciated in the context of year-round seasonal influenza. Seasonal influenza viruses evolve continuously and cause severe disease annually, particularly in the elderly, children, pregnant women and people with underlying chronic conditions. Each year, across the globe, there are an estimated 1 billion cases of influenza, of which 3–5 million are severe cases and 290 000–650 000 lead to influenza-related respiratory deaths (4). Outbreaks of influenza highlight the burden and severity of annual epidemics on the global population and countries' health systems, as evidenced by seasonal epidemics that have significantly affected low- and middle-income countries (LMICs); for example, the 2002 outbreak in Madagascar had an estimated 2.5% case–fatality ratio (5) (for comparison, the 1918–1919 pandemic had an estimated 2–3% case–fatality ratio (6)). Seasonal epidemics also highlight the economic burden due to direct medical costs and indirect costs, such as loss of productivity due to work absenteeism.

Influenza viruses continually circulate in animals, and at times, these viruses gain the ability to spill over and infect humans. These viruses are novel to humans and have the potential to cause a pandemic. The first detection of the avian influenza A(H5N1) virus in humans in 1997, and its subsequent re-emergence in 2003, sparked concern that a new and virulent pandemic virus predecessor had emerged, which led to renewed interest in pandemic preparedness planning. Other avian influenza viruses, such as A(H5N6) and A(H9N2), have emerged and spread among poultry, and have caused sporadic human cases with varying severity. In 2013, a new subtype, avian influenza A(H7N9), emerged among poultry in China and has caused human infections

that have been unusually severe when compared with previous human infections with H7 subtype viruses. Although avian influenza viruses have not yet gained the ability to spread efficiently from human to human, these viruses continue to emerge and to be a constant reminder that they are only a few mutations away from causing an influenza pandemic.

In 2011, the Review Committee on the Functioning of the International Health Regulations (IHR) (2005) in relation to pandemic (H1N1) 2009 concluded, “the world is ill-prepared to respond to a severe influenza pandemic or to any similarly global, sustained and threatening public health emergency” (7). Since the release of that report there has been a strong global movement to advance IHR (2005) compliance and the building of core capacities to strengthen pandemic preparedness and health security. Additionally, considerable achievements have been made in influenza prevention, control and preparedness; for example, expansion of the Global Influenza Surveillance and Response System (GISRS), adoption of the Pandemic Influenza Preparedness (PIP) Framework, improved detection and monitoring tools, recommendations on target populations for vaccination, expansion of vaccine production capacity in LMICs, and improved One Health collaborations (see Annex 1).

Despite the progress made, many challenges and gaps remain (see Annex 2). The most urgent of these challenges and gaps have led to two high-level outcomes for this strategy. First, our current prevention and control tools have limitations, including suboptimal effectiveness, annual requirement for seasonal influenza immunization, and limited options for treatments. Hence, there is an urgent need for **better tools to prevent, detect, control and treat influenza**, including more effective vaccines and antiviral drugs that would instil public confidence and uptake, especially in LMICs. A focused and consensus-driven plan will build on the knowledge gaps previously identified by the WHO Public Health Research Agenda for Influenza, and prioritize the activities that will drive the development and innovation of new and improved tools over the next decade. Second, ongoing public health events highlight that **strong national capacities for preparedness and response against influenza** are essential. When it is embedded in national action plans for health security (NAPHS), influenza serves as an ideal pathogen to build capacities for all major areas of IHR (2005) functionality. Programmes for influenza can enhance core capacities across the public health spectrum, including integrated surveillance with an understanding of severity for respiratory disease, more data on disease and economic burden linked to prevention programmes, and development or updating of national influenza pandemic preparedness and response plans to support pandemic readiness.

Since pandemic (H1N1) 2009, WHO has implemented considerable changes so that it is both better prepared to respond to pandemics and other health emergencies (e.g. the development of the WHO Health Emergencies Programme following the 2013–2016 Ebola crisis), and better equipped to support countries’ capacity-building efforts. Building on the Sustainable Development Goals (SDGs), the Thirteenth General Programme of Work (GPW13) for 2019–2023 outlines WHO’s strategic priority in ensuring that 1 billion more people are better protected from health emergencies. National systems and programmes designed to address seasonal influenza will ensure that countries have the capacity to respond to a pandemic. These programmes have the added benefit of contributing to overall health system strengthening and countries’ progress towards universal health coverage (UHC) – another strategic priority in the GPW13 – because they aim to ensure that all people and communities, especially those at the

highest risk, have access to high-quality and affordable vaccines and treatments against influenza.

Building on its 70 years of global health leadership and six critical functions (8), WHO developed the Global Influenza Strategy for 2019–2030 to enhance global and national pandemic preparedness, to combat the ongoing threat of zoonotic influenza, and to improve seasonal influenza prevention and control in all countries. The strategy presents a unifying vision, and global goals and priorities that will rely on commitments from WHO, countries and partners for full implementation.

The investment case for influenza prevention, control and preparedness

Pandemic preparedness is a vital component of the global movement to strengthen health security through the attainment of core capacities to prevent, detect and respond to infectious disease threats, including influenza. Linking efforts on influenza prevention, control and preparedness with those on national health security planning can establish political commitment and leverage key resources to support sustainability. Capacity-building and financing improve a country's ability to respond more rapidly and nimbly to influenza and other infectious diseases.

A severe pandemic can result in millions of deaths globally, with widespread social and economic effects, including a loss of national economic productivity and severe economic burdens on affected citizens and communities. Recent estimates place the economic burden – economic losses and valuation of lives lost – of a moderately severe to severe pandemic at about US\$ 500 billion, or 0.6% of global income (9). Many countries have underinvested in public health systems for early detection, response and containment of outbreaks that affect their countries, and are not prepared for an outbreak on the scale of a moderate or severe pandemic. The cost of financing pandemic preparedness has been estimated at US\$ 4.5 billion per year, or less than US\$ 1 per person per year, which is less than 1% of the cost estimates for responding to a moderately severe to severe pandemic (10). Investment in national and global pandemic preparedness provides significant economic benefits to health systems when emergencies occur; it also contributes to building core capacities for influenza and other emerging pathogens in support of IHR (2005).

The economic burden of seasonal influenza, especially in LMICs, is not fully understood, owing to a lack of standardization of cost analyses across countries. However, recent reviews have shown that direct costs due to seasonal influenza are higher in high-income countries (HICs), whereas indirect costs are higher in LMICs, and such costs are likely to affect the individuals that are least able to bear them (11). Further, vaccination is currently the best intervention for preventing and reducing the impact of influenza, and it provides cost savings to countries. A review of more than 140 studies showed that the per capita cost of seasonal influenza cases ranged from US\$ 30 to over US\$ 60, and that cost–effectiveness ratios for vaccination ranged from US\$ 10 000/outcome to more than US\$ 50 000/outcome (12).

Influenza is also posing a challenge for other global health threats, including noncommunicable diseases (NCDs), severe pneumonia and antimicrobial resistance (AMR). For example, studies have shown that respiratory viral infections, including those due to the influenza virus, increase

the risk of heart attack and stroke in the 3 days following infection (13), and frequently exacerbate chronic obstructive pulmonary disease (14). The link between severe pneumonia and influenza, especially in children in LMICs, has also been further investigated, including through the Pneumonia Etiology Research for Child Health (PERCH) Study.¹ Other studies have shown that up to 50% of pneumonia cases are linked to respiratory viruses, and up to 45% of pneumonia cases in children show evidence of viral–bacterial coinfections (15,16). And finally, inappropriate antibiotic use for viral respiratory infections, including influenza, continues to contribute to the increasingly serious problem of AMR. Although more data are needed, there is an established evidence base highlighting the relationships between influenza and these significant global health threats that affect both HICs and LMICs. By investing in influenza prevention, control and preparedness efforts, countries will realize secondary benefits beyond influenza throughout their health systems.

Influenza affects all countries, communities and individuals. Seasonal influenza viruses will continue to circulate, and influenza viruses with pandemic potential will continue to emerge. This strategy serves as a global call for all countries and partners to prioritize the implementation of influenza programmes as an investment for greater health system strengthening and pandemic preparedness.

¹ The PERCH Study has produced several publications on rationale, study design and analytic methods, preparatory analyses and subanalyses. The publications can be accessed at: <https://www.jhsph.edu/ivac/resources/perch-publications/>.

Vision: Attainment of the highest possible influenza prevention, control and preparedness to safeguard the health of all people.

Mission: WHO, countries and partners collaborate to optimize and align global and national capacities for prevention, rapid detection and response, to reduce the burden and impact of seasonal, zoonotic and pandemic influenza.

Goals:

1. Reduce the burden of seasonal influenza.
2. Minimize the risk of zoonotic influenza.
3. Mitigate the impact of pandemic influenza.

High-level outcomes for 2030:

1. Better global tools: a focused, consensus-driven plan leads to greater research, innovation and availability of new and improved tools for the prevention, detection, control and treatment of influenza.
2. Stronger country capacities: every country has a prioritized influenza programme that is evidence-based; is optimized to fit the country's needs; and contributes to national and global preparedness, response and health security.

Strategic objectives and actions

Four strategic objectives and 10 priorities support the vision and goals of the strategy, and outline a way forward for all stakeholders to attain the high-level outcomes by 2030.

- 1. Promote research and innovation to address unmet public health needs**
 - A. Promote research and innovation for improved and novel diagnostics, vaccines and treatments against influenza.
 - B. Promote operational research for influenza prevention, control and programme delivery.
 - C. Promote research to better understand the virus characteristics and host factors that drive the impact of influenza.
- 2. Strengthen global influenza surveillance, monitoring and data utilization**
 - A. Enhance, integrate and expand virological and disease surveillance.
 - B. Build a strong evidence base for understanding the impact and burden of influenza.
 - C. Develop effective influenza communication strategies across multiple sectors and between stakeholders.
- 3. Expand seasonal influenza prevention and control policies and programmes to protect the vulnerable**
 - A. Integrate nonpharmaceutical interventions (NPIs) into prevention and control programmes.
 - B. Design and implement evidence-based immunization policies and programmes to reduce transmission and disease severity.
 - C. Design and implement evidence-based treatment policies and programmes to reduce morbidity and mortality.
- 4. Strengthen pandemic preparedness and response for influenza to make the world safer**
 - A. Strengthen national, regional and global planning to enable timely and effective pandemic readiness.

The following sections further highlight each strategic objective, the priority actions needed to achieve each objective, and examples of supporting components that all stakeholders can tailor and incorporate into their implementation plans and programmes. Communications and enhanced animal–human interface collaboration are cross-cutting and are integrated throughout the strategic objectives, as appropriate. The role of the WHO Secretariat is outlined for each strategic objective, followed by key WHO assets and strategies that are aligned with the objective and will drive its implementation.

Strategic objective 1: Promote research and innovation to address unmet public health needs

This strategic objective focuses on the promotion of global research and innovation to fill urgent knowledge gaps in the current understanding of the influenza virus and host response; the aim is to advance the development of novel products and strategies, to make a measurable impact on the burden of mortality and morbidity due to influenza. Without more effective antiviral drugs and vaccines with stronger, broader and longer lasting immunity, countries will struggle to acquire public confidence and fully implement their influenza prevention, control and preparedness efforts. This strategic objective builds on the knowledge gaps identified by the WHO Public Health Research Agenda for Influenza, and prioritizes activities that will drive the development and innovation of new and improved tools for prevention, detection, control and treatment.

Action 1A: Promote research and innovation for improved and novel diagnostics, vaccines and treatments against influenza

Supporting components:

- i. Promote the development of improved, novel and universal influenza vaccines with increased breadth of protection, longer duration of protection, enhanced effectiveness against severe disease and decreased time for production.
- ii. Promote the development of more effective influenza treatments, including antiviral drugs, broadly reactive monoclonal antibodies and host-response immune modulators.
- iii. Promote the development and use of new diagnostics, surveillance and detection methods for influenza, such as next-generation sequencing and affordable point-of-care testing.

Action 1B: Promote operational research for influenza prevention, control and programme delivery

Supporting components:

- i. Investigate antibody landscape data and carry out research during outbreaks, including through clinical trials, to better define how prevention and control tools can be used most effectively.
- ii. Assess optimal strategies for the use of the currently available vaccines and antiviral drugs, and for the use of newly approved technologies and platforms for seasonal influenza prevention and control.
- iii. Support national regulatory authorities (NRAs) on approval pathways for the next generation of influenza vaccines and medicines, and strengthen processes for expedited review and recommendation of products during emergencies.

Action 1C: Promote research to better understand the virus characteristics and host factors that drive the impact of influenza

Supporting components:

- i. Evaluate mechanisms contributing to efficient transmission of viruses circulating in animals to humans.
- ii. Evaluate interventions to reduce the risk of transmission of zoonotic influenza in humans.
- iii. Evaluate host factors that determine the vulnerability of humans to influenza viruses.

Role of the WHO Secretariat in promoting research and innovation

The role of the WHO Secretariat in promoting research and innovation is to:

- develop and facilitate the implementation of a focused, consensus-driven plan that leads to greater research and innovation to meet the urgent need for better global tools;
- engage and convene funding and research partners – including global philanthropies, academia and industry – to facilitate coordination and collaboration;
- review and synthesize the generation and sharing of evidence and new developments;
- identify synergies between the strategy and the work accomplished by the WHO Research and Development Blueprint (17), including advances in areas of development of roadmaps and target product profiles, regulatory and ethical pathways, clinical trial design, and data and sample sharing;
- provide priorities, preferred product characteristics and roadmaps to shape global influenza research; and
- advocate for new ways of thinking and best practices within the context of the needs of vulnerable populations and low-resource settings.

Alignment with WHO assets and strategies

Other WHO assets and strategies that this strategy aligns with are:

- Public Health Research Agenda for Influenza;
- Global Action Plan for Influenza Vaccines (GAP) progress and final recommendations;
- WHO preferred product characteristics for next-generation influenza vaccines (18);
- public–private partnerships established through the PIP Framework and other WHO programmes; and
- Research and Development Blueprint.

Strategic objective 2: Strengthen global influenza surveillance, monitoring and data utilization

This strategic objective focuses on strengthening GISRS and global influenza monitoring, to generate data and information that can be used by policy-makers to make decisions. Quality surveillance data are critical for conducting risk assessments and understanding the impact and burden of influenza. Effective communication strategies are important to engage policy-makers and communities in prevention and control efforts, and to increase buy-in and confidence.

Action 2A: Enhance, integrate and expand virological and disease surveillance

Supporting components:

- i. Strengthen and support the evolution of GISRS towards an integrated surveillance system of laboratory and epidemiological data to support assessments of severity and public health decision-making.
- ii. Expand the capability for rapid risk assessment, effective information sharing and intersectoral investigation of and response to zoonotic influenza cases and other respiratory disease outbreaks.
- iii. Advance IHR (2005) core capacity-building (laboratory, surveillance, response, risk communication and coordination including at the animal–human interface) and promote sustainability through integration of influenza priority activities into NAPHS.

Action 2B: Build a strong evidence base for understanding the impact and burden of influenza

Supporting components:

- i. Improve the understanding of seasonality, and the disease and economic burden of influenza, especially in LMICs.
- ii. Develop systems to support the real-time evaluation of burden and severity of influenza, to understand the variable impact on public health, health systems and society.
- iii. Promote innovative modelling and use of new data sources to improve forecasting of emergence, timing and severity of influenza, and to better understand the impact of pharmaceutical interventions and NPIs.

Action 2C: Develop effective influenza communication strategies across multiple sectors and between stakeholders

Supporting components:

- i. Communicate information on risk and burden of influenza and related complications to policy-makers and other key decision-makers, to enhance understanding of impact and increase political commitment.
- ii. Support the development of risk communications plans and educational materials for effective use of pharmaceutical interventions and NPIs, to optimize prevention and control.

- iii. Support policies and programmes for community engagement and social interventions for reducing and mitigating the threat of seasonal and pandemic influenza, including factors related to vulnerability beyond medical risk.

Role of the WHO Secretariat in surveillance, monitoring and data utilization

The role of the WHO Secretariat in surveillance, monitoring and data utilization is to:

- provide ongoing risk assessments and situational awareness through the collection, analysis and communication of country information, thus contributing to global, regional and country decision-making (e.g. on the development of a candidate vaccine virus);
- monitor and regularly disseminate data on disease burden, economic burden and averted outcomes, to assist countries and policy-makers with the development and implementation of effective prevention and control programmes;
- provide leadership on global public health matters regarding the sharing of influenza data and viruses, including within the context of other international bodies and agreements, such as the Nagoya Protocol to the Convention on Biological Diversity;
- provide technical assistance and standards for developing estimates on influenza-related disease and economic burden, to allow countries to build country-level investment for influenza prevention, control and preparedness;
- identify synergies and support integration with national health security planning efforts; and
- strengthen partnerships with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE), to enhance information sharing between the public health and animal health sectors, and to expand rapid joint response capabilities at the country, regional and global levels.

Alignment with WHO assets and strategies

Other WHO assets and strategies that this strategy aligns with are:

- GISRS, including expert groups on burden of disease and modelling;
- the PIP Framework and its associated components;
- the Five-Year Global Strategic Plan to Improve Public Health Preparedness and Response 2018–2023; and
- Joint External Evaluations (JEE), NAPHS.

Strategic objective 3: Expand seasonal influenza prevention and control policies and programmes to protect the vulnerable

This strategic objective focuses on the establishment of seasonal influenza prevention and control programmes in all countries, to develop the necessary systems, which would also contribute to pandemic preparedness and response efforts. The two primary aims of an established seasonal influenza prevention and control programme are to protect those whose circumstances affect their vulnerability to seasonal influenza and related complications (e.g. at-risk groups, and migrant and displaced populations); and to contribute to UHC by providing access to tools for prevention and control of influenza, and information on the best use of such tools. The tools for the prevention and control of influenza include:

- NPIs to slow the spread of illness;
- vaccines (even if only for certain target groups in most countries) to reduce transmission, disease severity and incidence of serious complications and death; and
- antiviral drugs to treat the illness and reduce the risk of serious complications and death.

Action 3A: Integrate nonpharmaceutical interventions into prevention and control programmes

Supporting components:

- i. Communicate the benefits of integrating NPIs into seasonal programmes and pandemic influenza plans to policy-makers across sectors.
- ii. Provide educational materials on NPIs to the public, including settings and groups at highest risk for influenza.
- iii. Engage with local health authorities and communities to plan for deployment of community-level NPIs – for example, school closures and social distancing measures for schools, workplaces and mass gatherings – during seasonal epidemics and pandemics.

Action 3B: Design and implement evidence-based immunization policies and programmes to reduce transmission and disease severity

Supporting components:

- i. Facilitate the increased use of influenza vaccines globally, including through addressing vaccine misperceptions and hesitancy, and promoting the public financing of seasonal influenza vaccines for target groups.
- ii. Support countries to develop and implement national seasonal immunization policies for health care workers and other target groups, as recommended by the Strategic Advisory Group of Experts (SAGE) on Immunization (19), and to monitor vaccine uptake through national databases.
- iii. Promote studies to estimate vaccine effectiveness in reducing severe disease and mortality in target populations by vaccine type, vaccination history, birth cohort or immune imprinting, and timing of vaccine receipt, especially in LMICs.

Action 3C: Design and implement evidence-based treatment policies and programmes to reduce morbidity and mortality

Supporting components:

- i. Promote the appropriate, evidence-based and effective use of currently available antiviral drugs, and integration of antiviral drugs into treatment programmes.
- ii. Strengthen countries' capacities for triage, clinical management and treatment of patients with severe influenza.

Role of the WHO Secretariat in expanding seasonal influenza prevention and control

The role of the WHO Secretariat in expanding seasonal influenza prevention and control is to:

- provide guidance and support country-led approaches to embed influenza in broader communicable disease management and UHC packages for health prevention and promotion;
- convene advisory, technical and working groups to assess evidence for current methods for prevention and control of influenza;
- support NRAs to develop capacities to approve and monitor influenza vaccines and treatments;
- monitor country-level uptake and impact of influenza vaccines and treatments;
- improve coordination across internal WHO programmes, including health emergencies, health system strengthening, regulatory system strengthening and immunizations; and
- enhance and expand partnerships with other agencies, including the UN Children's Fund (UNICEF), to support implementation of influenza prevention and control programmes.

Alignment with key WHO assets and strategies

Other WHO assets and strategies that this strategy aligns with are:

- GISRS, including expert groups on antiviral drugs; and
- SAGE recommendations and the SAGE influenza working group

Strategic objective 4: Strengthen pandemic preparedness and response for influenza to make the world safer

This strategic objective focuses on the strengthening of national, regional, global and multisectoral collaboration, to ensure that preparedness efforts are better aligned, and the response to a pandemic can be more timely and effective. Influenza capacity-building will continue to strengthen IHR (2005) core capacities over time; however, countries and partners should continue pandemic planning efforts to provide better awareness of both the current state of readiness and how existing capabilities will be operationalized during the response to a pandemic.

Action 4A: Strengthen national, regional and global planning to enable timely and effective pandemic readiness

Supporting components:

- i. Support countries' national planning, which includes governance and regulatory processes, and mechanisms to develop, update and exercise national influenza pandemic preparedness plans, which include both pharmaceutical interventions and NPIs.
- ii. Support equitable access to a sufficient supply of vaccines, antiviral drugs and treatments.
- iii. Support country or regional capacities to stockpile (where applicable), acquire, distribute and administer countermeasures and supplies during a pandemic.

Role of the WHO Secretariat in strengthening pandemic preparedness and response

The role of the WHO Secretariat in strengthening pandemic preparedness and response is to:

- collaborate across internal WHO programmes and with external partners to ensure capacity-building efforts are aligned and communicated, ensuring resources are used optimally;
- provide technical assistance to support country preparedness and exercising of national influenza pandemic preparedness and response plans;
- identify synergies and support integration with national health security planning efforts; and
- develop or update guidance, including global vaccine preparedness plans for switching from seasonal to pandemic vaccine manufacturing; procurement, deployment and administration of vaccines, treatments and supplies; and NPIs.

Alignment with key WHO assets and strategies

Other WHO assets and strategies that this strategy aligns with are:

- GISRS and expert groups dedicated to pandemic severity, vaccine switch and detection;
- the PIP Framework and its associated components;
- the Five-Year Global Strategic Plan to Improve Public Health Preparedness and Response 2018–2023;
- JEE, NAPHS; and

- OpenWHO.²

² OpenWHO is WHO's interactive, web-based, knowledge-transfer platform offering online courses to improve the response to health emergencies. There are course offerings dedicated to seasonal, zoonotic and pandemic influenza. The platform can be accessed at <https://openwho.org/>.

Implementation of the strategy

This strategy provides a landscape of the global priorities in attaining the highest possible influenza prevention, control and preparedness to the end of 2030. Successful implementation will require WHO, countries and partners to integrate these priorities in their own policies, programmes and systems. In a world with limited resources and competing priorities, it is essential that all stakeholders build upon and align with current activities, and use common resources to promote sustainability. There are **five key enablers** that will help guide the activities of WHO, countries and partners as they implement the strategy:

- countries are at the centre;
- global influenza assets and strategies are strengthened and sustained;
- countries, industry and civil society continue to support and implement the PIP Framework;
- partnerships are strengthened and expanded; and
- value for money.

These enablers are discussed below.

Countries are at the centre: The primary aim of this strategy is to ensure that countries see a measurable impact in the reduction in the burden of seasonal, zoonotic and pandemic influenza. Many of the activities that follow from this strategy are dependent on country ownership, a country-level approach and a whole-of-government commitment. As countries develop and implement their influenza policies and programmes, they are encouraged to ensure that these policies and programmes are optimized for their own needs, and are integrated with appropriate existing systems that can become **sustainable** over time. Additionally, as countries further implement the IHR (2005), develop NAPHS and build their core capacities, integrating influenza can help to build political support and encourage dedicated national funding for influenza prevention, control and preparedness.

Global influenza assets and strategies are strengthened and sustained: These cross-cutting WHO assets and strategies bring together a wide network of partners and experts dedicated to developing a robust evidence base and building countries' core capacities for influenza. Implementation of this strategy will not only rely heavily on the expertise from these networks, but will also ensure their continued success, expansion and sustainability.

- **GISRS** is instrumental in promoting and advancing global and national influenza detection and monitoring for influenza; conducting risk assessments; understanding severity; and providing recommendations on which influenza virus strains to include in seasonal and pandemic influenza vaccines. Enhancing and improving GISRS is critical to the implementation of the strategy, providing support to optimize preparedness at national, regional and global levels.
- The **Public Health Research Agenda for Influenza** has facilitated discussion, coordination and interaction among influenza researchers, funding organizations and public health professionals globally to identify knowledge gaps and research priorities across five streams: reducing the risk of emergence of pandemic influenza; limiting the

spread of pandemic, zoonotic and seasonal epidemic influenza; minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza; optimizing the treatment of patients; and promoting the development and application of modern public health tools. All four strategic objectives in the Global Influenza Strategy include high-priority issues identified in the Public Health Research Agenda for Influenza. Strategic objective 1 on research and innovation will necessitate development of a focused and consensus-driven plan derived from the research agenda and beyond, to drive the development and delivery of novel and improved tools for prevention, detection, control and treatment of influenza.

- Upon the closure of the **GAP** in 2016, its Advisory Group issued five recommendations (20) requiring continued global coordination and WHO's leadership. These five recommendations span the strategy's strategic objectives and will drive the implementation of actions.
 1. Manufacturers in developing countries still require technical assistance and business acumen.
 2. Research and development of improved influenza vaccines and vaccination strategies need to be coordinated.
 3. The root causes of influenza vaccine hesitancy need to be identified and addressed in all countries.
 4. More evidence is needed on vaccine effectiveness in specific risk groups.
 5. An expert review of the initial GAP assumptions is needed to identify innovative ways of addressing global pandemic preparedness.

Countries, industry and civil society continue to support and implement the PIP

Framework: The PIP Framework facilitates the increased sharing of influenza viruses with human pandemic potential, and ensures greater equity of access to vaccines, antiviral drugs and other pandemic-related supplies.

Funding made available through the PIP Framework Partnership Contribution (PC) enables countries to strengthen pandemic influenza preparedness and response capacities across key areas of work – as outlined in the High-Level Implementation Plan (HLIP) – that are essential to the overall implementation and success of this strategy.

Partnerships are strengthened and expanded: Influenza prevention, control and preparedness require effective multisectoral partnerships and a whole-of-society approach. Successful implementation of the strategic objectives and actions of the strategy will require engagement by governments, nongovernmental organizations, expert networks, industry, civil society, military, academia and communities. Through its existing influenza programmes and initiatives, WHO has established many partnerships across governments, industry and civil society to promote influenza prevention, control and preparedness. WHO will continue to foster those partnerships and engage with additional non-state actors through the WHO Framework of engagement with non-state actors (FENSA) (21), to implement the broader influenza objectives and actions in this strategy.

Value for money: WHO needs to show that its activities, wherever they are conducted, are maximizing the impact derived from every dollar spent. WHO has launched a value-for-money

approach (22), and is fostering an organizational culture driven by results and impact. Implementation of this strategy will be guided by the five dimensions required to achieve value for money:

- *economy*: keeping inputs (human and financial resources) as lean as possible;
- *efficiency*: using those inputs to obtain or “buy” as much output as possible, especially through innovative partnerships, as outlined above;
- *effectiveness*: keeping the quality of WHO’s output as high as possible to have the greatest possible impact;
- *equity*: taking into consideration the extent to which outputs benefit and ensure coverage of the most vulnerable and hard-to-reach populations; and
- *ethics*: ensuring that inputs, outputs and outcomes uphold the fundamental ethical principles of respect, goodwill, justice and not causing harm.

Implementation, monitoring and evaluation of the strategy

The strategy outlines objectives and actions applicable to all stakeholders, including the three levels of WHO, and provides a time frame that is consistent with the SDGs. The WHO Secretariat will initially develop a costed 5-year implementation plan to correspond with the WHO GPW13 time frame of 2019–2023. The global influenza landscape is constantly evolving, and researchers and stakeholders continue to innovate and develop novel products, approaches and interventions to better prevent, detect, control and treat influenza. Therefore, implementation of the strategy will be flexible, so that game-changing technologies, innovations and priorities can be properly integrated.

The WHO implementation plan for this strategy will incorporate planned activities for 2019–2023 at the three levels of WHO, including those outlined in biennial workplans, existing grants and the PIP Framework PC HLIP workplans. After the first 5 years, WHO will review the strategy and implementation plan to assess progress; this will allow substantial developments made in influenza prevention, control and preparedness to define the way forward for the remainder of the implementation of the strategy.

WHO will regularly monitor six high-level measures within its implementation plans:

- countries with the capacities to detect, diagnose and report influenza;
- national, regional and global measures of burden and routine systems to measure severity;
- countries incorporating influenza programmes into national action plans that include prevention strategies for NPIs, vaccines and antiviral drugs, as appropriate;
- countries developing, updating, implementing and exercising pandemic plans;
- global production, distribution and uptake of vaccines; and
- global coordination of research and development.

Annex 1: Achievements in influenza prevention, control and preparedness since 2002

Many important achievements and advancements in the global influenza landscape have occurred since the development of the World Health Organization's (WHO's) last overarching influenza strategy, the 2002 WHO Global Agenda on Influenza Surveillance and Control (23), which outlined a series of prioritized activities to reduce morbidity and mortality from annual influenza epidemics and prepare the world for the next pandemic.

Enhanced Global Influenza Surveillance and Response System and improved virological surveillance and better detection methods

The Global Influenza Surveillance and Response System (GISRS) is a WHO-coordinated system of public health laboratories. Since its establishment in 1952, it has grown to over 150 institutions in more than 110 countries, and additional regional networks have been established across WHO regions. GISRS conducts year-round surveillance of influenza viruses, monitors the evolution of influenza viruses and provides recommendations for laboratory diagnostics, vaccines, antiviral susceptibility testing and risk assessment. Additionally, GISRS serves as a global alert mechanism for the emergence of influenza viruses with pandemic potential, and has broader benefits for other emerging respiratory pathogens, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). This unique system has enabled the development and adoption of new diagnostics, assays, technologies and tools, including FluNet for virological data and the tool for influenza pandemic risk assessment (TIPRA) (24), to assess the risk of influenza viruses with pandemic potential.

Improved epidemiological surveillance and monitoring

Since the 2002 WHO Global Agenda on Influenza Surveillance and Control, WHO has significantly improved the guidance and tools available to assist with national, regional and global epidemiological surveillance and monitoring. Since 1999, WHO had recommended a case definition for influenza-like illness (ILI); however, following pandemic (H1N1) 2009, WHO initiated a global review to develop influenza surveillance standards. The review resulted in the modification and clarification of the ILI case definition and the development of a new case definition for severe acute respiratory infection (SARI) (25). In 2015, WHO developed the *Manual for estimating disease burden associated with seasonal influenza* (26) to help countries to use surveillance data to generate disease burden estimates that inform national prevention and control measures, and global and regional burden estimates. Countries use the online WHO FluID platform (27) to regularly submit national epidemiological data, which contribute to information on global trends, spread, intensity and impact of influenza. FluID complements other existing platforms in the WHO regions as well as the virological data captured by FluNet. In 2017, WHO developed the pandemic influenza severity assessment (PISA) (28) tool to describe the epidemiological situation and assess the severity of an influenza epidemic or pandemic based on all available information; inform national and global risk assessments; and inform public health preparedness, response and recovery measures as well as resource allocation.

Pandemic Influenza Preparedness Framework

Following 4 years of negotiations, WHO Member States adopted the Pandemic Influenza Preparedness (PIP) Framework in 2011. This landmark agreement brings together Member

States, industry, civil society and other stakeholders in support of the framework's underpinning principle, which is that rapid and timely sharing of influenza viruses with human pandemic potential and genetic sequence data must be pursued on an equal footing with the sharing of benefits. WHO and manufacturers have entered into legally binding standard material transfer agreements (SMTAs), which ensure the provision of pandemic-related vaccines, antiviral drugs and diagnostics to countries through WHO. As of 2018, these SMTAs represent a commitment of more than 400 million doses of pandemic influenza vaccine, 10 million treatment courses of antiviral drugs, 250 000 diagnostic kits, and 25 million syringes in the event of a pandemic. The continued implementation and success of the PIP Framework are essential to global pandemic preparedness.

Through the PIP Framework's benefit-sharing mechanisms, influenza vaccine, diagnostic and pharmaceutical manufacturers using GISRS make voluntary annual partnership contributions to help fund country-level preparedness and response capacity-building activities, which are coordinated through the PIP Partnership Contribution (PC) High-Level Implementation Plan (HLIP).

Implementation of the International Health Regulations (2005)

The IHR (2005) are an international legal instrument that aims to prevent, protect against, control and enable public health response to the international spread of disease in ways that are commensurate with avoiding unnecessary interference with international traffic and trade. In May 2005, WHO Member States adopted the IHR (2005), which then entered into force on 15 June 2007. The IHR (2005) require States Parties to strengthen core public health capacities, including preparedness, surveillance and response. All States Parties were expected to begin implementing plans of action to ensure that core capacities required by the IHR (2005) were present and functioning throughout their territories by the deadline of 15 June 2012. In 2016, WHO, in collaboration with Member States and other partners, developed the Joint External Evaluation (JEE) tool to assess countries' capacities and assist them with identifying the most urgent needs within their health systems. Additionally, Member States developed the national action plans for health security (NAPHS) planning process, to address national gaps and accelerate implementation of the IHR (2005).

Countries, WHO and partners across the globe have contributed significant resources to building and strengthening national capacities to detect, prevent and control influenza. The IHR (2005) are not limited to specific diseases, although all human cases with a novel influenza A subtype are required to be notified by States Parties to WHO under the IHR (2005). However, the ongoing influenza capacity-building efforts positively contribute to countries' overall IHR (2005) core capacity requirements.

In 2018, the Five-Year Global Strategic Plan to Improve Public Health Preparedness and Response, 2018–2023 (29) was launched. This plan aims to strengthen the capacity of both WHO and Member States, and ensure implementation of the IHR (2005) through three strategic pillars: building and maintaining States Parties' core capacities required under the IHR (2005); strengthening event management and compliance with the requirements under the IHR (2005); and measuring progress and promoting accountability. WHO has the role of ensuring alignment of this strategic plan with the Global Strategy for Influenza. The ongoing efforts by WHO and its

partners to help countries develop influenza capacities advance implementation of the IHR (2005) and specifically contribute to the first two pillars in the Five-Year Global Strategic Plan to Improve Public Health Preparedness and Response.

Strategic Advisory Group of Experts on immunization recommendations

In 2012, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization issued updated recommendations for influenza vaccination in target populations, including pregnant women, health care workers, children aged 6–59 months, elderly persons and persons with certain chronic conditions (30). Although there are countries that implement a universal recommendation for all ages above 6 months to be vaccinated, the 2012 SAGE recommendations have helped countries to focus on their key target groups as indicated by national burden data. A new SAGE working group on influenza was established in December 2017, to review scientific evidence and relevant programmatic considerations to assess whether there is sufficient evidence to inform a revision of the global policy on the use of influenza vaccines.

Global Action Plan for Influenza Vaccines

The Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 as a 10-year comprehensive strategy to reduce the global shortage and inequitable access of pandemic influenza vaccines through three major approaches: increase evidence-based seasonal vaccine use; increase vaccine production capacity; and promote research and development of more effective vaccines. The overarching goal was to make available enough vaccines to immunize 70% of the world's population with two doses of pandemic vaccine within 6 months of the transfer of the vaccine virus strain to manufacturers. Through GAP, technology for production of influenza vaccines was transferred to 14 low- and middle-income countries (LMICs) (31). During the decade of the GAP, through the establishment of new production capacity and expansion of existing capacity, the estimated global annual seasonal influenza vaccine production capacity nearly tripled (from 500 million doses to 1.46 billion doses), and the potential global pandemic vaccine production capacity more than quadrupled (from 1.5 billion doses to 6.37 billion doses, of which over 1 billion doses could be contributed by GAP grantee manufacturers) (32).

Public Health Research Agenda for Influenza

WHO developed the Public Health Research Agenda for Influenza in 2009, to support the development of evidence to strengthen public health guidance and actions essential for limiting the impact of pandemic, zoonotic and seasonal epidemic influenza. In 2013, WHO published a progress review (33) of the research agenda; the review found that considerable funding had been dedicated to global influenza research since the spread of H5N1, and that much progress had been made to fill knowledge gaps, but that more work was needed. Further, the continually evolving nature of influenza viruses has spawned many new questions. In view of these challenges, WHO updated the research agenda in 2017 (34) to continue to promote influenza research in high-priority areas and address unmet public health needs over the next 5–10 years. This agenda provides a roadmap for short-term and long-term research activities that are aligned with the strategic objectives throughout this strategy.

Improved One Health collaborations

WHO collaborates with the Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE) to promote the One Health approach, and to facilitate establishing cross-sectoral coordination and response to public health threats at the human–animal–ecosystem interface. The 2010 Tripartite Agreement Concept Note (35) set out a collective strategic direction for the three organizations to take forward, and underlined their joint commitment to work more closely together in support of countries. FAO, OIE and WHO reaffirmed their commitment in 2017, citing achievements in the prevention and control of zoonotic influenza while promising to maintain this momentum (36).

WHO Health Emergencies Programme

Following the 2013–2016 Ebola crisis, the Sixty-ninth World Health Assembly adopted decision WHA69(9) regarding the reform of WHO’s work in health emergency management. The WHO Health Emergencies Programme (WHE) was officially launched in July 2016 to address the full risk management cycle, including prevention, preparedness, response and recovery (37) WHE leads and coordinates international responses to contain disease outbreaks, and provides effective relief and recovery to affected people. WHE has a common structure across headquarters, regional offices and country offices, comprising one workforce, one budget, one line of accountability, one set of processes and systems, and one set of benchmarks. The common structure of the programme across the three levels of the organization comprises five technical and operational departments: Infectious Hazards Management; Country Health Emergency Preparedness and the IHR (2005); Health Emergency Information and Risk Assessments; Emergency Operations; and Emergency Core Services. WHO’s Influenza Preparedness and Response Unit is located within WHE. In addition to capacity-building efforts, during a health emergency, including an influenza pandemic, WHE would manage the response as operationalized through the Incident Management System outlined in the WHO Emergency Response Framework (38).

Annex 2: Ongoing challenges in influenza prevention, control and preparedness

Epidemiological and virological surveillance

Influenza surveillance is fundamental to our understanding of the virus. Over the past decade, the Global Influenza Surveillance and Response System (GISRS) has been strengthened and improved through the work of the World Health Organization (WHO) and partners. The number of Member States sharing influenza viruses with GISRS increased to 130 in 2017. Although the number of Member States sharing laboratory and epidemiological data through FluNet and FluID has increased, 31% and 58% of Member States did not routinely share data on these respective WHO platforms during 2016–2017 (39). Some countries still lack the capacity to detect novel influenza viruses, which is a key component in the International Health Regulations (IHR) (2005) core capacities. Improvements in rapid and timely sharing of data and viruses are needed for accurate, ongoing risk assessments of influenza viruses with pandemic potential. Improved systems to understand severity are essential to developing appropriate actions in the event of a pandemic.

Disease and economic burden

Understanding influenza morbidity, mortality and economic burden is essential for countries to develop national influenza prevention, control and preparedness policies. These data enable policy-makers to prioritize influenza, establish political will, make informed evidence-based decisions, and inform the development of immunization and treatment programmes.

Most estimates of the disease and economic impact of influenza, along with analyses of risk factors for severe infections, have come from high-income countries (HICs). Despite considerable success with low- and middle-income countries (LMICs) generating their own burden estimates in the past decade, additional studies in these countries are required to better understand geographical burden as well as the burden of severe influenza among risk groups. Regional and global collaboration can play an important role in understanding burden of disease by pooling data or extrapolating data based on trends from neighbouring countries.

Pandemic preparedness

To aid countries with pandemic preparedness planning, WHO developed guidance on pandemic influenza risk management, which provides risk-based strategies and approaches to pandemic influenza preparedness and response, and encourages countries to develop sustainable and resilient pandemic preparedness plans (40). In addition, in January 2018, WHO published a checklist to help countries develop or update their plans (41). As of September 2018, only 12 countries had updated and published their plans since the publication of the interim guidance in 2013, 13 countries updated and published their plans between 2010 and 2013, 68 countries published their plans in or before 2009, and 101 countries either do not have an influenza preparedness plan or have a plan that is not publicly available (42). Because influenza capacity-building efforts contribute to countries' IHR (2005) core capacities, pandemic preparedness planning should be aligned with national health security efforts, such as the Joint External Evaluation (JEE) and national action plans for health security (NAPHS) planning processes and simulation exercises, to maximize efficiency and consistent utilization of existing systems.

Nonpharmaceutical interventions

Nonpharmaceutical interventions (NPIs), also known as community mitigation strategies, are a critical tool for limiting the transmission and spread of influenza, allowing people to better protect themselves and others, and they are the first line of defence against influenza in all countries. NPIs are the most readily available set of interventions; they can be on the personal level (e.g. better hand washing or the use of facemasks) or on the community level (e.g. social distancing in schools, workplaces and events). During the 1918 pandemic, NPIs were the only available set of interventions; modern research on 1918 mortality data and experience with NPI implementation has provided historic evidence on the effectiveness of early, layered NPI implementation, even in the context of a severe and highly transmissible pandemic (43). Since the 2009 pandemic, a number of countries have fully integrated NPIs into their national influenza pandemic preparedness plans or published NPI guidelines. Additionally, there have been more contemporary studies to assess the effectiveness of NPIs. However, more attention is needed to better educate policy-makers about the benefits of NPIs and their role in national influenza prevention and control strategies.

Vaccines

Vaccines against influenza were developed more than 70 years ago and they remain the most effective intervention for preventing infection and potentially reducing clinical severity (44,45). There are several challenges that affect the production of influenza vaccines. At least 90% of current influenza vaccines rely on embryonated eggs for production. Maintaining an adequate supply of eggs to meet the increased demand for vaccine during a pandemic could be further compromised if the pandemic virus is lethal to egg-laying poultry. Production of influenza vaccines with this technology is also a time-intensive process, requiring about 5–6 months between manufacturers receiving the vaccine strain and delivering the vaccine. Further, some influenza viruses are increasingly unfit to grow in eggs, and tend to undergo changes in antigenic characteristics upon passage in eggs. This underscores the need to diversify and optimize current production capabilities and technologies (i.e. cell-based, recombinant and adjuvanted vaccines) and seek new vaccines that offer stronger, broader, more long-lasting protection and can be produced more rapidly. To this end, in 2017, WHO published preferred product characteristics (46) for improved influenza vaccines and the development of new vaccines. The guidance suggests that efforts to understand the impact of influenza vaccination should be focused on severe outcomes in LMICs. It also promotes research on vaccine characteristics beneficial in LMIC settings, especially the development of vaccines that provide longer lasting protection.

Vaccination programmes

Because influenza viruses are especially prone to changes in their genetic make-up, current seasonal influenza vaccines are strain-based and rarely provide protection beyond 1 year. Hence, individuals must be vaccinated every year against the predominant circulating seasonal viruses. This annual vaccination requirement as well as varying (and sometimes low) vaccine effectiveness have been highlighted as reasons leading to vaccine hesitancy and misperception among those at increased risk for complications of influenza. Data on vaccine use are still sporadic and unreliable. In 2015, about 486 million doses of seasonal vaccine were distributed globally by members of the International Federation of Pharmaceutical Manufacturers and Associations (47); trends in distribution vary among WHO regions, with some showing progress, but others a decline in distribution. There are major disparities in the distribution of vaccine and,

by extension, the use of vaccine. Recent data show that 47% of the global population (i.e. residents of countries in the WHO Eastern Mediterranean Region, South-East Asia Region and African Region) received only 5% of distributed vaccines. National seasonal vaccination programmes ensure that appropriate systems are in place for vaccine deployment and are tested every year. Countries and the global community must understand and address key issues and barriers that affect influenza vaccine distribution, confidence, uptake, import and regulation, to strengthen seasonal vaccination programmes and thus pandemic preparedness.

Antiviral drugs and other treatments

Antiviral drugs and other treatments are a second intervention to improve influenza prevention, control and preparedness. As previously discussed, countries with strong national seasonal programmes, which would also include the use of antiviral drugs and other treatments, are at an advantage for pandemic preparedness. However, the current global use of antiviral drugs for seasonal influenza is low, thus limiting the current supplies and surge capacity given manufacturers match production with demand. As evidenced during the 2009 pandemic when WHO initiated the dispatch of 2.4 million antiviral drugs to 72 countries within a month of the declaration of the pandemic (48), antiviral drugs will have a prominent role during a pandemic, especially during the early months, because vaccines will be unavailable initially. Countries should properly account for antiviral drugs in pandemic preparedness efforts since they are feasible to stockpile.

Currently, three major classes of antiviral drugs are available: M2 inhibitors, neuraminidase inhibitors and polymerase inhibitors. The emergence of resistance to antiviral drugs is a public health concern. Given the role of antiviral drugs for both seasonal and pandemic influenza, it is imperative that these drugs be optimized, including through new formulations, delivery routes and therapy combinations. Additionally, alternative treatments, therapies and strategies should be further studied, including the use of monoclonal antibodies and adjunctive treatments (e.g. immune modulators).

Clinical management

Following the 2009 pandemic, WHO published a series of emergency guidelines for the clinical management of influenza virus infection which in turn were replaced with the 2010 *WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses* (49). WHO is currently developing consolidated guidelines for the clinical management of severe influenza-related illness with specific guidance for individuals at high risk of severe illness. These new guidelines will apply to seasonal, pandemic and zoonotic influenza across all resource settings. As new data and treatments become available, it will be essential that clinical management guidance is maintained, is updated in a timely manner, and addresses broad considerations beyond clinical medicine, including public health practice, social and economic policy, and economic development.

References

- ¹ Johnson NPAS, Mueller J. Updating the accounts: global mortality of the 1918–1920 “Spanish” influenza pandemic. *Bull Hist Med.* 2002;76(1):105–15. doi:10.1353/bhm.2002.0022.
- ² Spreeuwenberg P, Kroneman M, Paget J. Reassessing the global mortality burden of the 1918 influenza pandemic. *Am J Epidemiol.* 2018;187(12):2561–67. doi:10.1093/aje/kwy191.
- ³ Pandemic influenza risk management: a WHO guide to inform and harmonize national and international pandemic preparedness and response. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/259893/WHO-WHE-IHM-GIP-2017.1-eng.pdf?sequence=1>, accessed 4 January 2019).
- ⁴ Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet.* 2018;391(10127):1285–300. doi:10.1016/S0140-6736(17)33293-2.
- ⁵ Centers for Disease Control and Prevention. Influenza outbreak – Madagascar, July–August 2002. *MMWR.* 2002;51(45):1016–8 (<https://www.cdc.gov/mmwr/PDF/wk/mm5145.pdf>, accessed 4 January 2019).
- ⁶ Taubenberger JK, Morens David M. 1918 influenza: the mother of all pandemics. *Emerg Infect Dis.* 2006;12(1):15–22. doi:10.3201/eid1201.050979.
- ⁷ Implementation of the International Health Regulations (2005): report of the review committee on the functioning of the International Health Regulations (2005) in relation to pandemic (H1N1) 2009, report by the Director-General. Geneva: World Health Organization; 2011 (http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-en.pdf, accessed 4 January 2019).
- ⁸ About WHO: The role of WHO in public health [website]. Geneva: World Health Organization; 2018 (<http://www.who.int/about/role/en/>, accessed 4 January 2019).
- ⁹ Fan VY, Jamison DT, Summers LH. Pandemic risk: how large are the expected losses? *Bull World Health Org.* 2018;96(2):129–34. doi:10.2471/BLT.17.199588.
- ¹⁰ National Academy of Medicine. The neglected dimension of global security: a framework to counter infectious disease crises. Washington, DC: The National Academies Press; 2016. doi:10.17226/21891.
- ¹¹ De Francisco Shapovalova N, Donadel M, Jit M, Hutubessy R. A systematic review of the social and economic burden of influenza in low- and middle-income countries. *Vaccine.* 2015;33(48):6357–544. doi:10.1016/j.vaccine.2015.10.066.
- ¹² Peasah SK, Azziz-Baumgartner E, Bresee J, Meltzer MI, Widdowson MA. Influenza cost and cost-effectiveness studies globally – a review. *Vaccine.* 2013;31(46):5339–48. doi:10.1016/j.vaccine.2013.09.013.
- ¹³ Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med.* 2004;351:2611–8. doi:10.1056/NEJMoa041747.
- ¹⁴ Wedzhicha JA, Seemungal TAR. COPD exacerbations: defining their cause and prevention. *Lancet.* 2007;370(9589):786–96. doi:10.1016/S0140-6736(07)61382-8.
- ¹⁵ Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet.* 2011;377:1264–75. doi:10.1016/S0140-6736(10)61459-6.
- ¹⁶ Legand A, Briand S, Shindo N, Brooks WA, de Jong MD, Farrar J, et al. Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative. *Future Virol.* 2013;8(10):953–68. doi:10.2217/FVL.13.85.
- ¹⁷ An R&D blueprint for action to prevent epidemics: plan of action. Geneva: World Health Organization; 2016 (http://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf?ua=1, accessed 4 January 2019).
- ¹⁸ WHO preferred product characteristics for next-generation influenza vaccines. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/bitstream/handle/10665/258767/9789241512466-eng.pdf;jsessionid=E0048853CC4340B37C86785F532C9670?sequence=1>, accessed 6 February 2019).
- ¹⁹ Meeting of the Strategic Advisory Group of Experts on immunization, April 2012 – conclusions and recommendations. *Wkly Epidemiol Rec.* 2012;87:201–16 (<http://www.who.int/wer/2012/wer8721.pdf>, accessed 4 January 2019).
- ²⁰ The ten years of the Global Action Plan for Influenza Vaccines, report to the Director-General from the GAP Advisory Group. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/GAP_AG_report_to_WHO_DG.pdf?ua=1, accessed 4 January 2019).
- ²¹ Resolution WHA69.10. Framework of engagement with non-State actors. In: Sixty-ninth World Health Assembly, Geneva, 23–28 May 2016. Resolutions and decisions, annexes. Geneva: World Health Organization; 2016:27–9

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- (WHA69/2016/REC/1; http://apps.who.int/gb/ebwha/pdf_files/WHA69-REC1/A69_2016_REC1-en.pdf#page=1, accessed 4 January 2019).
- ²² WHO reform: better value, better health – strategy and implementation plan for value for money in WHO, report by the Director-General. Geneva: World Health Organization; 2017 (http://apps.who.int/gb/ebwha/pdf_files/EB142/B142_7-en.pdf, accessed 4 January 2019).
- ²³ Global agenda on influenza surveillance and control. Geneva: World Health Organization; 2003 (<http://archives.who.int/prioritymeds/report/append/62GlobAgenda.pdf>, accessed 4 January 2019).
- ²⁴ Tool for influenza pandemic risk assessment (TIPRA) – version 1. Geneva: World Health Organization; 2016 (http://www.who.int/influenza/areas_of_work/human_animal_interface/tipra/en/, accessed 4 January 2019).
- ²⁵ Global epidemiological surveillance standards for influenza. Geneva: World Health Organization; 2014 (http://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1, accessed 4 January 2019).
- ²⁶ A manual for estimating disease burden associated with seasonal influenza. Geneva: World Health Organization; 2015 (http://apps.who.int/iris/bitstream/handle/10665/178801/9789241549301_eng.pdf?sequence=1, accessed 4 January 2019).
- ²⁷ FluID: a global influenza epidemiological data sharing platform [website]. Geneva: World Health Organization; 2018 (http://www.who.int/influenza/surveillance_monitoring/fluid/en/, accessed 4 January 2019).
- ²⁸ Pandemic influenza severity assessment (PISA): a WHO guide to assess the severity of influenza in seasonal epidemics and pandemics. Geneva: World Health Organization; 2017 (http://www.who.int/influenza/surveillance_monitoring/pisa/en/, accessed 4 January 2019).
- ²⁹ Public health preparedness and response: implementation of the International Health Regulations (2005), report by the Director-General. Geneva: World Health Organization; 2018 (http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_8-en.pdf, accessed 4 January 2019).
- ³⁰ Meeting of the Strategic Advisory Group of Experts on immunization, April 2012 – conclusions and recommendations. *Wkly Epidemiol Rec.* 2012;87:201–16 (<http://www.who.int/wer/2012/wer8721.pdf>, accessed 4 January 2019).
- ³¹ Report of the Third WHO Consultation on the Global Action Plan for Influenza Vaccines, 15–16 November 2016. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/259727/WHO-HIS-TTI-17.6-eng.pdf?sequence=1>, accessed 4 January 2019).
- ³² McLean KA, Goldin S, Nannei C, Sparrow E, Torelli G. The 2015 global production capacity of seasonal and pandemic influenza vaccine. *Vaccine.* 2016;34:5410–3. doi:10.1016/j.vaccine.2016.08.019.
- ³³ WHO research agenda for influenza biannual progress review and report, 2010–2011. Geneva: World Health Organization; 2013 (http://www.who.int/influenza/resources/research/RA_Progress_Report_short.pdf, accessed 4 January 2019).
- ³⁴ WHO public health research agenda for influenza: 2017 update. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/259889/9789241513463-eng.pdf?sequence=1>, accessed 4 January 2019).
- ³⁵ Food and Agriculture Organization of the United Nations, World Organisation for Animal Health, World Health Organization. The FAO–OIE–WHO collaboration: sharing responsibilities and coordinating global activities to address health risks at the animal–human–ecosystems interfaces, a tripartite concept note. Geneva: World Health Organization; April 2010 (http://www.who.int/foodsafety/zoonoses/final_concept_note_Hanoi.pdf, accessed 4 January 2019).
- ³⁶ Food and Agriculture Organization of the United Nations, World Organisation for Animal Health, World Health Organization. The tripartite’s commitment: providing multi-sectoral, collaborative leadership in addressing health challenges. Geneva: World Health Organization; October 2017 (http://www.who.int/zoonoses/tripartite_oct2017.pdf, accessed 4 January 2019).
- ³⁷ WHO in emergencies [website]. Geneva: World Health Organization; 2018 (<http://www.who.int/emergencies/en/>, accessed 4 January 2019).
- ³⁸ Emergency response framework – second edition. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/258604/9789241512299-eng.pdf?sequence=1>, accessed 4 January 2019).
- ³⁹ Pandemic Influenza Preparedness Framework (“PIP Framework”) Advisory Group annual report to the Director-General under PIP Framework section 7.2.5. Geneva: World Health Organization; 2017 (http://www.who.int/influenza/pip/PIPAG_AR_2017.pdf?ua=1, accessed 4 January 2019).
- ⁴⁰ Pandemic influenza risk management: a WHO guide to inform and harmonize national and international pandemic preparedness and response. Geneva: World Health Organization; 2017

<http://apps.who.int/iris/bitstream/handle/10665/259893/WHO-WHE-IHM-GIP-2017.1-eng.pdf?sequence=1>, accessed 4 January 2019).

⁴¹ A checklist for pandemic influenza risk and impact management: building capacity for pandemic response. Geneva: World Health Organization; 2018 (<http://apps.who.int/iris/bitstream/handle/10665/259884/9789241513623-eng.pdf?sequence=1>, accessed 4 January 2019).

⁴² National plans for pandemic preparedness and risk management. In: Strategic partnership for International Health Regulations (2005) and health security (SPH) [website]. Geneva: World Health Organization; 2018 (<https://extranet-uat.who.int/sph/influenza-plan>, accessed 4 January 2019).

⁴³ Markel H, Lipman HB, Navarro JA, Sloan A, Michalsen JR, Stern AM, et al. Nonpharmaceutical interventions implemented by US cities during the 1918-1919 influenza pandemic. *JAMA*. 2007;298(6):644–54. doi:10.1001/jama.298.6.644.

⁴⁴ Jain VK, Rivera L, Zaman K, Espos, Jr. R, Sirivichayakul C, Quiambao BP, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *N Engl J Med*. 2013;369:2481–91. doi:10.1056/NEJMoa1215817.

⁴⁵ Arriola CS, Anderson EJ, Baumbach J, Bennett N, Bohm S, Hill M, et al. Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012–2013 season in the United States. *J Infect Dis*. 2015;212:1200–8. doi:10.1093/infdis/jiv200.

⁴⁶ WHO preferred product characteristics for next-generation influenza vaccines. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/258767/9789241512466-eng.pdf?sequence=1>, accessed 4 January 2019).

⁴⁷ Palache A, Abelin A, Hollingsworth R, Cracknell W, Jacobs C, Tsai T, et al. Survey of distribution of seasonal influenza vaccine doses in 201 countries (2004–2015). *Vaccine*. 2017;35. doi:10.1016/j.vaccine.2017.07.053.

⁴⁸ Evolution of a pandemic A (H1N1) 2009, April 2009 – August 2010 – second edition. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/handle/10665/78414/9789241503051_eng.pdf?sequence=1, accessed 4 January 2019).

⁴⁹ WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva: World Health Organization; 2010 (http://www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/, accessed 4 January 2019).