WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA

2017 UPDATE

SHORT VERSION

GLOBAL INFLUENZA PROGRAMME

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ABBREVIATIONS

BARDA Biomedical Advanced Research and Development Authority
CVVs Candidate Vaccine Viruses
FOI Force of Infection
GISRS Global Influenza Surveillance and Response System
GIP Global Influenza Program
IAV Influenza A Virus
IHR International Health Regulations
ILI Influenza-like Illness
KAP Knowledge Attitude and Practice
LMIC Low and Middle Income Countries
LAIV Live Attenuated Influenza Virus
NAIs Neuraminidase Inhibitors
NGS Next Generation Sequencing
POC Point of care
PPE Personal Protective Equipment
SIR Susceptible Infectious Recovered
SAGE Strategic Advisory Group of Experts on Immunization
TIV Trivalent Inactivated Influenza Vaccine
UNISEC Universal Influenza Vaccine Consortium
WHO World Health Organization
EXECUTIVE SUMMARY

Many of the limitations in addressing the public health impact of influenza disease (including the response to the 2009 influenza pandemic) are due to gaps in our understanding of the virus, and its effect on individuals and populations. To identify these knowledge gaps and evaluate their relative importance in public health decision-making, in 2009 WHO developed the WHO Public Health Research Agenda for Influenza.

The Research Agenda had five 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

The aim of the Research Agenda was to support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of pandemic, zoonotic and seasonal epidemic influenza. The Research Agenda has also facilitated discussion, coordination and interaction among researchers, funding organizations and public health professionals globally.

Few of the knowledge gaps identified in 2009 have been completely addressed. Some have not been addressed or have only partially been addressed since the biannual review of progress in 2010–2011 (World Health Organization, 2013). In addition, the constantly changing characteristics of influenza virus and its epidemiology may generate new knowledge gaps. Thus, it is imperative to fill these gaps and at the same time stimulate the efforts to address unmet public health needs. Recognizing these needs, the WHO Global Influenza Programme initiated the process of updating the WHO Public Health Research Agenda for Influenza in 2016.

To facilitate the process of updating the Research Agenda, in August 2016, technical working groups were established for the five research streams. Each working group comprises leading scientists, experts in influenza and public health practitioners, who provided their expertise and exchanged ideas through a web-based platform and via teleconferences. The aim of establishing the working groups was to help identify key accomplishments, unmet public health needs and major knowledge gaps and corresponding priority areas for influenza research in the next 5–10 years. Following several months of working remotely, the experts gathered at the Consultation on Updating the WHO Public Health Research Agenda for Influenza, held on 6–8 December 2016 in Geneva, Switzerland. The consultation provided a forum for more extensive face-to-face discussions, further facilitating the updating of the Research Agenda.

The updated Research Agenda emphasizes the high and highest public health research priorities in addressing unmet public health needs. It represents the outcome of the contributions of scientific researchers, public health workers, health-care professionals, vaccine developers and funding organizations. Implementation of the high public health research priorities outlined in this update are expected to benefit the global public health communities by reducing the burden of seasonal epidemic influenza and the risk and impact of pandemic influenza over the next 5–10 years.

* See http://www.who.int/influenza/resources/research/about/en/
This document is a short version of the research agenda in which only the research recommendations are outlined. For more details on the research recommendations and how they were developed or updated, please visit the full version of the research agenda with the background documents.

**STREAM 1: REDUCING THE RISK OF EMERGENCE OF A PANDEMIC INFLUENZA**

**Overall strategic objectives**

The overall objective is to recommend research to reduce the risk of emergence, amplification in farmed animals and transmission to humans of zoonotic influenza A viruses (IAVs).

H5 avian influenza viruses have been endemic in poultry for over 20 years, novel strains continue to evolve, and there is no prospect of their elimination in the next 10 years without major changes to management approaches. Additionally, new zoonotic influenza viruses have emerged from both poultry and pigs.

It is recommended that research focuses on four main areas of response:

- **improved capacity to find the viruses** – that is, improved surveillance;
- **improved understanding of the viruses** – that is, better knowledge of the viral, host and environmental factors that permit evolution and emergence of zoonotic viruses;
- **improved interventions to prevent spillover from animals** – that is, significant improvements in the ways that livestock are farmed, marketed and processed, and in the products consumed; and
- **improved vaccines and vaccination application for animals** – that is, an accompanying specific effort to develop, register and use more efficacious vaccines and effective vaccination programmes.

These four areas of focus do not represent a linear sequence; rather, they need to be addressed simultaneously. Discoveries in each area will highlight challenges and support particular approaches in the other areas of research.

These considerations underpin the prioritization approach adopted. The research recommendations are intended to direct the broad range of investigative skills needed to deliver a holistic response to the threat of pandemic influenza. There are no “silver bullets” – progress is needed across many relevant disciplines, including basic research, epidemiology and surveillance, pathology and pathogenesis, vaccine research and socioeconomic research.

In making the recommendations, it has not been possible to give detailed descriptions of all the matters that might be considered under each recommendation.

**Substream 1.1**

**Improved surveillance and detection of emergent IAVs with zoonotic or pandemic potential for risk assessment and response**

**Strategic objectives**

New and emerging IAV strains should be detected and analysed for zoonotic and pandemic potential before they are associated with human morbidity and mortality. Where humans have become infected, this should be detected before widespread transmission occurs. Testing should be reliable and cost effective, and should be harmonized internationally so that results from different sources can be usefully compared.
Research recommendations

1.1.1 Establish and implement systems for expanded, more comprehensive, sustainable and transparent IAV detection and reporting in farmed animals and wildlife (funding, social, political, economic and legal strategies, including multilateral obligations, to be addressed) (Highest priority, Long-term).  

1.1.2 Conduct research for more sensitive, specific, cost-effective and operationally convenient surveillance and detection strategies, including epidemiological designs and novel technologies, including “active listening” (Highest priority, Long-term).  

1.1.3 Harmonize strategies and laboratory testing for surveillance of zoonotic influenza at the human–animal interface and more broadly (Short-term).  

1.1.4 Expand uptake of surveillance data within risk assessment frameworks in order to better assess zoonotic and pandemic potential of novel IAV strains, and to direct appropriate responses (Highest priority, Long-term).  

Substream 1.2 Identification of virus, host and environmental determinants for infectivity, susceptibility, transmission and pathogenesis of potentially zoonotic IAVs

Strategic objectives  
Basic laboratory science will continue to elucidate the complex molecular and biochemical pathways and interactions that determine infectivity, susceptibility, transmission and pathogenesis of potentially zoonotic IAVs, including among avian, mammalian animal and human hosts. Studies will also lead to a more detailed understanding of environmental factors that lead to virus emergence, transmission and environmental persistence.

Research recommendations

1.2.1 Further define the host-to-host transmission pathways (e.g. aerosol, large droplet, contact or fomite) of IAVs from animal to animal, and from the animal or animal environment to humans, especially by occupational exposure and including persistence of the virus on farms, in markets, in processing centres and in products (Highest priority, Long-term).  

1.2.2 Investigate virus-specific factors associated with zoonotic and pandemic potential that confer cross-species infectivity, susceptibility, transmissibility and pathogenicity (Highest priority, Long-term).  

1.2.3 Investigate the host-specific factors, particularly in people and pigs as well as poultry, associated with susceptibility to infection, transmissibility and pathogenicity of IAVs of zoonotic and pandemic potential (genetics, genetic heterogeneity, species differences and immunity, including human age-specific immunity and “herd immunity”) (Highest priority, Long-term).
1.2.4 Determine scientifically and propose for adoption by public and animal health multilateral agencies the minimum set of genotypic and phenotypic analyses required or expected of IAVs from animal or human populations to inform risk assessment, and apply this to risk mitigation strategies for emergent viruses of concern (Short-term).

Substream 1.3
Management or modification of animal production and marketing systems for mitigation of the risk of zoonotic IAV emergence, geographic spread and transmission to humans

Strategic objectives
Promote technical, socioeconomic and behavioural research that will lead to the adoption of safer human practices during the farming, movement, trading, processing, showing, selling and consumption of animals and products of animal origin, with respect to reducing the risks of emergence of IAVs with zoonotic or pandemic potential and the subsequent infection of people with such viruses (Highest priority, Long-term).

Research recommendations
1.3.1 Develop, evaluate and implement, including through translational research, improved biosecurity measures (bio-exclusion) appropriate for the different production and marketing systems (Long-term).

1.3.2 Develop improved interventions following IAV detections and outbreaks – alternatives to “stamping out” that are equally effective in eliminating virus but that are more economically profitable, financially feasible and socially acceptable (Long-term).

1.3.3 Support studies, including translational research, to reduce the risk of transmission of IAVs (and other pathogens) associated with animal movements, farm to farm or farm to market (Long-term).

1.3.4 Develop strategies, including community engagement, to lead to behavioural changes, to reduce transmission of IAVs on farms, and in markets, agricultural fairs and slaughtering facilities (Long-term).

1.3.5 Evaluate the public health, economic, political and social impacts of intervention strategies under different epidemiological and field situations (Long-term).

Substream 1.4
Improving vaccines and their application in the animal host populations to reduce human exposure to zoonotic IAVs

Strategic objectives
Vaccines against IAVs in farmed animals are effective in some but not all situations. Problems of antigenic matching could potentially be managed, but issues relating to cost-effective delivery and effectiveness are not addressed in numerous production systems. Vaccination of animals is a major strategy to reduce the risk of human exposure in places where zoonotic IAVs are endemic in animals. Development and uptake of suitable products is of highest priority.
Research recommendations

1.4.1 Develop new (more efficacious, easily administered and cost effective) vaccines for particular animal populations (mass application for poultry, better vaccines for ducks and pigs, and a system to detect and minimize antigenic variation between vaccine and field viruses) (Highest priority, Long-term).

1.4.2 Develop systems to effectively vaccinate target populations as required, including behavioural, social, political and economic aspects of vaccination and vaccine uptake, supported by community engagement, data collection and the development of long-term indicators (Long-term).

1.4.3 Determine and communicate the benefits and risks of potent, antigenically matched vaccines and proper vaccination strategies (Highest priority, Short-term).

STREAM 2: LIMITING THE SPREAD OF PANDEMIC, ZOONOTIC AND SEASONAL EPIDEMIC INFLUENZA

Substream 2.1 Factors affecting person-to-person transmission

Strategic objectives
Understanding the relative importance of the different transmission modes of influenza – droplet, direct and indirect contact, and airborne transmission – is important for designing and evaluating interventions for each transmission mode. New studies have provided evidence on the importance of aerosols in influenza transmission. Thus, there is a need for a better understanding of the preventable risk factors of superspreading events and the various aerosol-generating procedures that increase the risk of transmission. Since the last review of progress in 2010–11 (World Health Organization, 2013), substantial work has advanced the understanding of influenza transmission in different epidemiological settings. However, future research should be directed towards better understanding which interventions (including antiviral medications and vaccination) would be most effective in reducing transmission in various settings.

Research recommendations

2.1.1 Investigate the relative importance of droplet, contact and airborne transmission in seasonal and pandemic influenza, to understand the effectiveness of various interventions to reduce transmission. (Long-term).

2.1.2 Investigate the details of aerosol transmission including the infectious dose, survival of the virus in aerosols and aerosol-generating procedures in clinical settings. (Highest priority, Short-term).
   • What constitutes an aerosol-generating procedure? (Highest priority, Short-term)
   • Infectious dose needed and duration of viral survival in aerosols (Short-term).

2.1.3 Investigate the importance of superspreading events and the factors involved in such events, to enable prevention (Long-term).

2.1.4 Examine the role of antiviral use and vaccination in modulating influenza transmission (Long-term).
Substream 2.2
Dynamics of virus spread at global and local levels

Strategic objectives
Gaining a better understanding of how influenza spreads in different settings at the global and local levels can assist in optimizing response measures. Factors that would influence seasonality and dynamics of influenza transmission include geography, climates, socio-cultural-economic frameworks, population structures and susceptibility, and interaction between respiratory viruses and influenza strains. New research on transmission of influenza A(H1N1)pdm09 in different settings has been published, but improving surveillance in resource-scarce settings remains a public health need.

Research recommendations

2.2.1 Conduct studies on feasible and effective surveillance in resource-limited settings, and to understand the seasonality and spread of influenza in different settings.
• Better surveillance in poorly resourced countries (Highest priority short-term).
• The implications of seasonality and differences in transmission (temperate versus tropical countries) on the timing of vaccination (short-term).

2.2.2 Assess the dynamics of spread of epidemic and pandemic influenza in different epidemiological settings (e.g. low-income, rural versus urban and tropical versus temperate climates).
• How virus spread is affected by the setting, and how it is influenced by different social structures and behaviours (Highest priority short-term).
• The transmission dynamics in vulnerable populations (e.g. low-income communities, refugees and migrants, and informal settlements and urban slums) (Highest priority short-term).
• The impact of local practices on delaying viral spread within and between countries (Long-term).

2.2.3 Assess factors that make novel (seasonal or newly emerged) viruses successful, including replacement of other viral strains, and whether the risk of subsequent respiratory infections is influenced by influenza infection or prevention.
• Identify the factors that make novel viruses successful, including replacement of other viral strains (Long-term).
• Assess whether influenza infection or prevention influences the risk of subsequent respiratory infections (Highest priority Long-term).

Substream 2.3
Public health measures to limit transmission

Strategic objectives
Understanding the effectiveness, timing and optimal implementation of public health measures is important for public health decision-makers in planning interventions and targeting limited resources. Many studies have been done to evaluate the effectiveness of both individual-level and community-level public health measures since 2009. However, the relative effectiveness of one public health measure compared with another is still unclear, as are the benefits of such measures relative to the costs of implementing the measures. There is also a lack of observational studies to assess the actual impact of public health measures in different settings.
Research recommendations

2.3.1 Study the relative effectiveness of surgical masks and fit-tested respirators, in addition to hand and respiratory hygiene, in preventing the spread of influenza in clinical settings. (**Highest priority** short-term).

2.3.2 Study the effectiveness, timing and optimal implementation of school closures, other social distancing measures, and environmental control methods in actual settings (Long-term).

STREAM 3: MINIMIZING THE IMPACT OF PANDEMIC, ZOONOTIC AND SEASONAL EPIDEMIC INFLUENZA

Introduction and overall objectives

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— in 2006 with GAP-I (World Health Organization, 2006) and in 2011 with GAP-II (World Health Organization, 2011) – articulated a multifaceted strategy to increase vaccine production and use.

The main objective of Stream 3 is to reduce both the burden of seasonal epidemic influenza, and the risk and impact of pandemic influenza.

Substream 3.1 Determining disease burden and social impact

Strategic objectives

Disease burden studies can help in determining the incidence and prevalence of influenza, and its severity, complications and socioeconomic impacts. Such studies may also provide information on possible prevention and control strategies (e.g. vaccination). In combination with the economic burden of influenza – especially in target groups defined by the Strategic Advisory Group of Experts (SAGE) (World Health Organization, 2005) and in different social settings – the cost–effectiveness or the general benefit of influenza vaccination can be further evaluated for the implementation of effective vaccination policies. Potentially, the cost–effectiveness or general benefit can also be extrapolated from seasonal settings to pandemic settings.

Research recommendations

3.1.1 Assess the timeliness, quality and sustainability of influenza disease surveillance. Conduct epidemiological projects to determine the timing, disease and economic burden of seasonal and pandemic influenza. Assess influenza vaccine effectiveness, impact and cost–benefit among WHO recommended target groups in countries seeking to introduce or expand influenza vaccine use (**Highest priority**).

3.1.2 Determine the best approaches for applying influenza disease burden data, coupled with cost–effectiveness analyses, to inform development or expansion of influenza control programmes in the context of competing priorities (Short-term).

3.1.3 Assess the impact of influenza in different socioeconomic settings (e.g. disadvantaged, underserved and indigenous populations) (Short-term).
3.1.4 Evaluate the social impact (e.g., disruptions in commerce, health-care systems, public safety and societal functions) of seasonal and pandemic influenza (Short-term).

**Substream 3.2**

**Improve immunogenicity, availability and delivery of influenza vaccines**

**Strategic objectives**
Seasonal influenza vaccines present significant challenges: they must be updated, produced, clinically evaluated for safety and efficacy, and administered annually. The overall efficacy of influenza vaccines depends not only on the match between the vaccine and circulating strains, but also on vaccine components (e.g., adjuvants) and host immune status. Improvements in vaccines and formulations that can provide longer lasting and a broader range of protection against evolving influenza strains may have many benefits. For example, such improvements may provide better protection, expand the supply of vaccines, and reduce the frequency of vaccination and production. In a pandemic, there is a need to address additional critical issues such as the availability of suitable attenuated candidate vaccine viruses (CVVs) and alternative potency assays for accelerated release, as well as safety, immunogenicity and rapid production and equitable distribution of vaccines.

**Research recommendations**

3.2.1 Investigate methods to improve the process for selecting vaccine strains and to characterize optimal vaccine strains, including the establishment of vaccine strain libraries (**Highest priority**).

These investigations require the development of high-throughput assays to determine the antigenic characteristics of influenza viruses and extensive studies on human serology, and to determine their impact on vaccine virus selection. In addition, there is a need to identify or develop improved cell lines for the generation of non-egg-based CVVs.

3.2.2 Conduct studies to enhance the clinical applications of existing vaccines, including improvements in production, duration and breadth of protection; safety and immunogenicity profiles; and dose-sparing formulations, especially for high-risk groups (**Highest priority**).

Research should be continued by developing optimal vaccination strategies that elicit improved breadth and durability of vaccine-induced protective immunity to influenza viruses. These studies must investigate the role of immunological priming for future vaccine responses, and the phenomenon of low antibody responses after repeated annual vaccination, which results in reduced vaccine effectiveness.

3.2.3 Systematically evaluate the steps in vaccine production to reduce bottlenecks in the production of vaccines, and improve the processes of rapid response, surge capacity, rapid deployment and tracking of vaccine usage (**Highest priority**).

Additional research activities require rapid WHO biosafety risk assessment of CVVs for expedited initiation of vaccine manufacture and distribution, and improvements of yields and stability of CVVs in multiple manufacturing platforms.

3.2.4 Conduct studies to optimize and standardize animal models to be used in preclinical evaluation of new vaccines (Short-term).
3.2.5 Develop new vaccines, vaccine platforms and formulations that are safe and have enhanced immunogenicity, as well as vaccine delivery systems with improved ease of storage and administration, especially for use in under-resourced settings (Highest priority).

There is a need to develop novel, broadly cross-protective vaccines, including approaches combining multiple strategies (e.g. different antigens, use of adjuvants and novel delivery systems); clinical trials to investigate the breadth and duration of the human immune response to broadly cross-protective vaccine candidates; and a diligent assessment of next-generation vaccine strategies in the context of pre-existing immunity.

3.2.6 Identify correlates of protection for different vaccines and correlates of priming, including development and standardization of methodologies (Highest priority).

Longitudinal cohort studies are required for the understanding of immunological responses to natural infection and the determination of novel correlates of protection.

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, with an emphasis on pharmacovigilance and reduction of disease burden for post-licensure vaccine evaluation in a wider range of settings (including children), and examine and develop ways to harmonize the regulatory processes (Short-term)

The research activities should address the development, evaluation or validation of:
- adaptive clinical trial designs to speed up vaccine development;
- clinical study designs to evaluate multiple candidates in the same trial;
- systems biology pipelines to predict safety and identify non-responders;
- human challenge models for preliminary assessment of candidate vaccines; and
- assays to identify, for example, susceptible subjects, appropriate challenge viruses and endpoints.

Substream 3.3 Public health policies to reduce the impact of disease

Strategic objectives
Public health programmes and policies are key in controlling the impact of seasonal and pandemic influenza. There has been progress in the development of effective immunization policies and the improvement of vaccine acceptability. However, this progress has mainly occurred in well-resourced countries, and there is still limited realization in under-resourced countries. There is a need for further evaluation of existing and new vaccination policies, and of the role of social science research on the impact of such policies on different societies, mainly within under-resourced countries.

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) (Long-term)

3.3.2 Study the role of social science research in establishing social, ethical and legal standards in the application of public health policy, and address the public perception of influenza and its impact on societies, particularly in under-resourced populations (Long-term).
Introduction and overall objectives
The 2017 update retains three major substreams and most of the research recommendations from the 2009 document. Updates include one new recommendation, integration of three others, and revisions to the scope of several recommendations. Members of the working group for this substream identified specific research initiatives or projects that could contribute key evidence to improve patient management. Unless specified, the updated recommendations apply across all age groups in diverse geographical areas and across the range of resource settings; however, there is a particular need for studies to be conducted in resource-limited settings. Within each substream, the highest priority recommendation has been indicated. Significant progress is deemed possible on all of these research topics within a relatively short time frame (i.e. <5 years).

Substream 4.1
Factors associated with pathogenesis and clinical severity

Strategic objective
The strategic objective of this substream is to improve the evidence base on disease pathogenesis in major risk groups and severe influenza-associated illness. This evidence base could then serve as a foundation for developing better clinical management strategies.

Research recommendations
4.1.1 Understanding the clinical spectrum and natural history of human disease, including risk factors (e.g. comorbidities, demographic characteristics and environmental factors, and pre-existing infections), viral replication kinetics and immune responses, and prognostic markers for severe disease and its complications (Highest priority).

• Undertake integrated studies of viral replication patterns; systemic, respiratory mucosal and lung immune responses; and other host responses and outcomes in key high-risk populations (e.g. chronic lung disease, cardiovascular disease, infancy, pregnancy, immunocompromise and morbid obesity), critically ill influenza patients and those with novel influenza A virus infections.

4.1.2 Assess the incidence, anatomical sites, etiology and pathogenesis of secondary bacterial infections associated with influenza, as well as optimal treatment modalities and prophylactic or preventive measures.
• Determine frequencies of antimicrobial-resistant bacterial coinfections, their susceptibility patterns and the efficacy of antimicrobial treatment strategies in influenza and other respiratory viral infections.
• Undertake studies to validate clinical or laboratory criteria for stopping antibiotics in influenza and other pneumonias associated with respiratory viruses.

4.1.3 Study the role of host genetic factors on susceptibility and severity of influenza virus infection.
• Aggregate available data and conduct additional studies of the whole exome or genome of persons with severe influenza pneumonia (and of appropriate family-based and population controls) to help identify genetic susceptibility variants.
Substream 4.2
Improve clinical management of patients

Strategic objective
The strategic objective of this substream is to develop better, cost-effective interventions (e.g. diagnostics, antiviral drugs, other therapeutics and supportive care strategies) to improve outcomes in patients with or at risk for severe influenza.

Research recommendations
4.2.1 Develop rapid, sensitive, affordable point-of-care diagnostic tests for detecting influenza virus and antiviral resistance.
- Assess the impact on patient outcomes and the cost–effectiveness of current POC influenza detection assays (e.g. empiric versus diagnostics-guided antiviral treatment).
- Validate the predictive value of phenotypic and genotypic assays for NAI susceptibility in clinical settings.

4.2.2 Identify clinical and laboratory markers, and develop improved point-of-care tools for the prognosis and management of influenza.
- Investigate the usefulness of monitoring patients with rapid influenza diagnostic assays and prognostic biomarkers assays, to inform clinical care and infection control.

4.2.3 Optimize the use of current antiviral treatments, including understanding barriers to availability and increased use for treatment of influenza.
- Determine whether empiric antiviral therapy added to standard care in patients with community-acquired pneumonia or severe acute respiratory infection during periods of influenza virus circulation is effective and safe, particularly in low-resource settings.

4.2.4 Optimize the effectiveness of current and novel antiviral treatments through development of new formulations, delivery routes or systems, antiviral drug combinations and strategies, to address emergence and treatment of antiviral resistance (Highest priority).
- Test the most promising antiviral therapy combinations, particularly those that have potential for wide-scale use, and use in high-risk groups and hospitalized influenza patients.
- Develop improved clinical trial designs, including pragmatic and adaptive trials that use clinically relevant, patient-oriented endpoints for treatment studies in severe influenza.
- Conduct additional trials of intravenous NAIs in hospitalized influenza patients, to determine efficacy and appropriate duration of therapy.
- Determine optimal dose regimens for oseltamivir treatment in pregnant women, neonates and infants with influenza.

4.2.5 Develop novel and effective treatment strategies, including adjunctive treatments (e.g. immunomodulators, immunoglobulins, and natural products and their active components).
- Examine the role of clinically promising adjunctive therapies in combination with antiviral therapy compared with antiviral therapy alone in hospitalized influenza patients.
- Conduct a large randomized controlled trial to investigate the efficacy and safety of adding low-dose systemic corticosteroids to standard care in critically ill influenza patients.
4.2.6 Optimize management of persons with or at increased risk for severe influenza disease and its complications, including intensive care practices that are based on influenza-specific evidence and are applicable across a range of resource settings.

- Conduct a systematic review to assess current best practices of supportive care applicable to management of critically ill influenza patients.
- Incorporate influenza diagnostic testing into ongoing and future studies of supportive intensive care management strategies for patients with severe pneumonia and acute respiratory distress syndrome.
- Determine whether non-invasive ventilation or high-flow nasal cannula supplemental oxygen therapy may be used safely and effectively in selected influenza patients, especially in resource-limited settings.

**Substream 4.3 Health-care capacity and response**

**Strategic objective**
The strategic objective of this substream is the effective delivery of care in major seasonal influenza outbreaks and pandemics at the population level.

**Research recommendations**

**4.3.1** Evaluate the effectiveness of prevention and control strategies included in pandemic influenza preparedness plans to improve patient care and reduce the impact of influenza on health-care systems, by studying responses to seasonal influenza epidemics.

**4.3.2** Conduct operational studies on surge capacity needs, including development of triage schemes, alternative models of care and strategies to maintain adequate staffing, in different smaller health-care and resource settings.

- Assess the feasibility and cost–effectiveness of large-scale use of POC diagnostic tests to help in the triage of patients presenting to health-care facilities during an outbreak.

**4.3.3** Undertake research to validate alternative health delivery systems for care of influenza patients, including home care, community facilities other than hospitals and other venues during periods of extraordinary demand (Highest priority).

- Test strategies to increase the ability to assess and monitor influenza patients outside of clinics and hospitals (e.g. use of available technology for text, voice and video transmission).
- Test strategies to assess the uptake and outcomes of early treatment of influenza patients with antiviral drugs through alternative facilities (e.g. pharmacies) and through telephone triage.

**4.3.4** Conduct studies to develop context-appropriate best practices that provide protection for health-care workers and other caregivers in different health-care settings.

- Conduct knowledge, attitudes and practices surveys among health-care workers to determine strategies to enhance influenza vaccine uptake and compliance with personal protective equipment (PPE) and other infection control recommendations.
- Determine the effectiveness of different PPE approaches (e.g. masks versus respirators, and goggles versus face shields versus no eye protection).
4.3.5 Identify evidence-driven clinical care pathways and principles that optimize health-care delivery in a range of resource settings.

4.3.6 Develop principles and practices for timely assessment and introduction of new interventions during public health emergencies, including funded systems for standardized clinical data collection, and rapid analyses and sharing of findings to inform clinical management and public health decisions.

- Develop a repository of observational and interventional clinical research protocols that have undergone scientific and regulatory vetting to facilitate rapid initiation, evaluation and dissemination of findings; and undertake these protocols, where appropriate, in inter-pandemic periods.

STREAM 5: PROMOTING THE DEVELOPMENT AND APPLICATION OF NEW PUBLIC HEALTH TOOLS

Substream 5.1 Next-generation sequencing and other emerging technologies

Strategic objectives
The research priorities are aimed at promoting applications of next-generation sequencing (NGS) and other new technologies to improve public health and clinical practices. Applications could include surveillance for early detection of novel strains; prediction of transmission dynamics; identification of signatures of individuals at risk for severe outcomes; and development and improvement of therapeutics, vaccines and diagnostics for influenza.

Research recommendations
Research recommendations for the Short-term:
- standardization of metadata for use across the Global Influenza Surveillance and Response System (GISRS) (new);
- development of a shared informatics infrastructure that would enable dissemination of NGS technologies throughout GISRS (new);
- development of NGS technology as a clinical diagnostic tool (new); and
- development of methods to integrate antigenic, structural, clinical and genetic data to improve surveillance and vaccine strain selection.

Research recommendations for the Long-term:
- near real-time availability of sequence data for use by the broad public health and scientific community worldwide (new);
- an NGS platform that provides both diagnostic results to clinical staff and real-time genomic data on currently circulating influenza viruses (new);
- exploring integration with data on the host microbiome; for example, impacts of infection on the microbiome as a whole, or markers and trends associated with disease severity;
- exploring systems approaches to generate new knowledge to identify clinically usable predictive markers for influenza (new); and
- building computational platforms and developing advanced data analytic tools that can successfully integrate multiscale diverse data sets towards quantitative models (new).
Substream 5.2  
Role of modelling in public health decision-making

Strategic objectives
Many key papers about the transmission dynamics of influenza include evidence from mathematical models of infectious disease transmission; these are sometimes referred to as epidemic models (Anderson, May & Anderson, 1992). Epidemic models are formally characterized by the presence of a force of infection (FOI) term; that is, a function that describes how the risk of infection as experienced by susceptible individuals changes over time. The best-known examples of mathematical models of infectious disease are the susceptible–infectious–recovered (SIR) type models (Hethcote, 2000), in which the amplitude of the FOI term depends on the number of infectious individuals at any given time.

Contemporary studies of infectious disease dynamics include several other advanced analytical techniques that are not strictly epidemic models. One example is antigenic cartography, in which maps of antigenically variable pathogens are produced (Smith et al., 2004). Several studies that fall within the remit of this stream are primarily empirical in nature, but nevertheless generate evidence about systems that are often associated with epidemic models. Therefore, this update exercise has defined infectious disease modelling in a broad sense as evidence that is based on advanced analytical or empirical techniques commonly associated with the disease dynamics of influenza.

Our strategic objective in revising these recommendations was to ensure that improvements in the underlying science of influenza modelling will be rapidly translated into improved forecasting, burden measurement, vaccination programme effectiveness and pandemic planning.

Research recommendations
These recommendations are all intended to be targets for substantial progress in the next 5 years. Strain forecasting beyond 12 months in the future may be a longer term objective. As described above, even though these recommendations cover similar topics, they all differ from those suggested in 2009.

5.2.1 Improve forecasting of influenza virus and disease
• Further improve short- and medium-term epidemiological forecasting of influenza disease.
• Consider which surveillance targets best support decision-making (~3 months).
• Incorporate exogenous (i.e. non-biological) factors into medium-term forecasts (~6 months).
• Improve strain forecasting for improved seasonal vaccination (~1 year):
  o forecasting the next antigenic cluster; and
  o forecasting which extant clade will dominate.

5.2.2 Improve disease burden estimates
• Refine burden and severity estimates through model-based data synthesis by incorporating serological, sentinel influenza-like illness (ILI), virological surveillance and e-health data.
• Characterize and understand interannual variation in severity and attack rates, and variation by subtype and clade.
• Use models to optimize novel surveillance systems for low- and middle-income countries (LMICs); for example, syndromic surveillance and the use of multiplex diagnostics.
5.2.3 Improve the evaluation and further optimization of seasonal vaccination
- Develop models for better evaluation of the impact of seasonal vaccination on disease burden, including cost–effectiveness analysis for LMICs.
- Improve mechanistic modelling of vaccine efficacy and estimate the impact of population immunity, using immunodynamic models with antibody landscape data from longitudinal and cross-sectional studies.
- Assess the impact of repeat vaccination (for live-attenuated influenza vaccine [LAIV] and trivalent inactivated influenza [TIV]) on individual antibody dynamics and disease risk, including evaluation of test-negative trial data and the potential limitations of such data.
- Use modelling to optimize novel vaccination strategies.

5.2.4 Improve pandemic preparedness and assessment
- Develop models to improve assessment of the pandemic potential of zoonotic strains.
- Develop novel methods for improved assessment of real-time pandemic severity.
- Improve methods for real-time forecasting of pandemic trajectories using serological, genetic and Internet data to improve denominator estimates.
- Forecast pandemic influenza; and
- Adapt seasonal forecasts or ensemble methods for pandemic situations.

**Substream 5.3 Strategic communication**

The research recommendations proposed in the 2009 Research Agenda included a range of important subjects considered critical to the influenza communication response. The current communication technical working group (TWG) aimed to more narrowly define research required for practical decision-making by leaders and response organizations. During the research period 2009–2017 WHO declared several Public Health Emergencies of International Concern; these emergencies included the H1N1 pandemic influenza, Ebola virus disease and Zika virus disease, each of which provided vital lessons for communication response. Communication is increasingly and repeatedly being recognized as a response mechanism that is just as important as epidemiology, laboratory and emergency responses.

To gain more insight into appropriate response methods, the TWG suggests that influenza research budgets be increased to fund more studies on the communication response, including how best to communicate scientific research findings. Given recent history and the lessons that continue to be learned, the group proposes that communication become a separate work stream, to heighten its importance in the response to and in the reduction of influenza burden of disease.

**Strategic objectives**

The communication substream of the 2017 Influenza Research Agenda should provide influenza-related evidence or (in lieu of influenza foci) emergency-related evidence on the following:
- real-time and comparable data collection methods – for example, rapid knowledge, attitudes and practice (KAP) surveys and big data methods enabling meta-analyses;
- behaviour change through community engagement (from social science and communication studies), to gain a better understanding of who influences individuals and community decisions;
- effective communication methods for low-income and low- and middle-income countries as defined by WHO, and low-resource settings – that is, those with low communication capacity according to International Health Regulations 2005 (IHR 2005) and Joint External Evaluation assessment – to implement a response during the influenza epidemic or pandemic;
- tracking and analysis methods to address the most effective measures to respond to misinformation and rumours;
- which methods are effective and which are ineffective in coordinating communication between subnational, national and international response stakeholders;
• communication responses throughout the phases of a pandemic, to be conducted simultaneously in a variety of cultural settings and in multiple nations;
• communication's potential influence in the discrimination of, for example, populations, countries and communities, and how that is related to ethical, social and political matters as well as to equity and justice;
• the cost–effectiveness of communication interventions to reduce the burden of disease;
• the most effective mix of communication approaches – mass media, social media and community or interpersonal for each target audience; and
• risk communication political, economic and social systemic factors, on both national and international scales, that influence health policy and mitigation of the health emergencies.

Research recommendations

5.3.1 Conduct and review international studies and experience in communication response during health emergencies from related disciplines (e.g. behavioural and social sciences, media studies and marketing), in order to improve strategic public health communication response and decision-making (Short-term).

5.3.2 Identify, develop and evaluate adaptable communication tools and methods that can accurately and sustainably be used for the rapid assessment and monitoring of knowledge, attitudes, practices and perception in different population groups, to guide effective communication efforts (Highest priority).

5.3.3 Identify, develop and evaluate innovative approaches, advocacy strategies and communication channels appropriate for different cultural settings and diverse target audiences, in order to change behaviour (Short-term).

5.3.4 Track, monitor and analyse different response methods during health emergencies to identify the communication methods that most effectively stop the spread of inaccurate and contradictory information, rumours, myths and narratives, and counteract their negative impact on the response (Short-term).

5.3.5 Study how ethical, social, economic and political factors influence communication interventions in national and international health crisis situations, in order to develop communication strategies to diminish the burden of disease (Short-term).

5.3.6 Determine best communication practices to increase health-care workers' uptake of influenza vaccine, and to improve their ability to impart information about influenza and the influenza vaccine (Highest priority).

5.3.7 Conduct studies to determine which strategies are effective and which are ineffective for coordinating communication between subnational, national and international stakeholders and partners, including studies on which stakeholders are the most effective decision-makers, in order to reduce the burden of influenza disease (Short-term).

5.3.8 Identify and make recommendations on the most effective ways to communicate new influenza research findings that will best increase knowledge and change behaviour among different audiences (Short-term).
References


