

Public Health Research Agenda for  
Influenza in the South-East Asia Region:  
A review of current status and needs



**World Health  
Organization**

Regional Office for South-East Asia



# Public Health Research Agenda for Influenza in the South-East Asia Region: A review of current status and needs



**World Health  
Organization**

Regional Office for South-East Asia

© **World Health Organization 2011**

All rights reserved.

Requests for publications, or for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – can be obtained from Publishing and Sales, World Health Organization, Regional Office for South-East Asia, Indraprastha Estate, Mahatma Gandhi Marg, New Delhi 110 002, India (fax: +91 11 23370197; e-mail: [publications@searo.who.int](mailto:publications@searo.who.int)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication does not necessarily represent the decisions or policies of the World Health Organization.

Printed in India

# Contents

	<b>Page</b>
<i>Executive summary</i> .....	v
1. Background .....	1
1.1 Influenza .....	1
1.2 Research agenda for influenza .....	2
1.3 WHO Public Health Research Agenda for Influenza .....	3
1.4 Research agenda in the South-East Asia Region.....	5
1.5 Consultation on Regional Framework for Public Health Research Agenda for Influenza .....	6
2. Influenza research globally .....	6
3. Influenza research in SEAR countries.....	8
3.1 Review of the literature .....	8
3.2 Search strategy .....	8
3.3 Results.....	9
3.4 Conclusions.....	15
4. Public Health Research Agenda for Influenza: Regional priorities .....	16
4.1 Priority influenza research for SEAR countries .....	17
4.2 Stream 1: Reducing the risk of emergence of pandemic influenza .....	21
4.3 Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza .....	22
4.4 Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza .....	22

4.5	Stream 4: Optimizing the treatment of patients .....	24
4.6	Stream 5: Promoting the development and application of modern public health tools .....	25
5.	The way forward.....	26

### **Annex**

1.	Influenza research by SEAR-country and by Area of Focus, 2005-2010 .....	28
----	--	----

## Executive summary

Influenza is a global public health challenge. Whether in its zoonotic, seasonal epidemic or pandemic forms, can lead to mild to severe illness, and even in death. Insufficient knowledge in many areas has hampered capacity to prepare and respond to pandemic influenza as well as zoonotic and seasonal influenza epidemics. This includes limiting the spread and reducing the impact of influenza, and research on nonpharmaceutical interventions that may be critical for resource-limited settings.

A literature review was conducted on the volume and nature of influenza research undertaken by South East Asia Region (SEAR) countries in the past five years (2005-2010). The review highlighted that even though a lot of research was undertaken on influenza, there was an imbalance in influenza research (volume and capacity) between Member States. The majority of the research focused on (1) limiting the spread of influenza; (2) minimizing the impact of influenza and (3) optimizing treatment of patients. Little research was conducted on (4) reducing the risk of emergence of pandemic influenza; and (5) promoting the development and application of modern public health tools.

The gaps in knowledge can only be filled by appropriately targeted research. Based on this need, the World Health Organization (WHO) recently coordinated the development of a Global Public Health Research Agenda for Influenza. A regional research framework is needed to adequately address the priorities and the specific needs in of countries in SEAR.

This working paper presents the draft Regional Framework for a Public Health Research Agenda for Influenza. This draft regional framework is aligned with the Global Public Health Research Agenda for Influenza and incorporates recommendations from regional committees that are involved in setting research agendas and building Member State research capacity.

The following five issues need to be considered in the regional framework:

- (1) What are the priority streams and areas of focus for SEAR countries in influenza research?

- (2) What capacity or collaboration is needed to enable the implementation of the influenza research framework in SEAR countries?
- (3) What resources need to be harnessed to enable the implementation of the framework?
- (4) What health research system issues need to be addressed to enable the implementation of the framework?
- (5) How will the framework be implemented, monitored and evaluated?

These issues were discussed during the regional consultation that was held on 18-20 August 2010 in New Delhi, India.

After finalization and endorsement of the regional framework, a number of steps are recommended for its implementation. First, working groups will be formed in accordance with the research streams and regional priorities to build momentum for researchers to undertake research in influenza. Second, resources for influenza research will be identified and harnessed. Third, institutional strengthening requirements will be addressed to maximize the research opportunities and outputs of the Region.

In the short to medium-term, the framework implementation will necessitate strong knowledge management to spur and maintain research momentum. Knowledge management can initially be conducted by WHO and the different Working Groups. Progress in the regional framework should be evaluated within two years after endorsement and implementation to ensure that issues are addressed and activities or targets adjusted.

# 1. Background

## 1.1 Influenza

Influenza is a global public health challenge. Whether in its zoonotic, seasonal epidemic or pandemic forms, it can lead to mild to severe illness, and even death. Seasonal influenza is highly infectious and places the very young, the elderly and persons with chronic medical conditions at serious health risks from potential infection and complications. Seasonal influenza epidemics can affect up to 15% of the population, and extrapolation from well-established evidence in temperate countries suggests that seasonal influenza epidemics can result in an estimated 250000 to 500000 deaths worldwide each year.<sup>1</sup>

In recent years, influenza A viruses in birds have caused outbreaks in some countries of the South-East Asian Region (SEAR) of the World Health Organization (WHO). Avian influenza A H5N1 devastated the poultry industry.<sup>2</sup> In Thailand, 64 million birds were culled to curb disease spread between 2004 and 2006.<sup>3</sup> This amounted to a USD \$3 billion loss for the poultry industry in the first year alone. In Myanmar, 750000 bird deaths were documented between 2006 and 2008.<sup>4</sup> The economic losses associated with bird mortality and interventions in Myanmar were estimated at US\$ 1.2 million. In addition to the disease in birds, four countries in SEAR (Bangladesh, Indonesia, Myanmar and Thailand) also reported human cases of avian influenza A H5N1 infection.<sup>5</sup> Together, these countries reported 193 cases, of which 154 were fatal. The human

---

<sup>1</sup> WHO Public Health Research Agenda for Influenza, 2010 - Countries in temperate regions are defined as those north of the Tropic of Cancer or south of the Tropic of Capricorn.

<sup>2</sup> Webster, R.G., Guan, Y., Poon, L., Krauss, S., Webby, R., Govorkovai, E., Peiris, M. 2005. The spread of the H5N1 bird flu epidemic in Asia in 2004. *Arch Virol Suppl*, 117-129.

<sup>3</sup> See Poultry, HPAI and Livelihoods in Thailand – A Review. Accessed from: [www.hpai-research.net/docs/Working\\_papers/wp04\\_2008.pdf](http://www.hpai-research.net/docs/Working_papers/wp04_2008.pdf)

<sup>4</sup> See Poultry, HPAI and Livelihoods in Myanmar – A Review. Accessed from: [www.hpai-research.net/docs/Working\\_papers/wp8\\_2009.pdf](http://www.hpai-research.net/docs/Working_papers/wp8_2009.pdf)

<sup>5</sup> Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO as of 5 July 2010. Accessed from: [www.who.int/csr/disease/avian\\_influenza/country/cases\\_table\\_2010\\_07\\_05/en/index.html](http://www.who.int/csr/disease/avian_influenza/country/cases_table_2010_07_05/en/index.html)

cases constitute 39% of the global case count and 52% of the global death toll. The threat of the H5N1 virus continues, especially if it develops the capacity for person-to-person transmission, leading to the emergence of another influenza pandemic.

The world recently witnessed the emergence of another influenza A strain: pandemic (H1N1) 2009. Since its initial detection in Mexico and the United States in April 2009, the pandemic virus spread quickly throughout the world. Twenty days after its original detection in the Americas, the virus was detected in Thailand.<sup>6</sup> Within the next month, the virus had spread to most SEAR countries, and by July 2010, 1945 deaths had been reported in SEAR.<sup>7</sup> Although the impact of this virus is yet to be determined, it has caused at least 15000 laboratory-confirmed deaths globally in one year, mainly in young and middle-aged adults.<sup>8</sup>

Although exactly when and where another influenza pandemic strain will emerge is unknown, it is important to maintain vigilance. Insufficient knowledge in many areas has hampered capacity to prepare and respond to pandemic influenza as well as zoonotic and seasonal influenza epidemics. This gap in knowledge can only be filled by appropriately targeted research. Public health resources need to be utilized and research efforts harnessed to develop and implement strategies that best improve response to a pandemic and that minimize morbidity and mortality. For this, a public health research agenda on influenza is needed. Based on the recent development of a global influenza research agenda, a regional research framework is needed to adequately address the priorities and the specific needs of the Region and its Member States.

## **1.2 Research agenda for influenza**

Research is an important component of public health investment because it enables the discovery of effective health products and health-care services; provides evidence for public health decision-making; helps address system issues to improve quality, adaptability and sustainability; and most

---

<sup>6</sup> Global update on Pandemic (H1N1) 2009. Accessed from [www.who.int/csr/disease/swineflu/updates/en/index.html](http://www.who.int/csr/disease/swineflu/updates/en/index.html)

<sup>7</sup> Laboratory-confirmed cases of pandemic (H1N1) 2009 as officially reported to WHO by States Parties to the IHR (2005) as of 4 July 2010. Accessed from [www.who.int/csr/don/2010\\_07\\_30/en/index.html](http://www.who.int/csr/don/2010_07_30/en/index.html)

<sup>8</sup> WHO Public Health Research Agenda for Influenza, 2010

important, it helps address health problems leading to a healthier, more productive population.<sup>9</sup>

Over the last few years and through the emergence of avian influenza AH5N1, attention increased to the importance of influenza research. A number of WHO guidance documents have highlighted the importance of research to address priority issues and gaps in knowledge.<sup>10</sup> Several animal and other organizations have also developed research priorities for influenza.<sup>11,12</sup> This culminated in November 2009 when WHO held a global consultation that finalized a global influenza research agenda. The WHO Public Health Research Agenda for Influenza has finalized in February 2010, and is available on the WHO website.<sup>13</sup>

### **1.3 WHO Public Health Research Agenda for Influenza**

The goal of the WHO Public Health Research Agenda for Influenza is to enable the development of the evidence needed to strengthen public health action for responding to pandemic, zoonotic and seasonal influenza in a way that minimizes the impact of the disease. The stated objectives of the WHO Public Health Research Agenda for Influenza are:

- Provide a framework reflecting public health research priorities for pandemic, zoonotic and seasonal epidemic influenza;
- Identify specific research topics, reinforce and prioritize their importance in meeting public health needs over a medium to long-term period (approximately ten years);
- Maintain a focus on relatively less well-addressed areas such as operational research and research with applications in under resourced countries;

---

<sup>9</sup> Zachariah, R., Harries, A.D., Ishikawa, N., Rieder, H.L., Bissell, K., Laserson, K., Massaquoi, M., Van Herp, M., Reid, T. 2009. Operational research in low-income countries: what, why, and how? *Lancet Infect Dis*, 9: 711–17.

<sup>10</sup> See (a) Influenza research at the human and animal interface. Report of a WHO working group. Geneva, World Health Organization, 2006, or (b) Influenza research: EU funded projects 2001-2007. Brussels, European Commission, 2007.

<sup>11</sup> See FAO-OIE-WHO Joint technical consultation, Verona, Italy, 7-9 October 2008.

<sup>12</sup> Nicoll, A., 2006, Human H5N1 infections: so many cases--why so little knowledge? *Euro Surveill* 11, 74-75.

<sup>13</sup> See [www.who.int](http://www.who.int)

- Facilitate discussion, coordination and interaction amongst researchers, donors and public health professionals; and
- Highlight the need and benefits of a multidisciplinary approach to address knowledge gaps in public health related to influenza and its control.

The research agenda has five identified streams with 3-4 areas of focus under each stream. The five streams and the areas of focus can be seen in Box 1. The streams identify the key pieces of information required for furthering policy development for both pandemic and inter-pandemic periods and for both seasonal and zoonotic influenza. Addressing these research categories should provide good scientific knowledge and an essential foundation to further inform public health practice and policy development for influenza.

**Box 1:** Outline of the WHO Public Health Research Agenda for Influenza

Stream	Area of Focus
Stream 1: Reducing the risk of emergence of pandemic influenza	1.1 Factors associated with the emergence of influenza viruses with zoonotic or pandemic potential
	1.2 Factors for human infection at the human/animal interface
	1.3 Surveillance at the human/animal interface
	1.4 Preventive measures to reduce the risk of emergence of zoonotic and pandemic influenza viruses
Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza	2.1 Factors affecting person-to-person transmission
	2.2 Dynamics of virus spread at global and local levels
	2.3 Public health measures to limit transmission
Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza	3.1 Determining disease burden and social impact
	3.2 Improve immunogenicity, availability and delivery of vaccines
	3.3 Public health policies to reduce the impact of disease

Stream	Area of Focus
Stream 4: Optimizing the treatment of patients	4.1 Factors associated with pathogenesis and clinical severity
	4.2 Improve clinical management of patients
	4.3 Health care capacity and response
Stream 5: Promoting the development and application of modern public health tools	5.1 Modern tools for early detection & monitoring of disease
	5.2 Role of modeling in public health decision-making
	5.3 Modern tools for strategic communication

## 1.4 Research agenda in the South-East Asia Region

SEAR countries have long embraced the importance of research in public health. The Region established a WHO Advisory Committee on Health Research (ACHR), which held its first meeting in India in 1976. The main role of the ACHR is to advise the Organization on matters relating to research policies, strategies and programme.<sup>14</sup> Further, the WHO Regional Office for South-East Asia (SEARO) has a research programme under Health Systems Development (HSD) that aims to support and strengthen national health research systems.

Based on recommendations from the 30<sup>th</sup> Session of the ACHR in March 2007, a Regional Task Force for Research on Avian Influenza was convened in March 2008 in Indonesia. The Regional Task Force found that the implementation of effective and evidence-based public health interventions was impaired by an incomplete knowledge base. Gaps existed in surveillance, clinical management, the molecular characteristics of the virus and its potential to initiate human pandemic, sociobehavioral change, socioeconomic impact, the animal–human interface and vaccine development.

More recently, a Regional Workshop on Research Priorities in Communicable Diseases was held by SEARO's Department of

---

<sup>14</sup> WHO South-East Asia Advisory Committee on Health Research, SEA-ACHR-31, 2007

Communicable Diseases (March 2009).<sup>15</sup> This workshop recommended that Member States include appropriate research agendas in national health policies and programme; allocate appropriate research funding; establish mechanisms to enable interface between researchers and policy-makers to facilitate translation of research into policy; and build institutional capacity for the conduct of research in communicable diseases.

## **1.5 Consultation on Regional Framework for Public Health Research Agenda for Influenza**

SEARO organized a consultative Regional Meeting on Public Health Research Agenda for Influenza in South-East Asia on 18-20 August 2010 in New Delhi, India. This followed the Global Public Health Research Agenda for Influenza; the objective was to set regional influenza research priorities.

The document is aligned with the global WHO Public Health Research Agenda for Influenza and incorporates the recommendations from the ACHR and Regional Task Force for Research on Avian Influenza. This document also provides recommendations on the way forward for implementation of the research agenda in SEAR.

## **2. Influenza research globally**

Many fundamental influenza research questions on vaccine development, surveillance and clinical management have been and continue to be addressed by various national and global institutions. These have been critical in supporting the public health response to influenza. One recent example was during the course of Pandemic (H1N1) 2009, where research on clinical outcomes associated with antiviral administration was conducted.<sup>16</sup> Clinical studies showed that antivirals were especially effective for treating patients at increased risk of developing complications from H1N1. This translated into international guidance by WHO on the recommended utilization of antivirals in the context of the pandemic.

---

<sup>15</sup> South-East Asia regional workshop on research priorities in communicable diseases, 2009.

<sup>16</sup> See [www.who.int/csr/disease/swineflu/notes/briefing\\_20100610/en/index.html](http://www.who.int/csr/disease/swineflu/notes/briefing_20100610/en/index.html)

However, many questions that have important public health policy implications have proven difficult to study, especially limiting the spread and reducing the impact of influenza.<sup>17</sup> This includes research on non pharmaceutical interventions that may be critical for limited-resource settings.

A recent review by Forrest and Webster (2010) identified a number of research gaps.<sup>18</sup> These gaps include (i) an understanding of the molecular determinants of influenza virus and the host that permit efficient transmissibility and pandemic potential; (ii) prospective surveillance in apparently healthy swine; (iii) the molecular determinants of high pathogenicity in poultry, pigs and people; (iv) the genetic basis of host susceptibility; (v) antigenic variability; (vi) the use of vaccine to control influenza; (vii) the role of wild birds as the reservoir of highly pathogenic avian influenza; (viii) the problems with vaccines; (ix) seasonality; (x) co infections; and (xi) anti-influenza drug resistance.

As part of pandemic planning, a number of countries built research components into their preparedness. The guiding strategies underpinning national research agendas on influenza are important to illuminate. In the United States, the National Institute of Allergy and Infectious Diseases (NIAID) identified a number of principles to guide future influenza research.<sup>19</sup> These are:

- Promoting innovative multidisciplinary research to enable quick utilization of findings;
- Integrating seasonal and pandemic influenza activities, since an enhanced understanding of seasonal influenza will help public health activities for pandemic influenza;
- Balancing basic research with targeted activities to ensure that policy areas beyond the capacity of one research group are addressed;
- Maximizing application of research by asking questions with broad applicability that can be utilized for various influenza strains or for other infectious diseases;

---

<sup>17</sup> WHO Public Health Research Agenda for Influenza, 2010

<sup>18</sup> Forrest, H.L., Webster, R.G. 2010. Perspectives on influenza evolution and the role of research. *Anim Health Res Rev*, 11(1):3-18.

<sup>19</sup> Influenza research at NIAID, National Institutes of Health, USA.

- Enhancing coordination and collaboration between government, private industry, WHO and other health organizations to enable rapid progress.

New tools are quickly being integrated into influenza research. One example is disease modeling, where even though it is still evolving and the number of practitioners globally remains small, collaboration between researchers has been successful in producing important policy recommendations. One example is the collaboration between Thailand's Ministry of Health (MoH), Emory University and John Hopkins University that produced a seminal paper on containing an influenza pandemic at source.<sup>20</sup>

Lessons learnt from research on influenza globally include; the importance of collaboration between different disciplines, countries and stakeholders; a shift from "one bug-one drug" approach to more flexible and far-reaching research impact<sup>11</sup>; and the enhanced utilization of new research methods such as modeling or assessment of disease burden techniques.<sup>9</sup>

### **3. Influenza research in SEAR countries**

#### **3.1 Review of the literature**

To assess the current status of influenza research in SEAR countries, a review of the literature was undertaken. The literature review assessed the volume and nature of the research published by SEAR countries on influenza. The review enabled classification of the research into the streams and areas of focus established by the WHO Public Health Research Agenda for Influenza.

#### **3.2 Search strategy**

The literature review was conducted using PubMed. PubMed was chosen for the literature review as it comprises over 19 million citations for biomedical literature from MEDLINE and life science journals, and it

---

20 Longini, I.M., Nizam, A., Xu, S., Ungchusak, K., Hanshaoworakul, W., Cummings, D.A.T., Halloran, M.E. 2005. Containing Pandemic Influenza at the Source. *Science*, 1083-1087.

enabled the use of MESH terms which are useful to explore publications based on key designated words. PubMed was researched systematically using the keywords: influenza, <country name>. The inclusion criteria for the literature review were studies published in English between 1 January 2005 and 20 June 2010 by the 11 Member States in SEAR. The exclusion criteria for the literature review were studies focusing on other diseases, e.g. Haemophilus influenza type B (Hib); studies stating virus names that incorporated the countries of interest but did not involve research on that country; or outbreak news reports in scientific journals that provided information about disease activity but were not research publications. The inclusion and exclusion criteria used for the search strategy were set to address the objectives of the literature review to provide a general understanding of research undertaken in the region. The search was limited to publications in English based on the linguistic capacity of the evaluator.

The publications derived from the search were inspected, and those with irrelevant titles were removed. Once publications were deemed to have met the inclusion criteria, they were assessed and categorized based on the abstracts and in some cases the full article.

The literature review addressed the following questions:

- What was the focus of the publication: seasonal influenza, zoonotic influenza or pandemic influenza?
- Based on the WHO Research Agenda for Influenza, which area of focus and stream did the publication objective address?
- What year was the article published?
- Was the corresponding author from a national or international institution?
- Did the publication involve a number of countries?
- If the research involved a number of countries, what other countries were involved?

### **3.3 Results**

A total of 600 articles were identified through the search strategy. Of these, 239 (39.8%) were excluded from the literature review based on the exclusion criteria. From the remaining 361 articles retrieved, 22 were

general review articles that did not fit into one particular research stream (see Annex 1 for table with data). Fourteen (3.8%) articles were multi country research publications which involved one or more SEAR countries. These multi country research publications also involved non SEAR countries including China, Laos, Philippines, Singapore, Sweden and Vietnam.

Of the 361 publications, the majority were from Thailand (n=184, 51%), India (n=100, 27.7%) and Indonesia (n=31, 8.6%). A number of countries did not have any influenza research articles identified through this review strategy (Bhutan, DPR Korea, Maldives and Timor-Leste).

The majority of the publications in the Region were on zoonotic influenza (55.6%), followed by seasonal influenza (26.1%) and pandemic influenza (18.3%). As can be seen in Figure 1a, the majority of publications in the last five years on seasonal and zoonotic influenza came from Thailand (53.3% and 54%, respectively) and the majority of publications on pandemic influenza were from India (50%). Since the start of pandemic (H1N1) 2009, a similar publication pattern can be seen (Figure 1B).

Figure 1a: **Research publications on influenza by SEAR-country, 1 January 2005–20 June 2010**

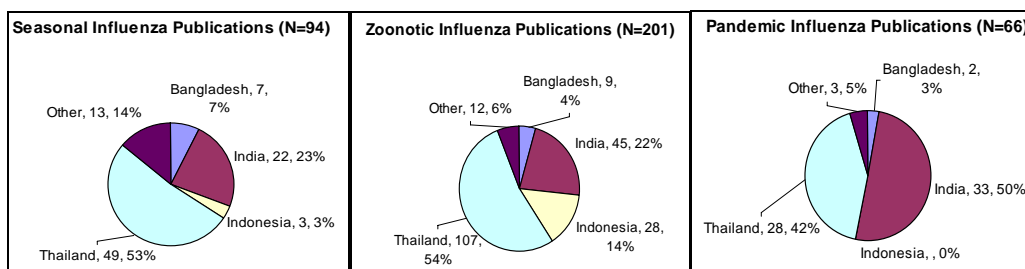
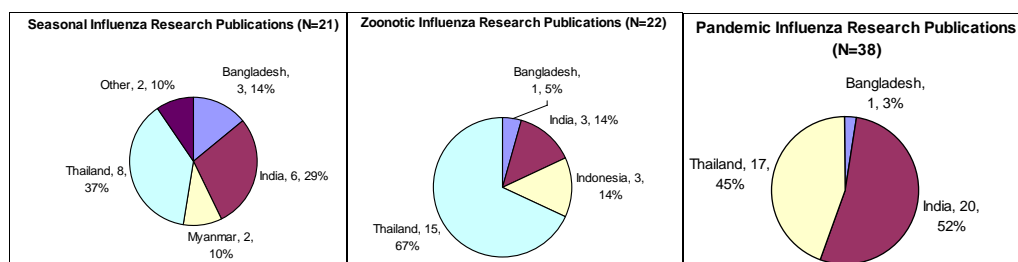


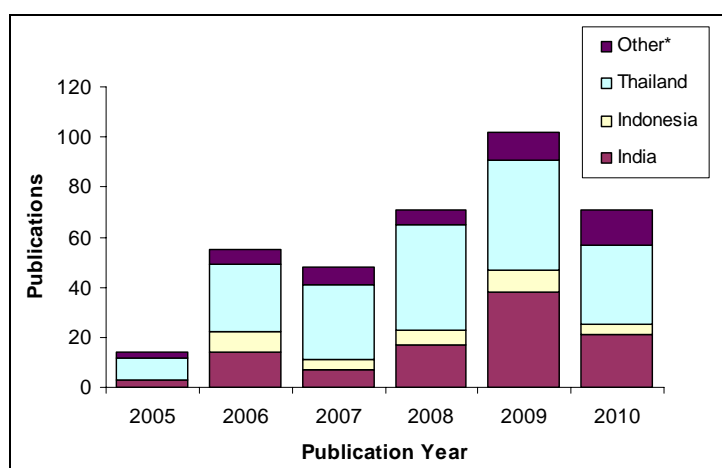
Figure 1b: **Research publications on influenza by SEAR-country, 1 Jun 2009 – 30 Jun 2010**



Zoonotic influenza dominated the influenza research agenda in a number of SEAR countries; it represented 58.1% of Thailand's influenza research (n=107), 45% of India's research (n=45), 90.3% of Indonesia's research (n=28) and half of Bangladesh's research (n=9). Most of Nepal's (n=6, 86%) and Myanmar's (n=3, 60%) publications were on seasonal influenza.

Figure 2 shows that the volume of research published yearly increased steadily over the last five years. A large increase in the number of publications was seen in 2009-2010 with the emergence of Pandemic (H1N1) 2009.

Figure 2: **SEAR countries publishing influenza research by year, 2005-2010**



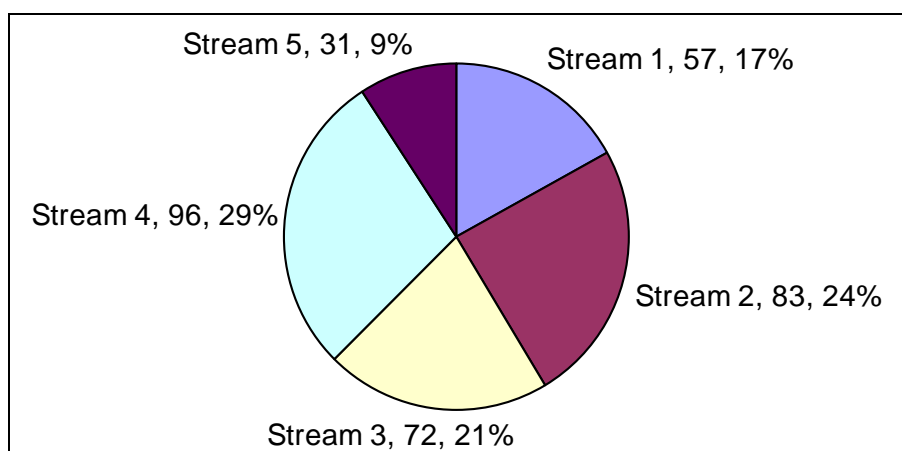
\*"Other" refers to Bangladesh, Myanmar, Nepal and Sri Lanka.

The majority of publications arising from SEAR countries had corresponding authors from national institutions (79.9%). However, there were large differences in this proportion based on the research country. For countries with more than 10 publications in the last five years, India had the highest proportion of corresponding authors from national institutes (97%), followed by Thailand (83.2%), Bangladesh (61%) and Indonesia (58.1%). For countries with fewer than ten publications in the last five years, Sri Lanka had all publications with corresponding authors from national institutions (n=2), Nepal had 42.9% (n=3) from national institutes, and all

of the Myanmar influenza research publications (n=5) listed corresponding authors from international institutions.

The majority (74%) of research articles published by SEAR-countries in the last five years fit into streams 2, 3 and 4 (Figure 3). These streams refer to research on limiting the spread of influenza (Stream 2), minimizing the impact of influenza (Stream 3) and optimizing treatment of patients (Stream 4). Only 17% of research in SEAR countries assessed factors associated with reducing the risk of pandemic influenza (Stream 1) and 9% looked at promoting the development and application of modern public health tools (Stream 5).

Figure 3: **Publication by stream, 2005-2010 (N=339)\***



\* Excludes 22 general reviews that could not be categorized in only one of the five streams

In Stream 1, research in all four areas of focus was undertaken in SEAR countries (Figure 4). This included research on preventing the emergence of a pandemic (n=20, 35%); many publications assessed animal intervention studies such as vaccination and biosecurity. The majority of Stream 1 research was conducted in Thailand, with 35 out of the 57 publications.

In Stream 2, the preponderance of publications was in only one area of focus: virus dynamics (n=60, 73%, Figure 4). Viruses from both animal and human infection were characterized and transmission patterns assessed. The majority of virus characterization studies were conducted in Thailand (n=23), India (n=20) and Indonesia (n=5). This emphasis on virus

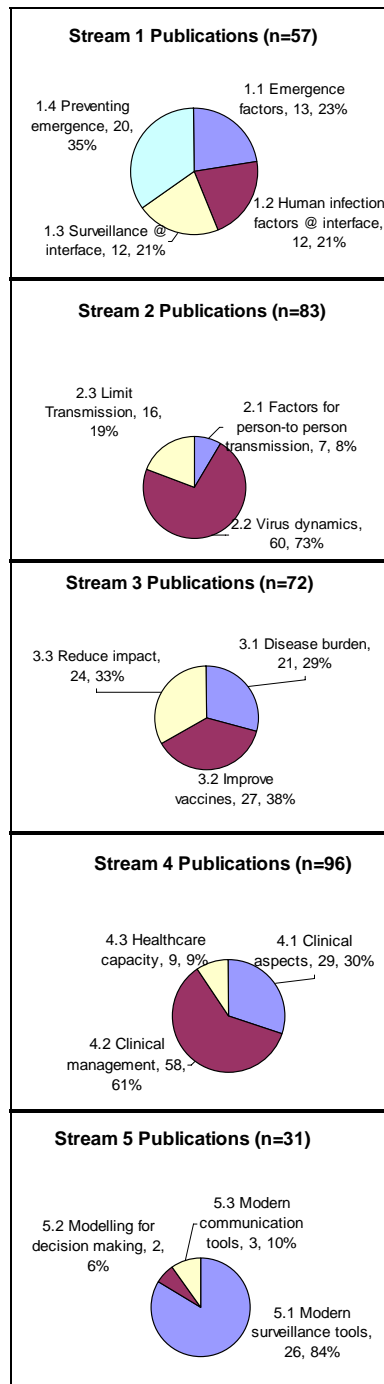
characterization probably reflects the need based on the avian influenza outbreaks in Indonesia and Thailand, as well as India's extensive laboratory capacity for virus sequencing. A few studies were conducted on issues relating to area of focus 2.1 (factors for person to person transmission), where environmental surface contamination, host factors and seasonality were assessed (n=7, 8%).

In Stream 3, research looked at all three areas of focus (Figure 4). Many studies focused on improving the delivery of vaccines, selecting and documenting candidate vaccine strains, using animal models in pre-clinical evaluation of new vaccines as well as assessing the safety and immunogenicity profiles (n=27, 38%). The majority of these studies were conducted in Thailand (n=17). Some studies assessed policies for reducing the impact of influenza (n=24, 33%) with emphasis on the impact of seasonal influenza vaccine, acceptability of vaccination and ethical conduct. Lastly, a number of disease burden studies considered the burden of influenza through influenza-like illness surveillance studies and social impact of influenza especially avian influenza in countries affected by the H5N1 virus (n=21, 29%). The majority of these studies were undertaken in Thailand (n=12).

For Stream 4, 61% (n= 58) of the publications were on improving clinical management of influenza including optimizing usage of antiviral treatments, assessing traditional herbal therapy formulations and developing diagnostic bed side tests for influenza. A number of publications also addressed area of focus 4.1; factors associated with pathogenesis and clinical severity, where hospital-based studies documented the clinical disease spectrum, risk factors for complications and prognostic markers (n=29, 30%).

Of all the five streams, Stream 5 had the least number of publications from SEAR countries (Figure 3). The majority of studies looked at the development and use of modern public health tools, assessed tools for the early detection and monitoring of influenza including health information systems, use of syndromic surveillance and laboratory-based systems (n=28, 84%, Figure 4). The majority of research in Stream 5 came from Thailand (21 out of the 31 publications).

Figure 4: **Publications by SEAR-countries by areas of focus in each Stream, 2005-2010**



### **3.4 Conclusions**

The literature review was undertaken to gain a general overview of the volume and nature of influenza research undertaken by SEAR countries over the past five years (2005-2010). The review highlighted that a lot of research has been undertaken across all five streams identified by the WHO Research Agenda, but that there was an imbalance in influenza research volume and capacity between Member states. The majority of the research focused on limiting the spread of influenza, minimizing the impact of influenza and optimizing treatment of patients. Over one-third (35%) of the research was conducted purely on two areas of focus: virus dynamics (n=60 publications) and clinical management (n=58 publications).

The research over the last five years focused on zoonotic influenza, and especially avian influenza AH5N1, which has affected a number of countries in the Region. The research focus may reflect the policy needs and disease priorities in the countries affected, but it can also reflect the health investment priorities within countries as well as from donors and other stakeholders. Even though the literature review did not examine the impact of research, there are clear examples where research led to public health policy. One example is from Indonesia, where a case series on data from human cases of avian influenza A H5N1 infection showed an association between early antiviral administration and recovery.<sup>21</sup> This led to the Ministry of Health's policy to instigate active surveillance at district level, where surveillance officers were mobilized to detect suspected human cases associated with poultry AH5N1 outbreaks to enable early antiviral administration.<sup>22</sup>

The research was primarily conducted by national research institutions. Collaboration between nations was also observed through the publication of a number of research studies that involved one or more SEAR country. This is a positive finding and reflects the flexibility in the research systems to collaborate and respond to a disease that knows no borders.

---

21 Kandun, I.N., Tresnaningsih, E., Purba, W.H., Lee, V., Samaan, G., Harun, S., Soni, E., Septiawati, C., Setiawati, T., Sariwati, E., Wandura, T. 2008. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. *Lancet* 372, 744-749.

22 See [www.searo.who.int/LinkFiles/Regional\\_Health\\_Forum\\_AVI\\_Indonesia.pdf](http://www.searo.who.int/LinkFiles/Regional_Health_Forum_AVI_Indonesia.pdf)

The literature review did not assess the quality of the research. However, such analyses would be useful at national level to determine if research studies undertaken within countries are valid and effectively provide answers to gaps in health policy decision-making.

The literature review methodology had limitations which likely underestimate the volume and nature of influenza research undertaken in SEAR countries. The search was conducted only for publications in the English language and in publications indexed by PubMed. This would imply that local or national research published in other languages or in different types of publication media would not be found through the search. This would include publications in journals not indexed by PubMed, especially socio-behavioral research which is more likely to be indexed by other databases. Further, the search strategy may have disadvantaged certain types of studies from being included in the analyses, such as local operational research which is relevant to a national audience for policy or decision-making. Another limitation is that the search terms focused on influenza, which may have excluded publications on modern communication or surveillance tools that have generic application and are not necessarily designed for influenza.

Even though other types of literature review methodologies are more systematic by exhaustively reviewing both published and unpublished work, these are much more intensive and generally focus on very specific literature review research questions. This was outside the objective and scope of the literature review for the purpose here.

#### **4. Public Health Research Agenda for Influenza: Regional priorities**

A global consultation was held to develop the WHO Public Health Research Agenda for Influenza in November 2009. The consultation brought together over 90 public health decision makers, academic and clinical researchers, donors and other key stakeholders from 35 countries. In the course of two days, breakout groups on the five research streams mapped what they considered the key research topics for public health needs during pandemic and inter-pandemic periods, and in relation to both seasonal and zoonotic influenza virus infections. The Research Agenda does not exhaustively list research questions under each stream, but rather provides a focused framework for key research needs. Since research

studies may address various aspects simultaneously, the different streams should not be considered mutually exclusive. Examples of the research gaps identified under each stream and area of focus can be seen in Box 2.

Implementing the global Research Agenda is contingent on consultation within WHO regions and individual countries to refine the strategies, set priorities and minimize duplication of efforts. Regional focus depends on country capacity, local issues and available resources.

For the SEA Region, the regional research agenda and the modalities for its implementation must address the needs of countries taking into account the differing levels of capacity for research and research management, differing emphasis placed on influenza as a public health priority and the differing population needs. Further, the regional agenda must take into account the general challenges facing Member States, highlighted through a variety of forums including the ACHR (March 2007) and the Regional Workshop on Research Priorities in Communicable Diseases (March 2009).

#### **4.1 Priority influenza research for SEAR countries**

As identified through the literature review, there are a number of gaps in influenza research undertaken by SEAR countries. There is high emphasis on a small number of research areas of focus and on avian influenza AH5N1. Only a few countries conducted influenza disease burden studies, which are necessary to help determine the magnitude of the problem and to establish adequate prioritization for influenza in the national public health agenda. Since public health resources available for research are limited, a priority-setting exercise was required. Even though prioritization of specific research questions should also be undertaken at country level according to local context, regional prioritization will help provide an overview about available capacity, opportunities for research collaboration and an avenue to determine where resources (such as technical assistance or external funding) can be harnessed to support the implementation of the research agenda.

Regional research priorities based on the global agenda were discussed and established during the regional consultative meeting held in New Delhi on 18-20 August 2010. The first step involved a priority-setting exercise where meeting participants ranked the importance and relevance

of the various research topics according to a standardized priority-setting method. The method selected for this exercise was adopted from the Council on Health Research for Development's (COHRED) Working Group on Priority Setting.<sup>23</sup> The COHRED method is a systematic approach that is characterized by inclusiveness, a participatory and transparent process, and the potential involvement of a broad range of stakeholders including researchers, government officials, inter- or non governmental agencies and donors. The underlying principles of the COHRED approach are to place country priorities first, work to ensure equity in health and to link research to action for development. The COHRED categories for research priority-setting are:

- (1) **Appropriateness:** should we do it?
- (2) **Relevance:** why should we do it?
- (3) **Chance of success:** can we do it?
- (4) **Impact of the research outcomes:** what do the stakeholders get out of it?

Each of the research topics listed under the 16 area of focus were assessed according to the four priority-setting categories. Scores were tallied and research topics ranked in terms of their research importance for SEAR countries.

After the formal priority-setting exercise, the participants discussed their individual priorities and provided suggestions in the plenary sessions about issues relevant on influenza research in the region. This included discussion about issues such as the use of traditional medicine and specific implementation research questions that were not highlighted in the global research agenda.

From the above processes, five to six priorities under each stream were identified as shown in the following sections.

---

<sup>23</sup> A Manual for Research Priority Setting using the ENHR Strategy. Council on Health Research for Development (COHRED). Document 2000.3, March 2000.

**Box 2: Examples of Research under each Stream and Area of Focus as per the WHO Public Health Research Agenda for Influenza**

Stream	Area of focus	Examples of research
Stream 1: Reducing the risk of emergence of pandemic influenza	1.1 Factors associated with the emergence of influenza viruses with zoonotic or pandemic potential	a) Virus and host factors (infectivity, transmissibility, pathogenicity) b) Environmental & animal husbandry factors
	1.2 Factors for human infection at the human–animal interface	a) Modes of disease transmission b) Human behavior & genetic factors
	1.3 Surveillance at the human–animal interface	a) Design joint surveillance activities b) Develop diagnostic tests for surveillance c) Develop mechanisms for reporting
	1.4 Preventive measures to reduce the risk of emergence of zoonotic and pandemic influenza viruses	a) Animal intervention studies (culling, vaccination, biosecurity) b) Strategies to reduce human risk (behaviour change, biosecurity) c) Assess impact of interventions
Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza	2.1 Factors affecting person-to-person transmission	a) Transmission types (droplet, airborne) b) Virus stability in environment c) Factors influencing infectivity (host factors such as age, antiviral use)
	2.2 Dynamics of virus spread at global and local levels	a) Implication of seasonality & geography b) Interaction influenza & other pathogens c) Impact of intervention type & timing (containment or border control)
	2.3 Public health measures to limit transmission	a) Effectiveness & feasibility of individual (hand hygiene, masks) & community (quarantine, reduction of gatherings) interventions

Stream	Area of focus	Examples of research
Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza	3.1 Determining disease burden and social impact	a) Assess disease incidence, severity, complications & risk groups b) Assess economic burden, social determinants of impact (e.g. disruption)
	3.2 Improve immunogenicity, availability & delivery of vaccines	a) New vaccines & formulations for delivery b) Optimize pre-clinical evaluation animal models and clinical trial methods
	3.3 Public health policies to reduce the impact of disease	a) Develop effective immunization policies & evaluate strategies to improve uptake
Stream 4: Optimizing the treatment of patients	4.1 Factors associated with pathogenesis and clinical severity	a) Virological factors (replication sites, viral load) & host responses in severity (e.g. genetic factors) b) Clinical spectrum & co infections
	4.2 Improve clinical management of patients	a) Point-of-care diagnostic tests, clinical markers & improve antiviral treatments b) Intensive care practices to reduce mortality
	4.3 Health-care capacity and response	a) Assess surge capacity needs, triage schemes, home care policies, protection of health workers, clinical data-sharing
Stream 5: Promoting the development and application of modern public health tools	5.1 Modern tools for early detection & monitoring of disease	a) Utilize technology for surveillance b) Mechanisms for global data sharing
	5.2 Role of modeling in public health decision making	a) Estimate key parameters for disease spread, measure effectiveness of policies
	5.3 Modern tools for strategic communication	a) Develop tools for communication with different populations & tools to gauge audience response

## **4.2 Stream 1: Reducing the risk of emergence of pandemic influenza**

The emergence of pandemic (H1N1) 2009 virus and the global spread of avian influenza AH5N1 have underscored the challenges in reducing the risks from influenza viruses with zoonotic and pandemic potential. Since zoonotic influenza has affected a number of countries in the SEA Region, the importance of coordination between public health and animal health agencies was considered vital for the purpose of influenza research. As highlighted in the global research agenda, reducing risks requires a better understanding of the underlying factors that contribute to the emergence of zoonotic and pandemic viruses and methods to assess what risks such viruses may pose to humans. Identification of effective control measures at the animal source and human behavioural modifications to reduce virus transmission at the human animal interface are also needed.

Based on the regional consultation and consideration of the above issues, the key research topic priorities identified were:

- (1) Develop diagnostic tests to support joint animal and human health surveillance systems.
- (2) Study the environmental and animal management/husbandry-specific factors associated with zoonotic and pandemic potential.
- (3) Investigate and develop animal intervention strategies (e.g. culling, vaccination, biosecurity) under different epidemiological and field conditions that can reduce the risk of zoonotic infection.
- (4) Investigate potential modes of transmission in human infection with animal viruses.
- (5) Conduct operational research to integrate animal and human health strategies for prevention.

### **4.3 Stream 2: Limiting the spread of pandemic, zoonotic and seasonal epidemic influenza**

Limiting human influenza transmission within local communities and institutions such as schools is difficult. Improvements in this area will require basic scientific and operational research to gain a better understanding of how influenza viruses are transmitted between people, the usefulness and feasibility of public health control measures at the individual and population levels, and an understanding of the dynamics of virus spread.

Through the regional consultation, the following research topics were identified as priorities for SEAR countries:

- (1) Study the transmission dynamics of influenza and the factors that influence infectivity in different settings and associated activities.
- (2) Examine the usage of surveillance data in assessing the needs and effectiveness of public health interventions in different situations, such as the identification of emerging of novel viruses; determining the time for initiation of public health interventions; selection of appropriate public health interventions; evaluation of effectiveness of interventions and guiding decision-making regarding cessation of public health interventions.
- (3) Conduct studies to understand the seasonality of influenza virus infection in different regions and its implication in the global spread of epidemic and pandemic influenza.
- (4) Examine the role of host factors such as age, pre-existing immunity, antiviral treatment and prophylaxis, and vaccination in modulating influenza transmission.
- (5) Investigate the relative importance of droplet, contact and airborne transmission in seasonal and pandemic influenza.

### **4.4 Stream 3: Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza**

Immunization against influenza is an essential public health intervention to control both seasonal epidemics and pandemic influenza. However, as

recognized by the global research agenda, many countries, particularly those that are underresourced, have not developed strategies to vaccinate their populations at risk for seasonal or pandemic influenza. This is related in part to insufficient local information on the burden of influenza disease and its social, economic and health determinants and impacts on the community. There also are marked differences between countries in terms of their respective capacities, priorities and resources to establish seasonal influenza vaccination policies and programmes, and to produce and distribute vaccine.

Based on the priority-setting exercise, the regional consultation identified the following key priorities:

- (1) Study the role of social science research such as its involvement in establishing social, ethical and legal standards in public health policy application; the public perception of influenza and its impact on societies, particularly in underresourced populations.
- (2) Determine best approaches for applying influenza disease burden data, coupled with cost-effectiveness analyses, to inform development or expansion of influenza control programme in the context of competing priorities.
- (3) Assess social determinants of health under different epidemiological settings (such as among the socially disadvantaged, indigenous populations etc.) and evaluation of the social impact (such as disruptions in commerce, health-care systems, public safety, social and political fabrics etc.) of influenza outbreaks and pandemics based on such determinants.
- (4) Evaluate the vaccine-preventable disease burden of influenza and the potential impact of immunization programme (e.g. vaccine demonstration projects).
- (5) Establish the economic burden of seasonal and pandemic influenza in conjunction with epidemiological studies.

Based on discussions, participants in the regional consultation also considered the following specific issues to be priorities for SEAR:

- Operational research into vaccine storage and delivery under different circumstances.

- Development of effective immunization policies using community-based input.
- To evaluate mechanisms to reduce bottlenecks in the production of vaccines and to improve the processes of rapid response, surge capacity, rapid deployment and tracking of vaccine usage.

#### **4.5 Stream 4: Optimizing the treatment of patients**

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

Based on discussions during the regional consultation and taking into account country capacities in case management, the following research priorities were identified for the Region:

- (1) Define the clinical spectrum and natural history of human disease, including risk factors (such as co-morbidities and demographic factors) and prognostic markers for severe disease and its complications.
- (2) Identify clinical markers and develop point-of-care tools for the prognosis and management of influenza disease.
- (3) Conduct studies to develop best practices that provide protection of health-care workers and other care givers in different health-care and resource settings.
- (4) Develop rapid, reliable, affordable point-of-care diagnostic tests for influenza virus.

In addition to the above topics that were identified in the global research agenda, the regional consultation identified other specific topics relevant to regional practice:

- Identify mechanisms to improve time-to-care since many patients delayed presentation until after one week post-onset of symptoms.

- Develop simple and inexpensive tools to assess oxygenation status.
- Develop modules to optimize patient care at community level.
- Conduct studies on the role of traditional medicine to support influenza patient care.

#### **4.6 Stream 5: Promoting the development and application of modern public health tools**

New public health tools need to be harnessed to help reduce the impact of seasonal epidemic and pandemic influenza in a globalized economy and a modernized world. Use of innovative communication channels, such as the Internet and mobile phone networks including text messaging, have the potential to facilitate outbreak investigation and rapid risk assessment and dissemination of accurate information. Mathematical modelling and risk communication are cross-cutting areas with potential applicability across all streams of research. Since this stream focuses on cross-cutting issues, it is important to consider findings on these topics arising from research on other diseases such as tuberculosis or HIV/AIDS and their disease control programmes. Further it is critical to assess the acceptability of new tools such as modelling among decision-makers to increase their utilization in influencing policy.

The regional consultation identified the following priorities based on the global research agenda:

- (1) Examine the timeliness and quality of data needs required for early detection of disease from local to district, regional, national and global levels for the respective stakeholders.
- (2) Conduct studies to identify, appraise, exploit and adapt modern technologies for early detection of epidemic and pandemic influenza as well as their application in surveillance at the human animal interface.
- (3) Conduct studies to improve model accuracy and realism, and incorporation of emergent interdisciplinary advances.
- (4) Conduct studies to review international evidence and experience on health and health crisis communication from relevant disciplines, such as behavioural and social sciences,

media studies, marketing, to gather and organize knowledge, as well as to stimulate new studies in areas where gaps have been identified to support evidence-based practice in strategic communication.

- (5) Identify, develop and evaluate communication tools and methods that can rapidly and monitor knowledge, attitudes, beliefs and practices in different population groups, to guide communication efforts.

## **5. The way forward**

In view of the regional research priorities based on the global research agenda adapted to the regional situation, the way forward involves a number of steps. SEAR countries may need to undertake similar national priority-setting exercises to further refine the key influenza research priorities and to advocate for the national scientific community to endorse the influenza research agenda as a public health priority.

Resources for implementation of the research agenda need to be harnessed at local, regional and global level. This can be achieved through advocacy by WHO and networks of influenza public health workers in-country. Even though the technical and financial resources and mechanisms required will vary according to the country, the type and topic of research, successful implementation and collaboration will depend on the availability of appropriate knowledge generation capacities including research method know-how, technologies (such as laboratory capacity), and capacity for research design and execution. These issues need to be assessed at country level and their availability secured before embarking on specific research activities to ensure validity of findings and maximum likelihood of success.

In the short-to medium-term, the framework implementation will necessitate strong knowledge management to spur and maintain research momentum. Knowledge management can initially be conducted by WHO to ensure that research activities are not duplicated, that research is designed in accordance with international standards and ethical practice, that the research outputs can influence policy, and lastly, that some research addresses the needs of specific target groups such as the poor and vulnerable. WHO can also play a role to enhance coordination between researchers in different countries and to identify mentors for researchers

embarking on novel research activities, or to provide standard research protocols aligned with best practice.

With WHO assuming the role of catalyst for stimulating framework implementation, institutional networking and collaboration will be encouraged so that the outputs of research are of maximum benefit to countries. Ultimately, the implementation of the influenza research agenda in the Region must be geared to enable better preparedness and response to influenza considering limitations in existing health systems and competing national health priorities.

## Annex 1

# Influenza research by SEAR-country and by Area of Focus, 2005-2010

Stream	Area of Focus	Country*											Total	
		BGD	BHT	DPRK	IND	INO	MLD	MYR	NPL	SLK	THA	TML		Multi
1. Reduce risk of emergence of PI	1.1 Emergence factors	1	0	0	3	1	0	0	0	0	8	0	0	13
	1.2 Human infection factors @ interface	3	0	0	0	2	0	0	0	0	7	0	0	12
	1.3 Surveillance @ interface	1	0	0	0	1	0	0	0	0	10	0	0	12
	1.4 Emergence preventive measures	0	0	0	4	4	0	0	0	0	10	0	2	20
Stream 1 Total		5	0	0	7	8	0	0	0	0	35	0	2	57
2. Limit spread of PI, ZI & SI#	2.1 Factors for H2H	1	0	0	1	1	0	1	1	0	2	0	0	7
	2.2 Virus dynamics	2	0	0	20	5	0	3	3	0	23	0	4	60
	2.3 Limit Transmission	3	0	0	6	0	0	0	0	0	7	0	0	16
Stream 2 Total		6	0	0	27	6	0	4	4	0	32	0	4	83
3. Minimize impact of PI, ZI & SI	3.1 Disease burden	0	0	0	6	3	0	0	0	0	12	0	0	21
	3.2 Improve vaccines	2	0	0	5	0	0	0	0	0	17	0	3	27
	3.3 Reduce impact	1	0	0	13	4	0	1	0	1	1	0	3	24
Stream 3 Total		3	0	0	24	7	0	1	0	1	30	0	6	72
4. Optimize treatment of patients	4.1 Clinical factors	1	0	0	4	5	0	0	1	0	18	0	0	29
	4.2 Clinical management	0	0	0	17	2	0	0	1	0	37	0	1	58
	4.3 Healthcare capacity	0	0	0	3	1	0	0	0	0	5	0	0	9
Stream 4 Total		1	0	0	24	8	0	0	2	0	60	0	1	96
5. Promote public health tools	5.1 Modern surveillance tools	1	0	0	1	2	0	0	0	0	21	0	1	26
	5.2 Modeling	0	0	0	1	0	0	0	1	0	0	0	0	2
	5.3 Modern communication tools	1	0	0	1	0	0	0	0	0	1	0	0	3
Stream 5 Total		2	0	0	3	2	0	0	1	0	22	0	1	31
Reviews	Reviews	1	0	0	15	0	0	0	0	1	5	0	0	22
Subtotal with Reviews		18	0	0	100	31	0	5	7	2	184	0	14	361
Excluded publications	Irrelevant/Excluded	6	0	0	15	103	13	0	5	2	61	0	34	239
Total with Excluded		24	0	0	115	134	13	5	12	4	245	0	48	600

\* BGD=Bangladesh, BHT=Bhutan, DPRK= DPR Korea, IND=India, INO=Indonesia, MLD=Maldives. MYR=Myanmar, NPL=Nepal, SLK=Sri Lanka, THA=Thailand, TML=Timor Leste & Multi=Multi-country.

# PI=Pandemic Influenza, ZI=Zoonotic Influenza & SI=Seasonal Influenza





**World Health  
Organization**

**Regional Office for South-East Asia**

World Health House  
Indraprastha Estate,  
Mahatma Gandhi Marg,  
New Delhi-110002, India



SEA-CD-220