

advance science to address unmet public health needs

2017 UPDATE

WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA



World Health Organization

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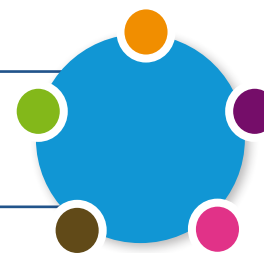
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WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA



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ABBREVIATIONS

BARDA	Biomedical Advanced Research and Development Authority
CVs	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.¹

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.

¹ See <http://www.who.int/influenza/resources/research/about/en/>

OUTLINE OF THE WHO PUBLIC HEALTH RESEARCH AGENDA FOR INFLUENZA – 2017 UPDATE

Stream 1 Reducing the risk of emergence of a pandemic influenza	
	1.1 Improved surveillance and detection of emergent IAV with zoonotic or pandemic potential for risk assessment and response
	1.2 Identification of virus, host and environmental determinants for infectivity, susceptibility, transmission and pathogenesis of potentially zoonotic IAVs
	1.3 Management or a modification of animal production and marketing systems for mitigation of the risk of zoonotic IAV emergence, geographic spread and transmission to humans
	1.4 Improving vaccines and their application in the animal host populations to reduce human exposure to zoonotic IAV
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 new public health tools	
	5.1 Next-generation sequencing and other emerging technologies
	5.2 Role of modelling in public health decision-making
	5.3 Strategic communication

INTRODUCTION

Background

The influenza virus, and its impact on individuals and populations, is not yet fully understood. As a result, the public health response to pandemic, zoonotic and seasonal epidemic influenza remains limited, as was seen during the 2009 influenza pandemic and the more recent H7N9 outbreaks in China. To outline directions and priority areas for future research on influenza, it is essential to first identify gaps in the current state of knowledge and to develop a clear understanding of shortcomings in data in diverse areas of influenza-related studies. Guiding researchers and practitioners into less explored and new avenues for research on influenza will help to identify new and current priority areas. A sustained research effort will inform public health decision-making, which in turn will support better allocation of limited financial resources.

In 2009, WHO's Global Influenza Programme developed the WHO Public Health Research Agenda for Influenza¹, as part of its effort to accelerate the pace of scientific progress and encourage exploration of those areas of influenza research that have the greatest public health impact.

The Research Agenda comprises 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

To evaluate the impact of WHO's initiative to encourage research on better prevention and control of influenza globally, a biannual progress review was conducted in 2010–2011 (World Health Organization, 2013). The review focused on the high-priority public health research topics in the five streams, and commissioned literature reviews for each topic.

Since the publication of the Research Agenda in 2009, followed by the publication of the progress review in 2013, much has been learned about influenza. Some knowledge gaps have been filled, but others remain challenging to the scientific community. There is also a need to address unmet public health needs and remaining and emerging knowledge gaps, and to stimulate new development. Thus, the Research Agenda, created to support evidence-based public health policy, needed to be updated to better serve as a vehicle for discussions among researchers, donors and funding agencies, and public health professionals worldwide. This updated Research Agenda will also be useful in strengthening coordinating efforts and direct actions to mitigate the impact of influenza on individuals and populations.

Overall objectives

The overall objective of the 2017 update was to identify high priority areas in influenza research for the next 5–10 years that could benefit the global public health communities in reducing the burden of seasonal epidemic influenza, and the risk and impact of pandemic influenza.

¹ See <http://www.who.int/influenza/resources/research/about/en/>

Outcomes

For each of the five streams defined in the 2009 Research Agenda, a list of updated high priority research recommendations with highest priority ones indicated was developed. For each stream, these recommendations are supported by an updated background document that summarizes the key accomplishments, unmet public health needs, and remaining and emerging knowledge gaps. The combined lists of updated high priority research recommendations form the WHO Public Health Research Agenda for Influenza: 2017 Update. Potential indicators and mechanisms for monitoring and evaluating the public health impacts of the research recommendations were discussed throughout the updating process. A list of such indicators was provided to WHO for consideration in the implementation of the research agenda.

Process

Technical working groups

To obtain the required expertise for updating the research agenda, a technical working group comprising relevant experts was established for each of the five streams. The goal for each working group was to develop the updated research recommendations, based on the updated background document that summarized a review of selected literature (i.e. all review articles and between three and five key original publications identified by the working group members). The literature review was undertaken to identify the major achievements, unmet public health needs, and remaining and emerging knowledge gaps, to form the foundation for the development of the updated research recommendations. The working groups also took into account the outcomes of the following scientific meetings:

- WHO consultation on national, regional and global estimates of the burden of influenza disease – July 2016, Geneva, Switzerland;
- Eighth WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses – August 2016, Chicago, United States of America (USA); and
- Options (IX) for the Control of Influenza meeting – August 2016, Chicago, USA.

Consultation meeting in December 2016

As part of the updating process, a technical consultation meeting was convened in Geneva on 6–8 December 2016. The meeting was attended by most of the working group members and representatives of partner organizations. The objectives of the meeting were to:

- review and assess key accomplishments in influenza research since the publication of the progress review in 2012;
- identify unmet public health needs, and remaining or emerging knowledge gaps;
- determine public health research priorities that could benefit the global public health community in reducing the burden of seasonal epidemic influenza, and the risk and impact of pandemic influenza; and
- identify potential indicators for monitoring and evaluating the impact of the updated research recommendations.

Two levels of technical input were gathered during the consultation meeting: those at the level of the working groups, gathered through in-depth discussions and reaching consensus during the breakout sessions; and those at the level of cross-working groups, gathered by addressing cross-cutting topics and sharing expertise during the plenary sessions.

All experts who were members of the technical working groups or attended the consultation meeting submitted the Declaration of Interest for WHO Experts forms which were carefully review by the WHO secretariats.

Public comment

After the consultation meeting in December 2016, the revised drafts of the updated research recommendations and background documents were opened for public comment for 2 months. Feedback was received from those with an interest in public health research on influenza and with a variety of expertise, including virology, epidemiology, clinical medicine, vaccine development, mathematic modelling, communication and public health policy. All public comments were reviewed and evaluated by the experts in the working group for the technical relevance in addressing unmet public health needs in the corresponding stream. The draft documents were then updated in response to the feedback.

Focus

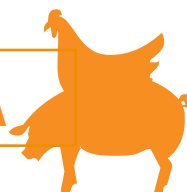
The efforts in updating the research agenda focused on:

- identifying unmet public health needs, and remaining and emerging knowledge gaps; and
- developing corresponding achievable high and highest priority research recommendations for the next 5–10 years that may benefit the global public health communities in reducing the burden of seasonal epidemic influenza, and the risk and impact of pandemic influenza.

Audience and stakeholders

The audience and stakeholders for this Research Agenda are researchers, public health professionals and policy-makers, and donors and funding organizations that are interested in advancing science to address unmet public health needs nationally and globally.

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.

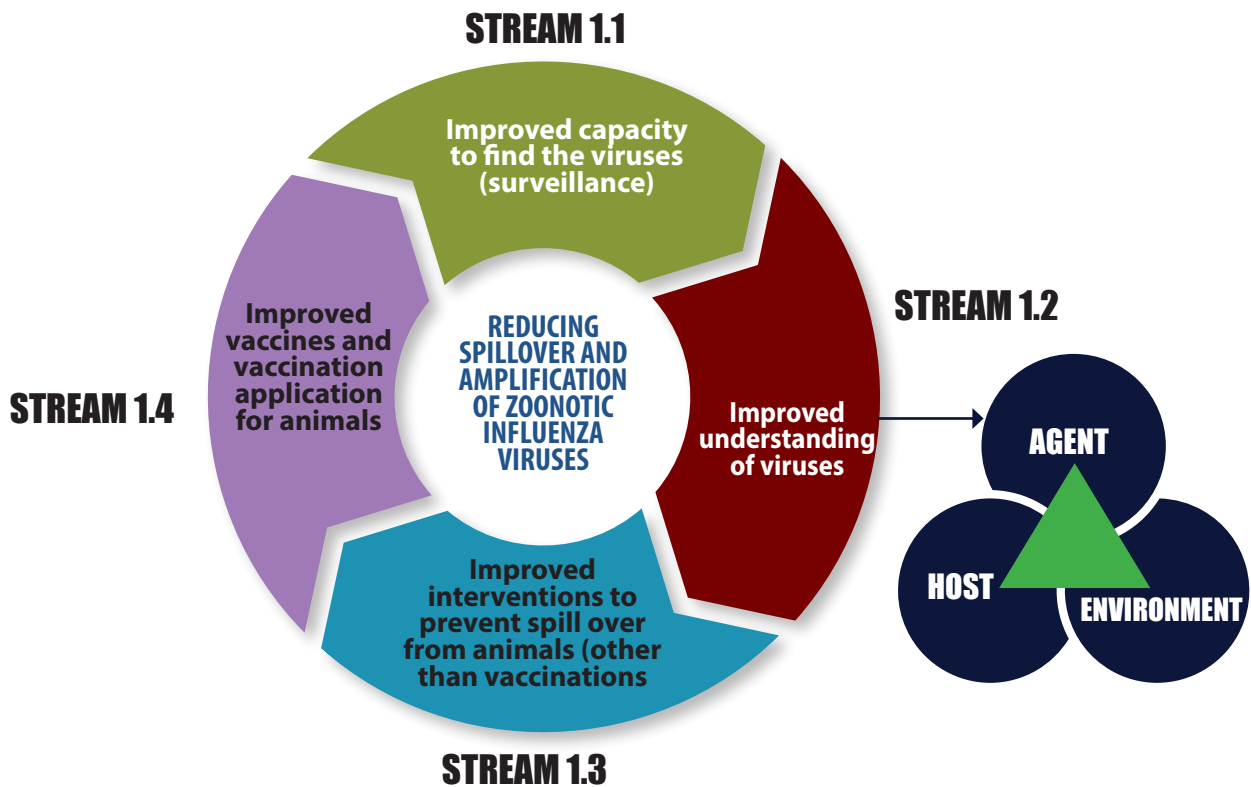
It is recommended that research focuses on four main areas of response:

- *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.

As indicated in Fig. 1 below, 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.



REDUCING SPILLOVER AND AMPLIFICATION OF ZOOONOTIC INFLUENZA VIRUSES
Figure 1

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.

Summary of major revisions with rationale

The recommendations for Substream 1.1 are similar to those in Substream 1.3 in the 2009 Research Agenda, but have been restated to be more focused. Concerns regarding serological tests for zoonotic IAVs in humans were also raised in the review of Recommendations 1.2.1 and 1.2.2 in the 2009 Research Agenda, but these issues are now covered in Recommendation 1.1.3 in the current document.

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).

*Revised from the 2009 Recommendations 1.3.1, 1.3.3 and 1.3.4. **Highest priority**, public health needs inadequately met, for long-term implementation.*

- 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”.

Revised from the 2009 Recommendation 1.3.2, with added elements. Highest priority, underpinning the unmet public health need identified in Recommendation 1.1.1. Requires long-term implementation.

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

Revised from the 2009 Recommendations 1.3.1 and 1.3.3, and including research reviewed under the 2009 Recommendations 1.2.1 and 1.2.2. Addressing a public health need that is currently met inefficiently. Should be fully implemented in the 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.

*Revised from the 2009 Recommendation 1.3.3. **Highest priority**, addressing an incompletely met public health need. Requires long-term implementation.*

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.

Summary of major revisions with rationale

There is little substantial modification from the intent of the recommendations in the 2009 Substream 1.1. A new recommendation (Recommendation 1.2.4) has been added, stating that there should be an agreed standardized set of data that will be expected to be associated with the initial report of a potentially new strain with zoonotic or pandemic potential, and that this set of data should be regularly updated to reflect the current understanding of the significance of reported IAV genotypes and phenotypes.

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.

*Revised from the 2009 Recommendations 1.1.3, 1.2.1 and 1.2.2. **Highest priority**, addressing inadequately met public health needs. Requires long-term implementation.*

1.2.2 Investigate virus-specific factors associated with zoonotic and pandemic potential that confer cross-species infectivity, susceptibility, transmissibility and pathogenicity.

*Revised from the 2009 Recommendation 1.1.1. **Highest priority**, addressing inadequately met public health needs for surveillance, vaccine development and novel therapeutic interventions. Requires long-term implementation.*

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”).

*Revised from the 2009 Recommendations 1.1.2 and 1.2.3, to more clearly express the importance of the complex effects of individual and population immunity, and the inherent susceptibility of host cells. **Highest priority**, addressing unmet public health needs. Requires long-term implementation.*

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.

*This is a new recommendation. **Highest priority**, meeting an inadequately met public health need. Requires short-term implementation to ensure that at any time scientific knowledge fully informs the reporting of and response to newly detected IAVs.*

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.

Summary of major revisions with rationale

Much of the focus of recommendations in Substream 1.4 of the 2009 Research Agenda is captured in this substream, with the inclusion of areas of research that were reported under Recommendations 1.1.3 and 1.2.2 of the 2009 Research Agenda. Hence, the recommendations have become more focused.

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.

*Revised from the 2009 Recommendations 1.4.1–1.4.3. **Highest priority**, addressing unmet public health needs. Requires long-term implementation.*

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.

Revised from the 2009 Recommendations 1.4.1–1.4.3. Addressing inadequately met public health needs. Requires long-term implementation.

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.

Revised from the 2009 Recommendations 1.1.3, 1.2.2 and 1.4.1–1.4.3. Addressing public health needs inadequately met, for long-term implementation.

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.

Revised from the 2009 Recommendations 1.1.3, 1.2.2 and 1.4.1–1.4.3. Addressing inadequately met public health needs, for long-term implementation.

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

Revised from the 2009 Recommendation 1.4.4. Addressing inadequately met public health needs. Requires long-term implementation.

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.

Summary of major revisions with rationale

Improvement of vaccines was addressed in the 2009 Substream 1.4. In the 2017 Research Agenda, improvement of vaccines is recommended as a separate objective to emphasize its importance, broad applicability and likely cost-effectiveness. Also, vaccine research is based on laboratory research in the first instance, and thus differs from the more behaviourally focused recommendations under the 2017 Substream 1.3.

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).

*Revised from the 2009 Recommendation 1.4.1. **Highest priority**, addressing unmet public health needs. Requires long-term implementation.*

- 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.

Revised from the 2009 Recommendation 1.4.1. Addressing inadequately met public health needs. Requires long-term implementation.

- 1.4.3** Determine and communicate the benefits and risks of potent, antigenically matched vaccines and proper vaccination strategies.

*Revised from the 2009 Recommendation 1.4.4. **Highest priority**, addressing unmet public health needs. Requires short-term implementation.*

STREAM 2: LIMITING THE SPREAD OF PANDEMIC, ZONOTIC 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.

Summary of major revisions with rationale

Five main research recommendations (Recommendations 2.1.1–2.1.5) were proposed for Substream 2.1 in the 2009 document. For the 2017 document, four recommendations were revised and one was deleted. For Recommendation 2.1.1, it was felt that, rather than investigating the modes of transmission and their relative importance, the focus should be on how to translate this into designing more effective interventions. We revised Recommendation 2.1.2 to focus mainly on aspects of aerosol transmission, because aerosol generation is important in transmission, especially in the clinical setting. What constitutes an aerosol-generating procedure was identified as an important research gap. Studying asymptomatic and subclinical infections is no longer deemed a priority in Recommendation 2.1.3, although it remains relevant for the modelling part of Stream 5; hence, the recommendation was revised to emphasize only research on the importance of superspreading events and factors involving such events. Recommendation 2.1.4 was revised to focus only on investigating how antiviral medications and vaccines can modulate transmission at the individual level, because data on interruption of transmission from use of antiviral medications are scarce. Recommendation 2.1.5 is no longer considered a high priority research and has been removed.

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. (2009 revised)

This is for long-term focus

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. (2009 revised)

- What constitutes an aerosol-generating procedure?
*This is **highest priority** and for short-term focus*
- Infectious dose needed and duration of viral survival in aerosols.
This is for short-term focus

- 2.1.3** Investigate the importance of superspreading events and the factors involved in such events, to enable prevention. (2009 revised)

This is for long-term focus

- 2.1.4** Examine the role of antiviral use and vaccination in modulating influenza transmission. (2009 revised)

This is for long-term focus

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.

Summary of major revisions with rationale

Three recommendations (Recommendations 2.2.1–2.2.3) were revised and one recommendation (Recommendation 2.2.4) was deleted in the 2017 document. Studying the seasonality and differences in virus transmission in different settings remains relevant for assessing the timing and effectiveness of vaccination. However, the focus in the first recommendation was directed to developing good surveillance systems in resource-limited settings, which remains an unmet public health need. For Recommendation 2.2.2, the original recommendation was retained with only slight modifications, to emphasize the need for studies on the dynamics of the spread of influenza in different settings and subpopulations, including low-income populations and refugees. There is mounting evidence of influenza prevention or vaccination increasing the risk of subsequent respiratory infections; therefore, a new sub-recommendation was included in Recommendation 2.2.3 to specifically address this topic. This recommendation was also refined to specifically target issues of co-circulation of viral strains, subtype replacement, viral fitness and other factors that make novel viruses successful. The last recommendation is no longer considered a research priority and has been removed because it overlaps one of the recommendations in Stream 2.3.

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. (2009 revised)
- Better surveillance in poorly resourced countries.
*This is **highest priority** and for short-term focus*
 - The implications of seasonality and differences in transmission (temperate versus tropical countries) on the timing of vaccination.

This is for long-term focus

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). (2009 revised)

- How virus spread is affected by the setting, and how it is influenced by different social structures and behaviours.

*This is **highest priority** and for short-term focus*

- The transmission dynamics in vulnerable populations (e.g. low-income communities, refugees and migrants, and informal settlements and urban slums).

*This is **highest priority** and for short-term focus*

- The impact of local practices on delaying viral spread within and between countries.

This is for long-term focus

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. (2009 revised)

- Identify the factors that make novel viruses successful, including replacement of other viral strains.

This is for long-term focus

- Assess whether influenza infection or prevention influences the risk of subsequent respiratory infections.

*This is **highest priority** and for long-term focus*

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.

Summary of major revisions with rationale

Three recommendations were revised (Recommendations 2.3.1–2.3.3), and one recommendation was deleted (Recommendation 2.3.4) in the 2017 document. Individual-level public health measures are always recommended and used during seasonal epidemics and pandemics to reduce transmission, and their feasibility and absolute effectiveness have been well studied since 2009. The first recommendation should now focus more on the relative effectiveness of various individual-level public health measures, particularly in clinical settings. The new Recommendation 2.3.2 combines the previous 2009 Recommendations 2.3.2 and 2.3.3; it has been refined to emphasize the need to conduct more observational studies (rather than modelling studies) to

evaluate the effectiveness and timing of community-level public health measures in actual settings. Recommendation 2.3.4, the last recommendation in the 2009 document, was deemed to no longer be a research priority because the topic was too broad and nonspecific; hence, it has been removed.

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. (2009 revised)

*This is **highest priority** and for short-term focus*

2.3.2 Study the effectiveness, timing and optimal implementation of school closures, other social distancing measures, and environmental control methods in actual settings. (2009 revised)

This is for long-term focus

STREAM 3: MINIMIZING THE IMPACT OF PANDEMIC, ZONOTIC 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 WHO Public Health Research Agenda for Influenza in 2009 outlined recommendations for minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza (Stream 3) and identified three major topics:

Substream 3.1: Determining disease burden and social impact

Substream 3.2: Improve immunogenicity, availability and delivery of influenza vaccines

Substream 3.3: Public health policies to reduce the impact of disease by immunization

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.

Summary of major revisions with rationale

Recommendations 3.1.1–3.1.4, given below, have been revised and merged from the 2009 recommendations, because the different topics are now summarized in several overlapping WHO documents, protocols and manuals. Specific topics that have been summarized are rates of influenza-like illness and other influenza-related illnesses requiring outpatient medical consultations, hospitalization and mortality rates, seasonality, clinical definitions, and disease and economic burden.

Much progress has been made on disease burden data since 2009; further progress requires the generation of influenza disease and economic burden estimates among WHO/SAGE vaccine target groups (e.g. pregnant women, health-care workers and those with pre-existing conditions). In particular, there is a need for information on the burden of severe illness among low- and middle-income countries. These estimates should be supplemented by estimation of annual coverage, effectiveness and impact of vaccines, including averted severe illness. Also, there is a need for further emphasis on determining the impact of vaccine coverage on disease burden, through disease burden studies and diligent evaluation of surveillance data.

The 2009 Recommendation 3.1.6 has been divided into two separate topics (see Recommendations 3.1.3 and 3.1.4 below) to address the research needs in a more specific manner.

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.

*Revised and merged from the 2009 Recommendations 3.1.1–3.1.4. This revised recommendation is considered as **highest priority** research.*

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.

This recommendation remains the same as it was in 2009, and research should be continued in the Short-term.

3.1.3 Assess the impact of influenza in different socioeconomic settings (e.g. disadvantaged, underserved and indigenous populations).

Revised from the 2009 Recommendation 3.1.6. This revised recommendation has been identified as 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.

Revised from the 2009 Recommendation 3.1.6. This revised recommendation has been identified as 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.

Summary of major revisions with rationale

Since 2009, much progress has been made and there have been many new developments; for example, the introduction, establishment, qualification or validation of novel immunological assays, and the implementation of various promising vaccine approaches beyond the conventional egg-based technology. In addition, some of the 2009 recommendations have already been addressed by several institutions such as WHO, the Biomedical Advanced Research and Development Authority (BARDA), European Union financed research consortia (e.g. UNISEC) and industry. As such, most of the recommendations (Recommendations 3.2.1–3.2.3 and 3.2.5–3.2.9) have been re-evaluated and revised to address the new landscape of traditional and novel influenza vaccines, including their characterization, immunological evaluation and regulatory requirements.

In addition, Recommendations 3.2.7–3.2.9 have been merged to reflect new developments and progress in the areas of clinical study designs, vaccine effectiveness studies, pharmacovigilance, post-licensing activities and alternative potency assays.

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.

Revised from the 2009 recommendations.

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.

*These activities are considered as **highest priority**.*

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.

Revised from the 2009 recommendations.

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.

*These activities are considered as **highest priority**.*

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.

Revised from the 2009 recommendations.

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

*These activities are considered as **highest priority**.*

3.2.4 Conduct studies to optimize and standardize animal models to be used in preclinical evaluation of new vaccines.

This recommendation is the same as the 2009 recommendation. These activities have been identified as 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.

This recommendation has been revised from the 2009 recommendation.

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.

*These activities are considered as **highest priority**.*

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

Revised from the 2009 recommendations.

This revision mainly addresses:

- the definition and validation of correlates of protection other than haemagglutination inhibition antibody (e.g. neutralizing antibodies, neuraminidase inhibition antibodies, other functional antibodies, cell-mediated immunity and systems biology) for novel vaccine candidates; and
- the development of biobanks of characterized human clinical trials, to help in the identification of biomarkers for vaccine development.

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

*These activities are considered as **highest priority**.*

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.

This recommendation has been revised from the 2009 recommendations, by merging Recommendations 3.2.7–3.2.9 into one topic.

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.

All of these research activities are considered as short-term projects.

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.

Summary of major revisions with rationale

The 2009 Recommendation 3.3.2 (Develop effective immunization policies using community-based input) has been successfully completed since the 2009 pandemic, with influenza vaccination policies now in place. In particular, these policies address pandemic preparedness and specific risk groups such as paediatric, the elderly and health-care workers. With the introduction of a “universal” influenza vaccine policy in the United States of America (USA), proven measures to improve vaccine compliance can be undertaken by health-care professionals (including retail and health system pharmacists), government programmes and community organizations. In addition, surveys on knowledge, attitude and practices to inform influenza vaccination policies have been conducted in many countries and in various vaccination targeted groups, for both seasonal and pandemic vaccines.

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).

This recommendation is the same as that of 2009. However, the discrepancy between the presence of influenza vaccination policies in many countries and their actual implementation should be analysed to better address the issue of bringing policy to practice. This research activity is considered 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.

This recommendation has been renumbered (it was formerly Recommendation 3.3.3) and it remains essentially the same as the 2009 recommendation. This research activity is considered Long-term.

STREAM 4: OPTIMIZING THE TREATMENT OF PATIENTS



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.

Summary of major revisions with rationale

Three recommendations from 2009 were combined to facilitate a cross-cutting approach. The priority was to undertake integrated studies of viral replication, host immune and other responses, and outcomes in high-risk populations and critically ill patients. In addition, there is a need for up-to-date data on bacterial coinfections and antimicrobial resistance, laboratory tools to identify patients needing antibiotics, optimal antimicrobial regimens and strategies to reduce secondary bacterial infections (e.g. antiviral therapy and probiotics). Understanding host genetic factors relevant to both influenza susceptibility and disease severity can help to identify the individuals and groups that should be targeted for enhanced prevention or treatment measures (e.g. immunotherapeutics). It might also lead to novel interventions with important public health benefits.

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.

*This recommendation is the **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.

Summary of major revisions with rationale

This substream was expanded to incorporate one new recommendation (Recommendation 4.2.3). The aim was to understand why antiviral therapy has not been used in many seriously ill and high-risk patients, as recommended by WHO and other public health organizations, and to focus more research on antiviral resistance. Also addressed was the key question of how critical influenza illness might differ from other infectious causes of critical illness, and the implications for intensive care unit (ICU) management (Recommendation 4.2.6).

The performance of rapid point-of-care (POC) influenza assays has improved; however, there is a need for more accurate and cost-effective POC tests that are broadly applicable, particularly for use in low-resource settings and in the monitoring of hospitalized influenza patients. Rapid assays for detecting antiviral resistance (e.g. to neuraminidase inhibitors [NAIs]) are also needed to guide patient care. Combinations of antiviral drugs with differing mechanisms of action offer potential

for a greater antiviral effect, reduced risk of resistance and better clinical outcomes. Several small clinical trials suggest that certain immunomodulatory agents added to antiviral therapy for severe influenza may improve outcomes, and further clinical trials are needed.

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.
 - Conduct a survey of clinical practice guidelines and country-level antiviral availability for seasonal influenza treatment.
- 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.

*This recommendation is the **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.

Summary of major revisions with rationale

Because this goal is shared with other infectious disease outbreaks and mass casualty events, the research questions and findings are potentially applicable to a range of issues that cause stress in health-care systems. The scope was refocused to be more influenza-specific (e.g. studies of seasonal influenza could evaluate the effectiveness of prevention and control strategies included in pandemic preparedness plans) and to emphasize application in resource-limited settings. The effectiveness of triage (e.g. by telephone, use of rapid POC diagnostics or outpatient monitoring), surge capacity strategies (e.g. alternative sites of care and alternative providers), and clinical care pathways are not well understood. Keeping health-care workers well so that they can perform their duties, and reducing the frequency and severity of nosocomial influenza outbreaks, are directly linked to the goals of reducing risks of influenza virus transmission (Stream 2) and using influenza-specific interventions for prevention (Stream 3). As with other outbreaks, rapidly characterizing the disease and assessing interventions are essential elements for improving clinical management. There is a need for systems to standardize clinical data collection with platforms appropriate for a range of health-care systems: identification of regional collaborating and international coordinating centres, to facilitate data analysis and sharing; and mechanisms to facilitate quick access to funding.

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.

*This recommendation is the **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.

Summary of major revisions with rationale

NGS and other emerging technologies form an entirely new section within Stream 5.

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.

Summary of major revisions with rationale

After a careful assessment of the evidence, we decided to replace the original structure of the recommendations with revised headings (see the background document for Stream 5 [Modelling]). We subdivided the original recommendations into separate topics, evaluated progress against those objectives and then aligned them with our strategic objectives.

Table 5.2 shows the relationship between the 2009 recommendations, the topics and the revised recommendations.

Table 5.2.
SUMMARY OF ORIGINAL RESEARCH RECOMMENDATIONS, IMPLIED UNDERLYING TOPICS AND PROPOSED TOPICS FOR REVISED RECOMMENDATIONS

Original research recommendation (2009)	Underlying topics for original research recommendations (2009)	Proposed topics revised research recommendations (2017)
5.2.1: Epidemiology	Estimation of key parameters	Forecasting, pandemics
	Disease burden	Burden
	Spillover	Pandemics
	Forecasting and nowcasting	Forecasting, pandemics
5.2.1: Evolution	Predicting evolution for vaccination	Forecasting
5.2.2: Interventions	Strain turnover forecasting	Forecasting
	Antigenic cluster forecasting	Forecasting
	Vaccines	Vaccines
	Other	Pandemics
	Logistics	Pandemics
5.2.3: Planning	Policy planning and strategic decision-making	Pandemics
5.2.4: Model realism	Immunological dynamics	Vaccines
	Social contacts and behaviour	Forecasting, pandemics

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 (Forecasting)
- 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 (Burden)
- 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 (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 (Pandemics)
- 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.

Summary of major revisions with rationale

- 5.3.1** Within this recommendation, the subtopics of behavioural and social sciences, media studies and marketing were numerous and broad, yet highly important. Therefore, we have kept the subtopics but are seeking research results that can be better used by decision-makers in communication response. There is a continuing need to look at the evidence of how global events shape local perceptions of risk as more and more people are connected. There is also a need to look at how traditional health behaviour theories hold in the modern global context.
- 5.3.2** To better ensure rapid response during an influenza outbreak or pandemic, evidence on public perception and actions needs to be gathered quickly. More emphasis should be placed on rapid KAP surveys and use of big data technologies, as well as the review of grey literature.
- 5.3.3** To reduce the burden of influenza disease, research must continue to identify the most effective ways to reach specific target audiences to increase knowledge or change behaviours. It is difficult to separate control measures (e.g. vaccination, cough etiquette and hand washing) from risk communication interventions; therefore, there is a continuing need for more in-depth research, particularly to assess timing of communication interventions in relation to other interventions.
- 5.3.4** Rumours and misinformation should continue to be studied but more emphasis should be placed on the best ways for decision-makers to manage rumours as opposed to the tone of rumours themselves or the methods by which rumours spread.

- 5.3.5** This recommendation was simplified to focus more on the need to determine how communication affects the burden of disease. There should be an emphasis on anthropological, political and social factors, where communication might bring about a better understanding of social bias and other factors affecting health outcomes.
- 5.3.6** This recommendation was added to address a concern about health-care workers' attitudes towards influenza vaccine, and their ability to answer questions about the vaccine and promote its use. Health-care workers are key in the promotion of influenza vaccine uptake; therefore, further studies are needed to determine the best KAPs for health-care workers, to enable them to effectively communicate with patients and communities.
- 5.3.7** This recommendation has been added to reflect the importance of communication coordination between subnational, national and international stakeholders, and the adverse outcomes of poor coordination.
- 5.3.8** This recommendation has been added to reflect the need to further disseminate new influenza research findings into information and interventions that will help audiences increase their knowledge and potentially change their behaviour to reduce the burden of influenza disease.

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.

This is modified from the 2009 Recommendation 5.3.1 and should be conducted over the 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.

This is modified from the 2009 Recommendation 5.3.2 and should be conducted as a 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.

This is modified from the 2009 Recommendation 5.3.3 and should be conducted over the 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.

This is modified from the 2009 Recommendation 5.3.4 and should be conducted over the 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.

This is modified from the 2009 Recommendation 5.3.5 and should be conducted over the 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.

*This is a new recommendation and should be conducted as a **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.

This is a new recommendation and should be conducted over the 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.

This is a new recommendation and should be conducted over the Short-term.

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