



WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

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1. Executive summary

Influenza, in its pandemic, zoonotic and seasonal epidemic forms, is a formidable public health threat throughout the world. Seasonal influenza is a highly communicable infection of the respiratory tract. Extrapolations from well established studies in temperate countries suggest that annual seasonal influenza epidemics can result in an estimated 250,000 to 500,000 deaths worldwide each year. Since its initial detection in April 2009, the pandemic (H1N1) 2009 virus has spread quickly throughout the world and caused at least 15,000 deaths in less than a year mainly in young and middle-aged adults. Zoonotic infection by avian influenza remains a threat to human and animal species in many regions of the world. The potential of such animal viruses to evolve into human pandemic viruses requires continuous monitoring. However, in many countries the magnitude of influenza's burden (both in human and animals) is unknown. Influenza is not considered a high priority disease in such countries where other more prominent and competing problems are threatening people's health.

The goal of the *WHO Public Health Research Agenda for Influenza* is to identify the evidence needed to better understand the disease impact, strengthen public health guidance and actions essential for limiting the impact of pandemic, zoonotic and seasonal influenza on individuals and populations. The research agenda aims to facilitate discussion, coordination and interaction among researchers, donors/funding agencies and public health professionals worldwide.

The agenda is a broad-based public health research strategy for influenza. It is built around areas of particular importance to public health decision-makers, especially those in less resourced countries. The research agenda is organized around a framework of five key research areas or "streams:"

- Stream 1: Reducing the risk of emergence of pandemic influenza
- Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
- Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
- Stream 4: Optimizing the treatment of patients
- Stream 5: Promoting the development and application of modern public health tools

Each research stream contains specific areas of focus, supported by a brief rationale and a list of research recommendations. The recommendations are expected to evolve over time. Realization of these areas of research can provide an evidence-based platform for policy decisions and public health practices to reduce the impact of all forms of influenza virus infection and associated morbidity and mortality globally.

Development of the research agenda is the result of input from public health decision makers, academic researchers and donor/funding agencies. Implementation of the research priorities outlined in the *WHO Public Health Research Agenda for Influenza* would be expected to provide benefits over a medium-to-long term period of approximately 10 years.

2. Outline of the WHO Public Health Research Agenda for Influenza

Stream 1	Reducing the risk of emergence of pandemic influenza
	1.1 Factors associated with the emergence of influenza viruses with zoonotic or pandemic potential
	1.2. Factors associated with human infection at the human-animal interface
	1.3. Surveillance at the human-animal interface
	1.4 Preventive measures to reduce the risk of emergence of zoonotic and pandemic influenza viruses
Stream 2	Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
	2.1 Factors affecting person-to-person transmission
	2.2 Dynamics of virus spread at global and local levels
	2.3 Public health measures to limit transmission
Stream 3	Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
	3.1 Determining disease burden and social impact
	3.2 Improve immunogenicity, availability and delivery of influenza vaccines
	3.3 Public health policies to reduce the impact of disease
Stream 4	Optimizing the treatment of patients
	4.1 Factors associated with pathogenesis and clinical severity
	4.2 Improve clinical management of patients
	4.3 Health care capacity and response
Stream 5	Promoting the development and application of modern public health tools
	5.1 Modern tools for early detection and monitoring of disease
	5.2 Role of modelling in public health decision making
	5.3 Modern tools for strategic communication

3. Introduction

Influenza, in its zoonotic, seasonal epidemic and pandemic forms, remains a formidable foe throughout the world. Seasonal influenza is a highly communicable, acute viral infection that predominantly affects the respiratory tract including the lungs. It can cause mild to severe illness and can lead to death. The very young, the elderly and persons with chronic medical conditions – a country's most vulnerable populations – typically face the highest risks of death and serious costly complications from seasonal influenza. Seasonal influenza epidemics can affect up to 15% of the population and extrapolation from well established evidence in temperate countries indicates that seasonal influenza epidemics can result in an estimated 250,000 to 500,000 deaths worldwide each year. However, in many under-resourced countries the magnitude and scope of annual influenza's burden are poorly understood. Prevention and control measures for both animal and human influenza are ceded a low priority in many of these countries in view of local competing public health priorities.

The emergence of the pandemic influenza A (H1N1) 2009 virus is a good example on how influenza can impact health systems around the world. Since its initial detection in Mexico and the United States in April 2009, the pandemic virus spread quickly throughout the world. Although the impact of the pandemic will take some time to be fully realized, pandemic H1N1 has caused at least 15,000 laboratory test confirmed deaths in less than a year, mainly in young and middle-aged adults in contrast to seasonal influenza by which over 90% of associated mortality occurs among the elderly. Experience from previous pandemics has demonstrated substantial health and economic-related costs around the world.

The continuous circulation and reassortment of influenza viruses in nature represents an ever-present public health threat to both animals and people. The highly pathogenic avian influenza (HPAI) (H5N1) virus has exacted a heavy toll on poultry and the national economies of affected countries since its initial emergence in 1997 and subsequent extensive geographical spread started in 2003. In addition, severe infections leading to death in human cases of HPAI (H5N1) virus infection have occurred and at much higher case fatality rate than that reported for seasonal epidemics. Concern about the pandemic potential of H5N1 spearheaded a renewed focus on pandemic planning and response.

The Need for a Public Health Research Agenda

Decreasing the risk and impact of influenza and providing critical information to decision makers and health authorities on how to handle such events could save large numbers of lives, prevent enormous health costs and economic loss, and mitigate potential societal disruption. However, insufficient knowledge in many areas has hampered efforts to more effectively plan for and address pandemic influenza as well as zoonotic and seasonal influenza epidemics. A robust scientific knowledge base, therefore, is an essential foundation to further inform modern public health practices and policy development related to influenza.

A number of WHO planning and guidance documents have highlighted the importance of research to fill gaps in our understanding of influenza disease and identified priority areas for immediate attention (1-4). Several animal and human health agencies and other organizations also have developed research priorities for influenza further supporting the need for extensive work in this area (5-12).

Despite these efforts, an overarching global public health research agenda for influenza has not been developed to date. International coordination to prioritize and facilitate the funding and implementation of such an agenda is needed. Previously identified research priorities have tended to focus on basic science questions and research and development related to antiviral drugs and vaccines. Although a public health research agenda must be underpinned by basic science, applied science and operational research are areas of particular importance to public health decision-makers, especially those in less resourced countries.

Scope of the Research Agenda

The *WHO Public Health Research Agenda for Influenza* takes into account issues raised by the (H1N1) 2009 pandemic, the global spread and zoonotic potential of HPAI (H5N1) and seasonal epidemics and outbreaks of human influenza. It is a broad-based public health research strategy for influenza and is not an exhaustive compilation of all possible research questions. Instead it is a focused, succinct framework of key research areas or "streams" related to public health control measures and policy development for influenza. Realization of this type of research can provide an evidence-based platform for policy decisions and public health practices to reduce the burden of influenza infection and associated morbidity and mortality globally. Implementation of the research priorities outlined in the *WHO Public Health Research Agenda for Influenza* would be expected to provide benefits over a medium-to-long term period of approximately 10 years.

4. Development of the WHO Public Health Research Agenda

The *WHO Public Health Research Agenda for Influenza* reflects two major WHO documents - the 2002 WHO Global Agenda on Influenza (13, 14) and the 2006-2007 WHO Strategic Action Plan for Pandemic Influenza (15).

Development of an interim document on influenza research agenda began in 2008. Two WHO consultations - a technical consultation on disease control strategies and measures to respond to pandemic influenza outbreaks (15), held in April 2008, and a global consultation on WHO's pandemic preparedness guidance (16), held in May 2008 - highlighted the lack of scientific evidence necessary to underpin public health decision making and develop recommendations on pandemic, zoonotic and seasonal influenza.

WHO developed an 'influenza research topics database' based on input from technical and public health experts, recommendations from various human and animal public health agencies and findings from previous influenza-related WHO technical consultations and publications. After a series of reviews, these topics were classified into research areas or 'streams' and served as the basis for the development of the research agenda.

WHO established a Programme Committee to strengthen the scientific and technical content of the research agenda in preparation for a global consultation meeting held on 17 to 20 November 2009. The Programme Committee was comprised of five Scientific Working Groups (SWG) each consisting of a Stream Lead and one or more Co-Leads, Rapporteur, other SWG Members and a WHO Point of Contact. The five SWGs were organized according to each of the five research streams. Each Research Stream Rapporteur, with input and discussion from other members of the stream, developed a background document that summarized the available evidence base for each of the research agenda streams.

In November 2009, WHO convened the first global consultation to review and finalize the *WHO Public Health Research Agenda for Influenza* and to facilitate its implementation. The consultation brought together over 90 public health decision makers, academic and clinical researchers, donors and other key stakeholders from 35 countries. In the course of two days, breakout groups reviewed the relevant sub-sets of research questions and discussed the proposed organization, content, rationale and global health importance of their designated research stream. The breakout groups incorporated additional research topics/questions considered vital but missing from the proposed list and undertook a 'road mapping' exercise to define the key public health needs related to their stream during pandemic and inter-pandemic periods (including both seasonal and zoonotic influenza virus infections).

A separate report on the consultation meeting summarizes these discussions on key public health research needs during the pandemic and inter-pandemic periods as well as proposed steps for the implementation of the research agenda at global, regional and country levels. This document, *WHO Public Health Research Agenda for Influenza*, which embodies the recommendations and findings of the global consultation, was finalized in February 2010.

5. WHO Public Health Research Agenda for Influenza

Goal

The goal for the development and implementation of a *WHO Public Health Research Agenda for Influenza* is to support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of pandemic, zoonotic and seasonal influenza on individuals and populations.

Objectives

The principal objectives of this research agenda are to:

- Provide a framework reflecting public health research priorities for pandemic, zoonotic, and seasonal epidemic influenza
- Identify specific research topics, reinforce and prioritize their importance in meeting public health needs over a medium-to-long term period
- Maintain a focus on relatively less well addressed areas such as operational research and research with applications in under-resourced countries
- Facilitate discussion, coordination and interaction among researchers, donors and public health professionals
- Highlight the need and benefits of a multidisciplinary approach to address knowledge gaps in public health related to influenza and its control

Organization of the Research Agenda

The research agenda is organized as a framework around five major public health research streams as follows:

- Stream 1: Reducing the risk of emergence of pandemic influenza
- Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza
- Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza
- Stream 4: Optimizing the treatment of patients
- Stream 5: Promoting the development and application of modern public health tools

Within each research stream, specific areas of focus are identified supported by a brief rationale and a list of research recommendations.

Stream 1: Reducing the Risk of Emergence of Pandemic Influenza

Many animal species and a vast variety of influenza virus subtypes and strains contribute to the overall evolution and ecology of influenza and to the potential for zoonotic and pandemic influenza. The emergence of the pandemic (H1N1) 2009 virus and the global spread of HPAI (H5N1) have underscored the challenges in reducing the risks from influenza viruses with zoonotic and pandemic potential. Both the public health risks from zoonotic infections with influenza viruses such as H5N1 as well as the potential risks of emergent pandemic strains must be considered. Reducing each of these risks requires a better understanding of the underlying factors that contribute to the emergence of zoonotic and pandemic viruses and methods to assess what risks such viruses may pose to humans. Identification of effective control measures at the animal source and human behavioral modifications to reduce virus transmission at the human-animal interface are also needed.

1.1 Factors Associated with the Emergence of Influenza Viruses with Zoonotic or Pandemic Potential

Rationale: It has been possible to reconstruct the genetic events that likely led to the emergence of past pandemic viruses. For example, the 1918 pandemic virus may have emerged after adaptive mutation(s) from an avian virus while the pandemic (H1N1) 2009 virus appears to have originated from reassortment between several different viruses circulating in pigs and other animals. However, the genetic processes and external factors leading to the emergence of pandemic influenza viruses remain incompletely understood (e.g. the potentials for mutation and genetic reassortment, as do factors associated with infectivity, transmissibility, and pathogenicity) and on the ecological/human/animal interface level (e.g. potential external drivers of emergence, host range, persistence in the environment and animal husbandry practices). Further, while it is well known that the genetic composition of circulating influenza viruses evolves continually, the specific changes or combinations of changes that predict pandemic potential in these variants are not known.

Research Recommendations:

- 1.1.1 Investigate virus-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility and pathogenicity)
- 1.1.2 Assess the animal host-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility and pathogenicity)
- 1.1.3 Study the environmental and animal management/husbandry-specific factors associated with zoonotic and pandemic potential (e.g. infectivity, transmissibility)

1.2 Factors Associated with Human Infection at the Human-Animal Interface

Rationale: Measures to control or prevent zoonotic influenza infection must be based on a clear understanding of risk factors associated with human infection. Studies of past pandemics have highlighted the importance of domestic poultry and pigs in the evolution and emergence of animal influenza viruses which can be transmitted to humans. However, specific risk factors, activities and behaviors that have led to instances of human infections with animal influenza viruses have been difficult to elucidate. Further complicating our understanding is the diversity of settings/activities in which people interact with animals (e.g. households, commercial farms, live animal markets, scavenging animal species). In addition, the actual modes of transmission from animals or the environments remain unclear for many settings.

Research Recommendations:

- 1.2.1 Investigate potential modes of transmission in human infection with animal viruses
- 1.2.2 Study the role of human behavioral factors associated with infection by animal viruses
- 1.2.3 Determine the genetic or other factors related to human susceptibility to infection with animal viruses

1.3 Surveillance at the Human-Animal Interface

Rationale: Surveillance for animal and human infections can give advance warning of the circulation of animal influenza viruses with zoonotic or pandemic potential. Surveillance systems can also help to assess the effectiveness of prevention and control measures. Evaluation and adaptation of strategies and surveillance systems are required to ensure their effectiveness in different settings and in countries with varying capacity and resources.

Research Recommendations:

- 1.3.1 Develop research strategies for joint animal and human health surveillance systems to monitor influenza viruses with zoonotic or pandemic potential in countries with varying capacity and resources
- 1.3.2 Develop diagnostic tests to support joint animal and human health surveillance systems
- 1.3.3 Perform operational research to evaluate and improve joint animal and human health surveillance systems
- 1.3.4 Develop research to establish social, political, economic and legal strategies for animal influenza outbreak reporting

1.4 Preventive Measures to Reduce the Risk of Emergence of Zoonotic and Pandemic Influenza Viruses

Rationale: The primary measure to reduce the risk of human infection with animal influenza viruses is the control of influenza in animals. For example, properly implemented poultry vaccination, culling of infected birds and decontamination of live animal markets have been used to control HPAI H5N1 and in some instances have been temporally associated with a decline in reported poultry and human infections. Since it is highly improbable that all influenza viruses can be eliminated from animal populations, secondary measures are needed to reduce the infection risks of humans when exposed to infected animals. In addition to reducing morbidity and mortality associated with human infections, reducing both circulation of viruses in animals and human exposure may decrease the risk of emergence and establishment or potentially pandemic strains.

Research Recommendations:

- 1.4.1 Investigate and develop animal intervention strategies (e.g., culling, vaccination, biosecurity) under different epidemiological and field conditions that can reduce risk of zoonotic infection
- 1.4.2 Develop human intervention strategies related to the animal-human interface (e.g., behavioral and legal approaches, biosecurity measures etc.) in different social and cultural contexts
- 1.4.3 Conduct operational research to integrate animal and human health strategies for prevention
- 1.4.4 Assess and evaluate the public health, social and other impacts of intervention strategies under different epidemiological and field conditions to optimize their effectiveness

Stream 2: Limiting the Spread of Pandemic, Zoonotic and Seasonal Epidemic Influenza

The rapid global spread of the pandemic (H1N1) 2009 virus, as well as the spread of seasonal influenza viruses within local communities and institutions such as schools, illustrates how difficult it is to limit human influenza transmission. Improvements in this area will require basic scientific and operational research to gain a better understanding on how influenza viruses are transmitted between people, the usefulness and feasibility of public health control measures at the individual and population levels and an understanding of the dynamics of virus spread. This information, in turn, can support science-driven public health policies and decision making. Underpinning these efforts must be a robust and continuous global surveillance system for influenza.

2.1 Factors Affecting Person-to-Person Transmission

Rationale: Influenza viruses can be transmitted by respiratory droplets, direct and indirect contact and small airborne particles. However, the relative importance of each of these routes, the role virological, environmental, epidemiological and host-specific factors play in the transmission and establishment of infection under different epidemiological settings remain unclear. Refinement of recommendations for infection control and social distancing measures would benefit from a better understanding of influenza transmission and virus characteristics.

Research Recommendations:

- 2.1.1 Investigate the relative importance of droplet, contact and airborne transmission in seasonal and pandemic influenza
- 2.1.2 Study the transmission dynamics of influenza and the factors that influence infectivity in different settings and associated activities
- 2.1.3 Investigate the potentials for transmission of influenza during different stages of infection in humans from incubation to recovery
- 2.1.4 Examine the role of host factors such as age, pre-existing immunity, antiviral treatment and prophylaxis, and vaccination in modulating influenza transmission
- 2.1.5 Study the stability of human influenza viruses on different environmental surfaces and under varying conditions (e.g. humidity, temperature, presence of organic matter) and its relevance in the transmission of influenza virus

2.2 Dynamics of Virus Spread at Global and Local Levels

Rationale: Early observations of the pandemic (H1N1) 2009 virus have highlighted the role of travel and school outbreaks as early amplifiers of transmission in communities. Population mobility, factors that influence seasonal versus year-round circulation of human influenza viruses, transmissibility of variant strains and population-level susceptibility are some of the other factors that would likely affect transmission dynamics at global and local levels. A better understanding and assessment on the dynamics of influenza spread is needed to optimize use of public health measures.

Research Recommendations:

- 2.2.1 Conduct studies to understand the seasonality of influenza virus infection in different regions and its implication in global spread of epidemic and pandemic influenza
- 2.2.2 Assess the dynamics of spread of epidemic and pandemic influenza in different epidemiological settings (e.g. rural vs. urban, tropical vs. temperate climates etc)
- 2.2.3 Study the interaction between influenza strains and other respiratory pathogens, and their effect on transmission and spread
- 2.2.4 Study the application and timing of response strategies during early spread of human cases of pandemic influenza virus including containment and border control policies

2.3 Public Health Measures to Limit Transmission

Rationale: Individual, household and community-level public health measures have been used during seasonal epidemics and pandemics to reduce transmission; however, their effectiveness remains unclear. These measures are not easy to implement and can incur substantial costs. For these reasons, public health decision makers need a firmer evidence base to support their use.

Research Recommendations:

- 2.3.1 Study the effectiveness, cost-effectiveness and feasibility of measures at the individual level such as hand hygiene, masks and respirators
- 2.3.2 Study the effectiveness, cost-effectiveness and feasibility of measures at the community level such as contact tracing and quarantine, school and workplace closures, reduction in mass gatherings and environmental control methods such as UV filters, air circulation and natural ventilation
- 2.3.3 Research on factors needs to be considered in the selection, timing and optimal implementation of individual and community public health measures
- 2.3.4 Examine the usage of surveillance data in assessing the needs and effectiveness of public health interventions in different situations such as the identification of emerging of novel viruses; determining the time for initiation of public health interventions; selection of appropriate public health interventions; evaluate effectiveness of interventions and guiding decision-making regarding cessation of public health interventions

Stream 3: Minimizing the Impact of Pandemic, Zoonotic and Seasonal Epidemic Influenza

Immunization against influenza is an essential public health intervention to control both seasonal epidemics and pandemic influenza. The *WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply* [1] articulated a multi-faceted strategy to increase vaccine production and use. However, many countries, particularly those that are under resourced, have not developed strategies to vaccinate their populations at risk for seasonal or pandemic influenza. This is related in part to insufficient local information on the burden of influenza disease and its social, economic, and health determinants and impacts to the community. There also are marked differences between countries in terms of their respective capacities, priorities and resources to establish seasonal influenza vaccination policies and programmes, and to produce and distribute vaccine. Overall, vaccine availability and accessibility is limited for seasonal, zoonotic and pandemic influenza and public health authorities need to make decisions about prioritization of its effective use. Such differences most clearly recognized during pandemic situation.

3.1 Determining Disease Burden and Social Impact

Rationale: Disease burden data are not available from many countries, especially those that are under resourced. While data are generally more available for well-resourced countries, there is limited information about influenza's complications and its toll in pediatric and other high-risk populations. The appearance of variant disease patterns may signal changes in the circulating influenza viruses. Well-designed disease burden studies can assess the incidence and prevalence of influenza, its severity, complications and socioeconomic impacts. Such studies may also provide information on possible prevention and control strategies such as vaccination policies. In addition, assessment of the local social determinants of health and the impact of influenza pandemics on such determinants can have the potential to be a powerful driver for public health policy development in all countries.

Research Recommendations:

- 3.1.1 Conduct epidemiological research to determine disease burden and its social impact including assessment of the incidence of influenza disease, its severity and complications, the identification of at-risk groups and the role of seasonality
- 3.1.2. Determine the optimal methods for influenza disease surveillance and the conduct of burden studies
- 3.1.3 Evaluate the influenza vaccine preventable disease burden and the potential impact of immunization programs (e.g. vaccine demonstration projects)
- 3.1.4 Establish the economic burden of seasonal and pandemic influenza in conjunction with epidemiological studies
- 3.1.5 Determine best approaches for applying influenza disease burden data, coupled with cost-effectiveness analyses, to inform development or expansion of influenza control programs in the context of competing priorities
- 3.1.6 Assess social determinants of health under different epidemiological settings (such as socially disadvantaged, indigenous populations etc.) and evaluation of the social impact (such as disruptions in commerce, health care systems, public safety, social and political fabrics etc.) of influenza outbreaks and pandemics based on such determinants

3.2 Improve Immunogenicity, Availability and Delivery of Influenza Vaccines

Rationale: Seasonal influenza vaccines present significant challenges: they must be updated, produced, clinically evaluated for safety and efficacy and administered every year. The overall efficacy of influenza vaccines depends not only on vaccine match with circulating strains, but also on vaccine components such as adjuvant and varying host immune status. Improvements in

vaccines and formulations that can provide longer-lasting and a broader range of protection against influenza may provide better protection, expand the supply of vaccines and reduce the frequency of vaccination and production. During a pandemic, critical issues related to the safety, immunogenicity and rapid production and equitable distribution of vaccines are highlighted.

Research Recommendations:

- 3.2.1 Investigate methods to improve the vaccine strain selection process and to characterize optimal vaccine strains including the establishment of vaccine strain libraries
- 3.2.2 Conduct studies to enhance the clinical applications of existing vaccines including improvements in the production; duration and breadth of protection; safety and immunogenicity profiles and dose-sparing formulations, especially for high-risk groups
- 3.2.3 Evaluate systematically to reduce bottlenecks in the production of vaccines and to improve the processes of rapid response, surge capacity, rapid deployment and tracking of vaccine usage
- 3.2.4 Conduct studies to optimize and standardize animal models to be used in pre-clinical evaluation of new vaccines
- 3.2.5 Develop new vaccines, vaccine platforms and formulations that are safe and have enhanced immunogenicity; vaccine delivery systems with improved ease of storage and administration especially for use in under-resourced settings
- 3.2.6 Identify correlates of protection for different vaccines and correlates of priming, including development and standardization of methodologies
- 3.2.7 Develop innovative clinical trial methodologies to study the effectiveness and safety of novel vaccines for pre-licensure and post-licensure vaccine evaluation and vaccine effectiveness studies
- 3.2.8 Expand studies on pharmacovigilance and reduction of disease burden for post-licensure vaccine evaluation in a wider range of settings that likely vary by geography and in at-risk groups including children
- 3.2.9 Examine and develop ways to harmonize the regulatory processes, especially for rapid international safety monitoring and standardized evaluation of vaccine potency

3.3 Public Health Policies to Reduce the Impact of Disease

Rationale: Public health programmes and policies to combat seasonal influenza are limited principally to well-resourced countries with access to vaccines and a well-organized health care infrastructure. Implementation of similar programmes are challenging for under-resourced countries with unique and competing health issues, inadequate public health financing system and insufficient medical infrastructures. In the context of a pandemic, all countries face the difficult issues of how influenza immunization policies will be developed, implemented and evaluated.

Research Recommendations:

- 3.3.1 Evaluate existing and new policies and strategies to optimize vaccine uptake and improve vaccine acceptability (e.g. policies targeting risk groups versus the general population)
- 3.3.2 Develop effective immunization policies using community-based input
- 3.3.3 Study the role of social science research such as its involvement in establishing social, ethical and legal standards in public health policy application; the public perception of influenza and its impact on societies particularly in under-resourced populations

Stream 4: Optimizing the Treatment of Patients

Improved clinical management can substantially reduce the incidence of severe infection and associated complications for zoonotic, seasonal epidemic and pandemic influenza. Optimization of clinical management must be underpinned by a better understanding of the pathogenesis of influenza infections, advances in laboratory diagnosis, development and application of effective antiviral drugs and other treatment modalities and access to good quality health services.

4.1 Factors Associated with Pathogenesis and Clinical Severity

Rationale: There are many gaps in our basic understanding of how and why influenza viruses cause disease in people and what influences illness severity. Host immune responses, underlying comorbidity, age and opportunities for prior exposure to related epidemic and pandemic influenza virus strains and the properties of the circulating virus can all impact disease severity. In addition to host and viral factors, secondary bacterial pneumonia can influence disease outcome.

Research Recommendations:

- 4.1.1 Investigate the role of virological factors (including replication sites, duration and viral load levels) and innate and adaptive immune and other host responses in the severity of disease and associated complications
- 4.1.2 Define the clinical spectrum and natural history of human disease, including risk factors (such as co-morbidities and demographic factors) and prognostic markers for severe disease and its complications
- 4.1.3 Assess the incidence, anatomical sites, etiology and pathogenesis of secondary bacterial infections associated with influenza, as well as optimal treatment modalities and prophylactic and/or preventive measures
- 4.1.4 Study the role of pre-existing infections (e.g. TB, HIV) and other viral co-infections (e.g. dengue and other respiratory viruses) in the severity of influenza disease
- 4.1.5 Study the role of host genetic factors on susceptibility and severity of influenza infection

4.2 Improve Clinical Management of Patients

Rationale: The nonspecific clinical presentation of influenza makes it difficult to distinguish from other febrile or respiratory illnesses. Rapid and reliable diagnostic testing can facilitate the institution of timely and appropriate antiviral treatment and infection control measures. Rapid tests are commercially available but limited in their diagnostic capabilities. Although antiviral drugs can reduce the duration and severity of illness and help control outbreaks, they are not widely used for treatment or prophylaxis in both under- and well-resourced countries during annual epidemics. They must be taken soon after the onset of illness and resistance can develop. Expansion and optimization of the current repertoire of antiviral drugs and development of clinical research to assess efficacy of putative adjuvant treatment modalities such as immunomodulators, passive immunotherapy and traditional medicine that are suitable for use in under-resourced areas would be most beneficial.

Research Recommendations:

- 4.2.1 Develop rapid, reliable, affordable point-of-care diagnostic tests for influenza virus
- 4.2.2 Identify clinical markers and development of point-of-care tools for the prognosis and management of influenza disease
- 4.2.3 Optimize the effectiveness of current and novel antiviral treatments through development of new formulations, delivery routes or systems, and synergistic antiviral drug combinations

- 4.2.4 Develop novel and effective treatment strategies including adjunctive treatments (e.g. immunomodulators, immunoglobulin, natural products) that are applicable in low resource settings and easy to administer in pediatric and intensive care settings
- 4.2.5 Optimize management of persons with or at increased risk for severe disease and complications including intensive care practices that are applicable across a range of resource settings

4.3 Health Care Capacity and Response

Rationale: The availability and quality of health services influences the impact of both seasonal epidemic and pandemic influenza. The same virus that may have a modest impact on morbidity and mortality in countries with well-organized health systems can be devastating in other countries where healthcare systems are sub-optimal.

Research Recommendations:

- 4.3.1 Evaluate the effectiveness of global, national and local responses to pandemic, epidemic and zoonotic influenza, and development of new assessment tools
- 4.3.2 Conduct operational studies on surge capacity needs, including development of triage schemes in different health care and resource settings, and surge planning to maintain adequate staffing
- 4.3.3 Research to develop alternative health delivery systems for care of patients including home care, community facilities other than hospitals and other venues
- 4.3.4 Conduct studies to develop best practices that provide protection of health care workers and other care-givers in different health care and resource settings
- 4.3.5 Studies to identify evidence-driven clinical care pathways and principles which optimize health care delivery in a range of resource settings
- 4.3.6 Studies to develop principles and practices for rapid assessment and introduction of new interventions during health emergencies, including systems for clinical data collation, sharing and assessment in real time

Stream 5: Promoting the Development and Application of Modern Public Health Tools

New public health tools need to be harnessed to help reduce the impact of seasonal epidemic and pandemic influenza in a globalized economy and a modern world. Use of innovative communication channels, such as the internet and mobile phone networks, have the potential to facilitate outbreak investigation and rapid risk assessment and dissemination of accurate information. Mathematical modelling and risk communication are cross-cutting areas with potential applicability across all streams of research.

5.1 Modern Tools for Early Detection and Monitoring of Disease

Rationale: Some countries use state-of-the art approaches for early disease detection and monitoring such as syndromic surveillance in hospital emergency departments and tracking of over-the-counter pharmaceutical purchases. Computerized health-care and laboratory-based information systems are also in place in some countries for seasonal epidemic influenza and are adaptable to monitor pandemics. Other innovative technologies are utilized in remote areas and/or under-resourced countries such as mobile phones to collect and transmit health data in real-time, provide feedback and train health workers. Other examples are WHO's "eHealth" initiative and the United Nations Foundation's "Health for Development". Applicability and the utilization of their full potential in influenza disease and pandemic surveillance in different settings and contexts require further investigation, with special attention to issues related to integration and interoperability of several existing initiatives.

Research Recommendations:

- 5.1.1 Conduct studies to identify, appraise, exploit and adapt modern technologies for early detection of epidemic and pandemic influenza as well as their application in surveillance at the human-animal interface
- 5.1.2 Research to develop, integrate and continuously evaluate innovative approaches and channels for influenza surveillance and monitoring with other existing disease monitoring systems
- 5.1.3 Conduct studies to develop efficient mechanisms to address the global challenges for sharing information, data, clinical specimens and viruses with consideration for local, ethical, legal and research perspectives
- 5.1.4 Examine the timeliness and quality of data needs required for early detection of disease from local to district, regional, national and global levels for the respective stakeholders

5.2 Role of Modelling in Public Health Decision Making

Rationale: Evidence-based public health decision making requires access to information. However, information is often incomplete, evolving and derived from an increasingly complex array of sources such as basic science researchers, epidemiologists, social and political scientists, economists and others. Modelling is a useful tool that can incorporate diverse data to inform public health policy and decision-making. Applications include: the analysis of the evolution of seasonal influenza to assist in vaccine strain selection; the analysis of epidemiological data to estimate key parameters determining influenza spread; assessing the potential impact of various pharmaceutical and public health control measures; and real time modelling to provide situational awareness and forecasts of evolution and spread. Also of significant interest is building capacity in the use of such modern tools in under-resourced countries is a priority. Modelling is a fast-evolving discipline. It is anticipated that advances in coming years of relevance to public health will include (but are not limited to) computational structural biology; integration of epidemiological and geographical data into phylogenetic models; within-host and population-level susceptibility models; behavioral modeling; assessing the impacts of climate change on transmission and the utilization of novel data sets on contact patterns and population mobility.

Research Recommendations:

- 5.2.1 Studies to assess the application of modelling to understand epidemiological and evolutionary processes and estimate key parameters for pandemic and seasonal influenza.
- 5.2.2 Examine the application of modelling to assess public health impact of influenza and the effectiveness of interventions.
- 5.2.3 Evaluate the application of modelling to assist public health policy planning and strategic decision making.
- 5.2.4 Conduct studies to improve model accuracy and realism, and incorporation of emergent interdisciplinary advances.

5.3 Modern Tools for Strategic Communication

Rationale: Communication is a key strategy in epidemic and pandemic management. The SARS outbreak in 2003 reinforced that a timely and transparent public information policy could help reduce excessive and inappropriate public health responses and minimize the social disruption and economic consequences of a fast-moving global epidemic. Increased investment in identifying effective approaches and in developing and evaluating new tools where needed will benefit influenza prevention and control efforts and also have broader applicability for public health. The specific challenge is to provide clear, credible and appropriate communication to meet the needs of diverse communities and retain public trust in a dynamic process characterized by uncertainty.

Research Recommendations:

- 5.3.1 Conduct studies to review international evidence and experience on health and health crisis communication from relevant disciplines, such as behavioural and social sciences, media studies, marketing etc. to gather and organize knowledge, as well as to stimulate new studies in areas where gaps have been identified to support evidence-based practice in strategic communication
- 5.3.2 Identify, develop and evaluate communication tools and methods that can rapidly, accurately and over time for the assessment and monitoring of knowledge, attitudes, beliefs and practices in different population groups, to guide communication efforts
- 5.3.3 Identify, develop and evaluate communication tools and approaches for communicating in different cultural settings, which engage and empower individuals and communities to practice and promote appropriate risk reduction measures
- 5.3.4 Study the dynamics of inaccurate and contradictory information, rumours, myths, narratives etc. through tracking, monitoring and analysing different communication sources and channels, and to develop effective ways to respond
- 5.3.5 Study the potential ethical, social, economic and political dimensions of communicating in national and international crisis situations and develop strategies for working within constraints and maximizing opportunities

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