Strengthening the WHO Global Influenza Surveillance Network (GISN)

REPORT OF THE 3rd MEETING WITH NATIONAL INFLUENZA CENTRES (NICs) HELD IN HAMMAMET, TUNISIA, 30 NOVEMBER TO 3 DECEMBER 2010

World Health Organization
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Executive summary

- For nearly 60 years the WHO Global Influenza Surveillance Network (GISN) has worked to reduce the threat to public health posed by influenza. Today, thanks to the coordinated, dedicated efforts and expertise of laboratories worldwide, the network is able to continuously monitor the evolution, distribution and global spread of influenza viruses.

- The timely data and other information generated by the GISN, along with its comprehensive range of guidance, recommendations and other public health products and resources, are the foundations of global influenza preparedness and response activities. For example, through its virological surveillance activities, the GISN continuously assesses the ever-evolving epidemic and pandemic risks posed by influenza viruses. These activities form the basis of the twice yearly recommendations made by WHO on the composition of seasonal influenza vaccines, and allow for the development and production of vaccines to protect against seasonal and pandemic influenza using viruses and reagents provided by the GISN.

- In recent years, concerted efforts in many WHO Member States have led to significant increases in trained personnel and equipped laboratories, with a resulting expansion both in geographical surveillance coverage and in the capacities of influenza laboratories. These efforts have been supported through the provision of training workshops, equipment and reagents by a broad range of national and international agencies. In addition, initiatives such as the WHO Shipment Fund Project (SFP) have facilitated the timely and efficient sharing of clinical specimens and/or virus isolates.

- Building and strengthening partnerships remain central to improving the quality, timeliness and efficiency of GISN activities. Strengthening collaboration and coordination with stakeholders outside the network, such as international agencies and veterinary, research and commercial partners, will help the GISN to build sustainable capacity, develop synergies, mutually leverage funding and other resources, and avoid needless duplication of efforts.

- Although the 2009 H1N1 pandemic presented a number of significant challenges, the GISN proved to be efficient and robust by mounting a rapid and comprehensive response. The pandemic also provided a valuable opportunity to gain experience, learn important lessons and assess the effectiveness of pandemic planning. Increased awareness of the threat posed by influenza and of the resources needed to address it also led to renewed capacity-building and other benefits for influenza laboratories in all WHO regions.

- Despite these recent gains, major challenges remain in maintaining momentum and in sustaining newly expanded and enhanced capacities. Key activity areas include further increasing laboratory capacity and maintaining quality standards; strengthening global influenza surveillance and reporting; improving virus and information sharing; strengthening pandemic preparedness; and improving GISN communication and coordination activities.

- In all settings, national political will and ministry of health commitment remain key requirements for sustainable influenza surveillance and response activities in the long term. Advocacy activities highlighting the importance of the GISN in the public health response to influenza will continue to be needed.
Preface

The WHO Global Influenza Surveillance Network (GISN) is a well-established global public health collaboration that enjoys broad recognition and support from countries around the world. The strength of the GISN lies in its ability to continuously monitor the evolution, global distribution and spread of human influenza viruses, while being uniquely placed to detect and respond to the emergence of viruses with the potential to cause a human influenza pandemic. GISN activities form the basis of the twice yearly WHO recommendations on the composition of influenza vaccines, which for several decades have been a core component of the work of the WHO Global Influenza Programme (GIP).

At this important point in the history of influenza – immediately in the aftermath of the 2009 H1N1 pandemic – efforts to maintain and strengthen the functioning of the GISN have a particular and heightened relevance. To this end, regular meetings with National Influenza Centres (NICs), other GISN members and partner agencies outside the GISN are vital for reviewing the status and capacity of the Network in order to identify gaps and weaknesses, and to determine what actions need to be taken. As part of ongoing efforts in this area, WHO convened this 3rd global meeting with NICs to:

- provide a forum for sharing the lessons learnt in responding to the 2009 H1N1 pandemic;
- review GISN capacity and functioning at global, regional and national levels to identify both its strengths and weaknesses in relation to seasonal influenza epidemics and during the 2009 H1N1 pandemic; and
- identify the priority actions needed in the short term to address current gaps and to improve the quality, timeliness and efficiency of GISN activities.

Meeting participants were drawn from a broad and diverse range of institutes and sectors including: NICs, WHO Collaborating Centres (WHOCCs) on influenza, Essential Regulatory Laboratories (ERLs), H5 Reference Laboratories and WHO staff from country offices, regional offices and headquarters; as well as representatives from a number of GISN external partners, including international agencies, veterinary organizations and vaccine manufacturers.

WHO wishes to express its thanks to the WHO Mediterranean Centre for Health Risk Reduction and to colleagues in the Ministry of Health, Tunisia and the NIC, Tunisia for their assistance and support during the organizing and convening of this meeting.
1. Overview

GISN activities directly address ongoing public health needs

Even before the 2009 H1N1 pandemic, perceptions of influenza and its related public health needs were changing. The established view of a mild seasonal disease confined to older age groups in temperate countries was being replaced by a far more complex picture in which influenza was increasingly recognized as a serious and ongoing public health issue worldwide. In addition, the re-emergence of human cases of highly pathogenic avian influenza A(H5N1) in 2003 led to far greater awareness of the threat posed by pandemic influenza, and heightened the expectations of populations that preparedness and response measures would be taken, effective vaccines and other interventions made available, and relevant and accurate information shared.

Through the GISN, WHO coordinates the efforts and expertise of influenza laboratories worldwide to help countries address the threat posed by influenza. At the national level, NICs provide the Ministry of Health with up-to-date laboratory-based influenza surveillance data and other information needed to make evidence-based decisions on policies and actions. Together with epidemiological data, NIC virological data allow for the comprehensive national surveillance of influenza. NICs are the primary resource for monitoring influenza virus activity in countries, and play a vital role in informing national authorities of current GISN recommendations and guidance. In many countries, the NIC also supports and coordinates sub-national laboratory capacity-building.

NICs contribute to global influenza surveillance and response efforts through the timely reporting of virological surveillance data to the WHO FluNet\(^1\) platform, and by the prompt forwarding of clinical specimens and/or virus isolates to WHOCCs and other reference laboratories. The viruses received (or recovered from clinical specimens) are propagated by the receiving WHOCC or other reference laboratory for detailed antigenic and genetic characterization. This enables the refinement of diagnostic reagents, and supports subsequent key public health activities such as the selection and development of candidate vaccine viruses and required standardization reagents. Each year WHOCCs provide NICs with updated reagents for the detection and identification of influenza viruses, and support other NIC capacity-building and quality-assurance activities, for example by providing training.

Information sent to FluNet is available in real-time from the WHO web site, with public access to selected nationally aggregated data. The virological data collected through FluNet are analysed jointly with epidemiological data – for example, as reported to the recently launched WHO FluID\(^2\) platform. The results are then used as the basis of the publically available WHO reports\(^3\) on the global spread and intensity of influenza. FluNet data are a key element in developing the twice yearly WHO recommendations on the composition of seasonal influenza vaccines.

WHO updates and makes available a range of influenza surveillance, preparedness and response guidance, recommendations and other public health resources; undertakes a range of national, regional and global capacity-building activities (including the provision of training

\(^1\) [www.who.int/flunet](http://www.who.int/flunet)
Experiences and lessons learnt from the 2009 H1N1 pandemic

Although the 2009 H1N1 pandemic presented a number of significant challenges, the GISN was able to mount an efficient, rapid and comprehensive response. Highlights included the prompt detection, identification and characterization of the pandemic virus and the rapid subsequent development of candidate vaccine viruses. The timely availability of diagnostic protocols and large-scale provision of kits by GISN WHOCCs allowed for an accelerated programme of influenza testing by NICs and other laboratories.

During the pandemic, laboratory capacity increased at both national and sub-national level. In some countries, the decentralization of diagnostic testing to sub-national laboratories was an important step in meeting the need for clinical diagnosis while enabling the NIC to focus on influenza surveillance. In some regions, formal WHO recognition of NICs proved to be very useful in strengthening their credibility.

Since its inception in 2005, the WHO SFP has proved to be a practical mechanism for enhancing the efficiency of shipping clinical specimens and/or virus isolates. During the pandemic, a total of 316 shipments from 81 countries were sent with the support of the WHO SFP to WHOCCs and H5 Reference Laboratories for confirmatory diagnosis, and detailed antigenic and genetic characterization. The WHO SFP also provided essential laboratory equipment, supplies and reagents for a number of countries.

The exchanging of information and updated reagents within the GISN was also rapid and sustained. From the very beginning of the pandemic, regular WHO teleconferences were held between WHOCCs, ERLs, NICs and a range of partner organizations. GISN surveillance and communication activities formed the foundation for the development and implementation of a range of public health interventions, including the prompt provision of an effective vaccine.

Identified weaknesses in GISN activities included difficulties in ensuring the broad and comprehensive representativeness of virus samples, with associated gaps in reporting from some countries. As a result, the global data may be biased and thus suboptimal. This highlights the importance of sustained national support to NICs from ministries of health, and in some cases the need to authorize NICs to share viruses and surveillance data in accordance with the obligations contained in internationally binding agreements such as the International Health Regulations (IHR, 2005).

An almost overwhelming workload and volume of meetings, teleconferences and other events was reported by many laboratories and other stakeholders centrally placed in the response. Conversely, for others there was a lack of up-to-date quality information. One weakness identified in GISN communication activities was the delayed issuing of definitive WHO recommendations on the appropriate biosafety level for handling and isolating pandemic A(H1N1) 2009 viruses. These recommendations were perceived as not keeping pace with the evolving situation, resulting in the maintenance of unnecessarily high containment levels thus limiting both virus isolation and sharing. In addition, as the volume of useful information and

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4 www.who.int/entity/csr/disease/avian_influenza/guidelines/eqa_project/en/index.html
5 www.who.int/entity/csr/disease/influenza/FAQInfluenzaLogistics.pdf
6 www.who.int/ihr/en/
guidance resources increased on the WHO web site, it became difficult to locate specific
documents. In a number of cases, the translation of key documents into other languages was
not considered to be timely.

**Importance of partnerships**

Building and strengthening partnerships is central to improving the quality, timeliness and
efficiency of GISP activities at all levels. Strengthening collaboration and coordination among
key stakeholders including other international agencies and public health sectors, and among
veterinary, research and commercial partners will help to build sustainable capacity, develop
synergies, mutually leverage funding and other resources, and avoid the needless and costly
duplication of efforts. As financial constraints increase in the current global economic climate,
these will become crucial objectives.

The range of current and potential GISP partnerships is very broad with large variations in the
degree of current implementation at national, regional and global levels. Collaborative efforts
continue to be needed in:

- policy development;
- laboratory and other capacity-building;
- diagnostic technologies and reagent development;
- clinical management;
- the conducting of both basic and operational research;
- the surveillance of animal influenza; and
- vaccine development and production.

Efforts in all these areas should reflect national priorities and be integrated into existing
national public health strategies.

Examples of initiatives for building and sustaining national capacity in low-resource settings
include national bilateral cooperative agreements and associated research agreements with the
Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In
many countries these have been important catalysts for capacity-building and research, and
have led to substantial gains in national influenza surveillance capabilities. In collaboration
with WHO, CDC is aiming to expand the use of bilateral cooperative agreements to additional
countries; implement sustainability cooperative agreements to support the gains already made
with increasing ministry of health ownership; and support enhanced data analysis to determine
the burden of diseases and their local impact. In collaboration with WHO and other partners,
targeted studies of the impact of influenza vaccine use in various settings will be conducted to
help determine the feasibility of vaccine use in such settings and to guide vaccine policy
development.

In some countries, NICs are hosted within the International Network of Pasteur Institutes
(RIIP). In addition, the United States Agency for International Development (USAID), in
collaboration with WHO and other partners, is supporting the establishment and strengthening
of laboratory capacity in some resource-scarce countries. The United States National Institute
of Allergy and Infectious Diseases (NIAID) Centers of Excellence for Influenza Research and
Surveillance (CEIRS) Network is working to expand the capability to conduct both basic and
applied influenza research and to build the evidence base for improved influenza prevention,
diagnosis and treatment approaches.
As understanding of influenza at the animal-human interface improves, it seems increasingly likely that coordinated and complementary national, regional and global surveillance of animal and human influenza will bring considerable mutual benefits. The GISN therefore maintains regular channels of communication with networks for animal influenza surveillance, such as the OIE–FAO Network of Expertise on Animal Influenza (OFFLU), undertakes joint activities, and promotes the reciprocal attendance of meetings.

Technical cooperation between the GISN and vaccine manufacturer organizations such as the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) continues to be an essential part of ensuring the timely supply of seasonal vaccines. The 2009 H1N1 pandemic highlighted the importance of proactive communication and collaboration mechanisms in enabling a timely industry response to arising events. Other partnerships with the commercial sector are instrumental in supporting laboratory functioning. For example, significant service and equipment-maintenance benefits could be realized through the use of centralized commercial agreements between suppliers and WHO headquarters and regional offices.

In the area of pandemic vaccine development, implementation of the 2006 WHO Global Action Plan to reduce the anticipated gap between potential vaccine supply and demand during an influenza pandemic continues to receive support from the United States Health and Human Services (HHS) Biomedical Advanced Research and Development Authority (BARDA). Since 2006, BARDA has worked with international partners including WHO to assist countries in building and enhancing a broad range of capacities, particularly in vaccine development, in order to prepare for and respond to novel influenza viruses with pandemic potential.

Although a range of technical and commercial partners have been identified, and in some cases collaborations established, there remains a need to optimize current partnerships and networking activities and to identify new potential partners and synergies. The key principles of partnership development include the need to continually define the essential requirements of the GISN and to match associated gaps and priority needs with the complementary goals and expertise of external agencies and other organizations. To ensure partnership success in capacity-building efforts, activities must lead to national independence and long-term sustainability. Lessons may also be learnt in some countries from other surveillance networks successfully integrated into national strategies, such as those for polio. During an influenza pandemic there will be a need for supplementary response partners in sectors such as logistics (transportation, storage and distribution), security and emergency management. Advanced preparations for working in partnership in all these areas should be part of national pandemic preparedness planning and associated table-top and other role-coordination exercises.

2. GISN capacity and strategic development

At global level

Following the 2nd global meeting with NICs in Barcelona in December 2008, the WHO GISN has continued to expand with the addition of 16 newly recognized NICs, one WHOCC and one H5 Reference Laboratory. As of December 2010, the GISN consisted of 136 NICs in 106 countries, six WHOCCs, 11 H5 Reference Laboratories and four Essential Regulatory Laboratories (ERLs). As the number of countries with an NIC has increased, the percentage of
the world’s population covered by the GISN has also increased. However, coverage remains partial with significant regional variation. In the WHO African Region, for example, it is estimated that around 57% of the population live in areas with no NIC-based influenza surveillance capacity in place.

Preliminary results from the WHO Global NIC Survey 2010 completed by 104 laboratories indicate that laboratory capacity for the virological surveillance of influenza has been enhanced worldwide. An increasing number of NICs now report playing an active role in seasonal specimen collection and expanded use of sub-national laboratory networks, a clear shift to molecular techniques for influenza testing (particularly the use of real-time RT-PCR), an increasing use of standardized case definitions, and the use of a broad range of selection criteria for forwarding specimens to WHOCCs and other laboratories. In addition, NICs increasingly report direct involvement in the surveillance of influenza-like illness (ILI) and/or acute respiratory infection (ARI), the proactive surveillance of severe ARI (SARI), and the surveillance and diagnosis of other respiratory diseases.

The survey also indicated that the proportion of NICs performing cell-culture virus isolation has decreased, even though the absolute number of NICs using this technique has increased. In addition, the proportion of laboratories reporting the capacity to isolate viruses in embryonated eggs fell globally. Almost all responding NICs reported shipping clinical specimens and/or virus isolates to a WHOCC, with a subset of NICs also reporting the forwarding of H5/H7/H9 samples to a WHOCC or H5 Reference Laboratory.

Data collected by WHO through a 2010 questionnaire designed to assess NIC capacity to monitor antiviral susceptibility and perform genome sequencing for seasonal and pandemic influenza viruses indicate that just under half of 91 responding laboratories perform antiviral susceptibility testing. However, there is wide regional variation ranging from 12% in the WHO Eastern Mediterranean Region to 83% in the WHO Western Pacific Region. Notably, only 13% of laboratories reporting this capacity also indicated the use of a quality-control programme. Almost all laboratories that do not conduct antiviral susceptibility testing submit virus isolates for such testing to other laboratories – usually a WHOCC. Viral gene sequencing capacity was reported by around half of all responding laboratories with a further 10% having access to external facilities. Laboratories performing gene sequencing use a broad range of techniques with about 80% submitting sequence data to a public and/or private database. Almost all laboratories not currently monitoring antiviral susceptibility and/or lacking gene-sequencing capabilities reported these to be priority objectives requiring equipment procurement and training.

Self-reported levels of pandemic preparedness in the WHO Global NIC Survey 2010 are high with almost all laboratories reporting the existence of a national pandemic preparedness plan incorporating a laboratory-response component. In addition, national surveillance of influenza in animals was reported by almost all laboratories, and between 2007 and 2010 the number of laboratories reporting BSL-3 capability (n = 42) almost doubled.

At regional level

Prior to the re-emergence of human cases of highly pathogenic avian influenza A(H5N1) in 2003, very few laboratories in the WHO African Region were undertaking virological surveillance of seasonal influenza and, despite improvements, the burden of influenza in the region remains relatively poorly documented. Today, influenza surveillance falls under one of the six strategic directions which guide the work of the WHO Regional Office for Africa.
close collaboration with partner organizations, impressive progress has been made in influenza laboratory capacity-building, with essential equipment, supplies and reagents having been procured to support resource-poor countries in the region.

As of November 2010, the Africa Influenza Laboratory Network coordinated by the WHO Regional Office for Africa was composed of 29 influenza laboratories in 24 countries including 12 NICs in 11 countries. A categorization system is used to map the distribution of capacity – ranging from Category-5 facilities which do not have influenza laboratory capacity or access to PCR diagnostic technologies to Category-1 facilities which possess the full range of technologies and which act as regional hubs of the GISN. At present, eight countries in the region have a Category-1 laboratory. Almost all 29 laboratories of the Africa Influenza Laboratory Network share weekly data with WHO, while 21 laboratories in 19 countries participated in the WHO EQAP in 2010.

Between 2005 and December 2010, the number of NICs in the WHO Region of the Americas increased from 23 to 28 in 22 countries with the designation of five new NICs in Central America. Following equipment and reagent purchases coordinated by the WHO Regional Office for the Americas and supported by training missions, PCR diagnostic capacity became almost universally available in the region at national level. Such capacity was significantly boosted as a result of the 2009 H1N1 pandemic. A corresponding increase occurred in the number of NICs participating in the WHO EQAP (from four in 2007 to 25 in 2010) with all laboratories achieving results greater than 80%. A primary focus of the activities of the WHO Regional Office for the Americas remains the strengthening of preparedness and capacity-building at sub-national and local levels in order to decentralize clinical diagnostic capability, enhance surge capacity and ensure that NICs function as national reference laboratories.

Although the WHO South-East Asia Region comprises only 6% of the world’s land area, it is home to a quarter of the world’s population. There are currently 10 NICs in eight countries, one regional influenza reference laboratory, one H5 Reference Laboratory and two national diagnostic laboratories. A number of countries in the region are currently strengthening their sub-national laboratory networks. In view of the threat posed by avian influenza A(H5N1), which has become endemic in some parts of the region, focused efforts to build regional capacity for laboratory diagnosis, antiviral susceptibility monitoring and influenza vaccine production are already under way.

Influenza surveillance in the WHO European Region is based upon the collation and analysis of epidemiological and virological data provided by clinical and laboratory networks. The latter network consists mainly of 51 NICs in the European Region – which also has one WHOCC and two H5 Reference Laboratories. Currently, national influenza laboratories in 10 Member States perform influenza surveillance but are not recognized by WHO as an NIC. In addition to supporting the introduction and enhancement of sentinel surveillance systems in these countries, the WHO Regional Office for Europe is supporting the capacity-building required in these laboratories for NIC recognition. NICs and national influenza laboratories in almost all WHO Member States in the European Region participate in regional reporting through the EuroFlu platform, with automatic uploading of data to the global WHO FluNet – and increasingly the WHO FluID – reporting platforms to avoid the need for multiple data submission by laboratories. The WHO Regional Office for Europe has modified the EuroFlu platform to include the collection of data on SARI, as well as data on the pandemic A(H1N1)

7 The NICs of EU/EEA Member States provide data through the EU network EISN: www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/index.aspx
2009 virus. NICs in European Union (EU) and European Economic Area (EEA) Member States form the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) which is coordinated by the European Centre for Disease Prevention and Control (ECDC) in Stockholm, Sweden. The CNRL has its own capacity-building programmes for contributing towards strengthened global influenza surveillance. These programmes are coordinated in partnership with the WHO Regional Office for Europe. Many NICs in the European Region have excellent capacities and some provide support to other laboratories through training, missions and information sharing. During the 2009 H1N1 pandemic, European NICs detected over 157 000 cases and laboratories gained much experience, particularly those that had only recently put in place the use of real-time RT-PCR testing. Evaluations of laboratory and other responses to the pandemic have been conducted by the WHO Regional Office for Europe and by a number of countries.

Influenza surveillance is also a high priority for the WHO Regional Office for the Eastern Mediterranean and for Member States of the region. However, although national influenza surveillance is conducted in many countries, only 12 countries in the Eastern Mediterranean Region have an NIC and very little is known about the circulation of influenza viruses in the national populations. In addition, 11 of the 22 countries, areas or territories in the Eastern Mediterranean Region have experienced outbreaks of avian influenza, with four countries reporting cases of human infection. In order to address this situation and strengthen surveillance, a trilateral agreement was established with the Naval Medical Research Unit Number 3 (NAMRU-3), which is an H5 Reference Laboratory and functions as a regional reference laboratory with technical expertise in influenza surveillance, virus isolation, serotyping and molecular characterization. Through the continuing provision of training, supplies, laboratory services and other support NAMRU-3 helps to ensure the efficient functioning of NICs in the region.

Influenza surveillance in the WHO Western Pacific Region is integrated into the Asia Pacific Strategy for Emerging Diseases (APSED). First developed in 2005, a new updated strategy (APSED 2010) has now been adopted which includes a focus on building regional surveillance and other capacities. One key objective is to move away from the simple forwarding of viruses and towards enhanced local laboratory surveillance and response capabilities to allow for a more-comprehensive understanding of the burden and impact of influenza – especially in developing countries of the region. The region has 21 NICs in 15 countries and three WHOCCs. Of the 21 NICs, 19 participated in the WHO EQAP (Panel 8) with 18 scoring 100%. All NICs in the region have real-time RT-PCR capacity and 20 have viral isolation capacity, with the remaining NIC expected to acquire this ability shortly. In the past 22 years, 76% of the influenza viruses selected for influenza vaccine development have been provided by countries in this region.

At national level

During the 2009 H1N1 pandemic, the development and use of national diagnostic algorithms was supported in a number of countries by the donation or provision of real-time RT-PCR equipment and reagents. This enabled the effective monitoring of virus circulation, especially given the greatly increased sensitivity of real-time RT-PCR detection compared to earlier technologies such as the direct fluorescence antibody (DFA) test. Such activities resulted in a shift towards real-time RT-PCR testing, the ability to diagnose infection with other respiratory viruses, and the establishment of gene-sequencing and antiviral susceptibility monitoring activities.
National influenza surveillance has also been significantly strengthened in recent years through the expansion of sentinel surveillance activities and improvements in the virological surveillance capacities of sub-national laboratory networks. Such trends can be seen as part of national efforts to enhance core NIC surveillance capacity by decentralizing the molecular diagnosis and reporting of influenza infection to sub-national networks. In some countries, this meant that for the first time there was daily monitoring of circulating influenza viruses associated with ILI/ARI, SARI, and with outbreaks and fatal cases. Analysis and notification of laboratory surveillance results were strengthened as was the integration of clinical, epidemiological and virological data.

However, in many countries there remains a need for the development of syndromic surveillance to supplement virological surveillance to better understand the patterns of influenza, especially in tropical zones. There is also a need to further develop sentinel SARI surveillance to support the surveillance of ILI/ARI in order to determine the true burden of influenza in many countries. The 2009 H1N1 pandemic highlighted that many countries lacked accurate baseline data on the burden of respiratory diseases (especially severe diseases) needed to place the pandemic in context.

Antiviral susceptibility monitoring is already undertaken in a number of countries, and during the 2009 H1N1 pandemic further improvements were made as the screening of known mutations at public health laboratories was simplified, and communication channels and collaboration between national and sub-national facilities were enhanced. However, antiviral susceptibility monitoring capacity at national level is still lacking in many parts of the world.

In all settings, national political will and ministry of health commitment remain key requirements of sustainable surveillance and response activities in the long term. Advocacy activities highlighting the importance of influenza therefore continue to be needed. Initiatives to build sustainable capacity through an appropriate mixture of country-specific, regional and global activities will help to strengthen the ability of countries to monitor and respond to the threat of influenza, as well as improve national influenza preparedness as part of meeting the requirements of the IHR (2005).

Challenges in building and sustaining capacity

Despite all the recent gains in GISN capacity reported at global, regional and national levels, specific recurring challenges remain in sustaining and further strengthening GISN activities. These include:

- a lack of political leadership and support in some settings for NIC capacity-building, or significant challenges in maintaining current political will;
- the continuing need to further strengthen global influenza virological surveillance;
- the need to further increase the capacities and geographical coverage of NICs and other influenza laboratories in almost all regions of the world, and to ensure the regular and timely shipping of clinical specimens and/or virus isolates to WHOCCs and other laboratories;
- high turnover of laboratory staff, often related to funding issues, resulting in a continual need to train staff;
- the need to procure equipment, supplies and reagents, and to certify and maintain equipment such as biosafety cabinets and PCR machines;
• inadequate virological, epidemiological and clinical surveillance of influenza, and lack of systematic coordination both within and between these sectors;
• logistical constraints in shipping clinical specimens and virus isolates, in particular where flight routes are indirect or where additional national procedures are added to IATA shipping requirements;
• the need for regional reference laboratories to support capacity-building activities in some regions;
• unclear reporting channels in some settings, for example where the official chain of reporting does not include the NIC or where reporting responsibilities are not clearly defined;
• the need for further collaboration with veterinary and other animal-sector organizations and lack of joint studies at the animal-human influenza interface; and
• the need to improve the accessibility of WHO documentation, including through the timely translation of key documents into other languages, and to strengthen GISN communication activities.

Broader challenges include the repeatedly missed opportunities to put in place national long-term plans for disease prevention and control following major disease outbreaks, and to establish prompt and coordinated response mechanisms. In the face of competing demands for resources by other health programmes, many new-found influenza-related public health capabilities will need to be built, strengthened and made sustainable, for example by incorporating the surveillance of other respiratory viruses. In a time of severe global financial constraints and “influenza fatigue” following a pandemic that was less severe than expected, effective strategies are now needed to sustain activities, overcome challenges and consolidate the improvements made.

3. Current approaches to strengthening the GISN

To improve the quality, timeliness and efficiency of GISN activities, efforts are now needed to capitalize upon and sustain the significant gains made in many parts of the world during the response to the 2009 H1N1 pandemic. Shortly before the onset of the pandemic a series of actions was proposed at the 2nd global meeting with NICs held in 2008 in Barcelona. A number of actions were followed up and implemented during the pandemic and specific improvements made. However, the pandemic also revealed a number of ongoing weaknesses in key GISN activity areas. Following working-group and plenary discussions, the following issues were highlighted and corresponding action points proposed (section 4). To avoid undermining the effectiveness of the GISN, the setting out of issues and proposed action points is intended to be both sufficiently ambitious and yet realistic. In all settings, laboratories will have to perform within their allocated resources and budgets.

**Highlighting the importance of the GISN and raising the profile of NICs**

Almost all the NICs, WHOCCs and other laboratories upon which the GISN is built are national entities requiring sustained political, financial and logistical support by governments. Such support is a primary necessity for maintaining and enhancing the capacity and functioning of the GISN. Decision-making bodies should therefore be provided with a clear explanation of what public health benefits can be expected from the GISN and what support is needed to achieve its goals. Politicians need to be continually reminded that both seasonal and pandemic influenza pose serious public health and economic threats, requiring constant
monitoring, preparation and response efforts. At the global level, one efficient way of getting this message across would be through the issuing of high-level statements on influenza by WHO and others at international meetings such as the annual World Health Assembly.

At national level, fuller recognition and committed support for the work of NICs and other laboratories by the ministry of health and other government departments would bring significant benefits. In line with activities already under way in the WHO European Region, an annual letter of recognition of NIC status sent from WHO regional offices or headquarters to each NIC and copied to their respective ministry of health could help NICs to secure continued recognition and sustained funding. The issuing of such a letter of recognition could be based upon a standard checklist of NIC core activities. The critical reliance of the GISN on the activities of NICs, WHOCCs and other laboratories during the 2009 H1N1 pandemic, and in responding to the threat of both seasonal influenza epidemics and possible future pandemics, should be highlighted more broadly to support advocacy efforts with governments and other authorities. Obtaining support from the pharmaceutical or diagnostic industry may also be feasible in some settings, but sensitivities surrounding the involvement of commercial interests – and the legislative and other rules governing this – will vary considerably from country to country.

**Increasing laboratory capacity and maintaining quality standards**

As NICs and other influenza laboratories work to build up advanced capacities such as antiviral susceptibility monitoring and gene sequencing, the requirement for skilled, well-trained staff and for coordinated quality assurance increases. For example, the interpretation of functional assays for measuring antiviral susceptibility is complicated and requires sufficient expertise and funding. As more antiviral drugs are licensed, the number and complexity of antiviral-susceptibility assays are likely to increase.

In countries with low-level resources, simultaneously maintaining high standards in all activity areas would be difficult, with potential adverse effects on the quality and efficiency of the core activities outlined in the WHO Terms of Reference (TORs) for NICs. In particular, the proper maintenance of the additional laboratory equipment and the staffing required could be financially and logistically problematic for some NICs leading to procedures such as egg- or cell-culture isolation of influenza viruses being dropped. The feasibility of appropriate equipment maintenance in countries with limited resources must therefore be addressed, for example through the negotiation of centralized maintenance contracts covering several years.

There are also concerns that the increasing use of PCR-based molecular testing methods by NICs is displacing established virus-isolation and characterization techniques. Such trends may increase the demand on WHOCCs to conduct virus isolation, potentially undermining both the timeliness and efficiency of detailed virus characterization and other WHOCC activities. This situation will be exacerbated if a very clear distinction is not maintained between “unsubtypable” viruses which WHOCCs prioritize for further characterization and “unsubtyped” viruses known to be influenza type A but for which no attempt at subtyping has been made by the originating laboratory. Strengthened efforts are needed to share and update primers and to provide guidance on the proper use and limitations of molecular assays and on the shipping of “representative” clinical specimens and virus isolates. Improved guidance on conducting PCR testing and on the use of WHO PCR kits will also help to standardize results across different laboratories.

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8 [www.who.int/entity/csr/disease/influenza/TORNICs.pdf](http://www.who.int/entity/csr/disease/influenza/TORNICs.pdf)
The provision of reference reagents, kits and protocols, along with appropriate analytical services, training courses and secondment opportunities, help to improve laboratory capacity and maintain standards. Such activities are regularly undertaken by WHO, WHOCCs and a range of partner agencies and other organizations. At present, standard reference reagents and kits for the detection and characterization of influenza viruses, and for the development and validation of diagnostic tests, are made available by a small number of major resource initiatives such as the CDC Influenza Reagent Resource (CDC-IRR). This approach is based upon the centralized provision of standard reagents and kits to all GISN laboratories and greatly aids the harmonization and comparability of testing in different laboratories, and the maintaining of quality standards. However, these initiatives are dependent upon political will and upon success in advocating the importance of influenza as a global public health threat. Competing demands coupled with stagnating or slow economic growth may limit the funding of such resources and alternative approaches should be considered.

Regular training in the use of both established and emerging technologies, and in data management, will help to keep the knowledge and skills of laboratory staff up to date and reduce the impact of personnel turnover. In addition to participation in organized training courses, innovative approaches such as appropriate online training resources for selected topics could increase the availability of training and reduce costs. Efforts to maintain the standards of laboratory testing and virus-isolation activities include external quality assessment initiatives such as the WHO EQAP and the annual meetings of the PCR Working Group. Other harmonization initiatives include the forthcoming WHO Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza.

In addition to laboratory capacity for the direct identification of viruses from clinical specimens and virus cultures, the ability to detect influenza infection using serological methods should also be maintained in suitably equipped NICs. This will allow for the conducting of national serological surveys and provide diagnostic back-up capacity.

**Strengthening global influenza surveillance and reporting**

**Decentralization of activities**

The efforts now being made in many countries to protect and enhance core NIC surveillance capacity by decentralizing the molecular diagnosis and reporting of influenza infection to sub-national networks are beneficial and should continue. In countries where there is a well-functioning sub-national network, the primary laboratory diagnosis of seasonal influenza infection is not a core NIC activity. Suitable national strategies and systems should instead be in place for patient diagnosis and treatment. In other settings, rolling out capabilities to sub-national laboratories should be carefully implemented to ensure that appropriate quality standards are met and sustained, and that testing outcomes are reported to NICs for the purpose of national, regional and global surveillance and reporting. Efforts should also be made to ensure that the forwarding of influenza-positive specimens to the NIC is adequate, timely and efficient.

**Recognizing differences in NIC capacities**

While extensive testing and characterization may be possible in some NICs, in other settings the priority will be the prompt and efficient forwarding of selected clinical specimens and/or virus isolates to WHOCCs or other reference laboratories. Despite differing widely in their
range of capabilities and available resources, the notion of “graded” NICs is considered to be potentially detrimental to the goodwill and collaborative nature that underlies the GISN. In all settings, algorithms and other guidance on virus sampling, testing and prioritization – and on virus isolation, characterization and forwarding – are needed if NICs are to avoid becoming overburdened and their important public health functions and outputs undermined.

**Monitoring antiviral drug resistance**

The early detection of emerging antiviral resistance is an essential element in the developing, refining and updating of national policies on the use of antivirals as part of both seasonal and pandemic influenza preparedness and response activities. Although national circumstances will vary, some capacity for monitoring antiviral susceptibility is required in all WHO regions to ensure comprehensive virological surveillance, and to avoid overloading the capacity of WHOCCs. At the national level, monitoring antiviral susceptibility and conducting gene sequencing can be viewed either as national public health activities inherent to influenza surveillance or as clinical or research issues for well-funded NICs and WHOCCs. In either case, unrealistic demands must not be placed upon countries lacking sufficient laboratory capacity and capabilities.

**Towards comprehensive national surveillance**

In many settings there is a need to strengthen the sentinel surveillance of ILI/ARI and SARI, and to systematically integrate the data produced with the results of NIC virological surveillance. In particular, a lack of epidemiological data undermines the development of good clinical management practices for the prevention and effective treatment of influenza. Although standards and mechanisms for sharing virological data have existed for decades there are a number of challenges in reporting epidemiological data. Overcoming these challenges will require the establishing of integrated surveillance expertise and systems, or the strengthening of existing national and regional systems.

As the 2003 SARS epidemic clearly demonstrated, respiratory viruses other than influenza pose a serious global health threat requiring a rapid response. Expanding the scope of the GISN beyond influenza to include the capacity to rapidly detect and respond to other respiratory viruses could further enhance its public health value. Careful consideration must however be given to the limits of current laboratory capacity. The expertise and participation of NICs are vital in building and implementing well-functioning national systems for the comprehensive surveillance of respiratory diseases.

**Collaboration with agencies working in the animal sector**

Despite recent improvements in the exchange of viruses, reagents, and virological and epidemiological information, collaboration between the GISN and the veterinary and animal influenza surveillance sector remains irregular. A number of joint technical initiatives with the OIE–FAO Network of Expertise on Animal Influenza (OFFLU) have been conducted including OFFLU contributions to the WHO H5/H9 vaccine virus selection process, and reciprocal participation in major meetings. However there remains considerable scope for improved cooperation and collaboration in areas such as the tracking of virus mutations and associated risk assessment, harmonization of nomenclature decisions (particularly where these can have adverse public health and/or commercial repercussions), improved development of both human and animal vaccines, and the conducting of joint serological studies and other research into zoonotic influenza infection.
Efficiency of reporting mechanisms

Regular and timely reporting to the WHO FluNet and other reporting platforms is an essential element of global influenza virological surveillance, and of subsequent public health decisions such as the twice yearly WHO recommendations on seasonal influenza vaccine composition. In some WHO regions, established regional reporting mechanisms other than FluNet (such as EuroFlu) have been introduced and used. To avoid potential confusion, the need for double data entry and possible delays in the global sharing of data, efforts are being made in both WHO headquarters and regional offices to ensure that timely laboratory data are available in all relevant databases at both regional and global levels.

The efficiency of GISN reporting activities may also be improved if NICs were to evaluate, and if necessary revise, their reporting strategies. During the influenza season, weekly reporting appears to be appropriate but during other periods less-frequent reporting may be adequate. Such adjustments would not however apply to any unusual findings whenever they occur during the year, and such findings should be reported immediately in accordance with the IHR (2005) and with the WHO TORs for NICs.

In November 2010 a new WHO FluNet home page was launched with additional facilities for downloading and viewing data, such as real-time charts of influenza virus activity by country or regions. Further development and enhancement of the WHO FluNet platform is ongoing.

Improving virus and information sharing

Significant obstacles – including several beyond the scope of GISN activities – remain in ensuring the regularity and timeliness of representative virus sharing. However, many previous logistical difficulties in shipping specimens from influenza laboratories have been successfully addressed in all regions as a result of the WHO SFP. In 2011 – after six years of implementation – a review of the performance of the SFP is planned with major stakeholders.

In general, the shipment of seasonal viruses is not problematic except in a number of countries where specific national requirements can cause significant delays. For the shipment of highly pathogenic A(H5N1) viruses, the stringency of national regulations varies widely. Whereas some countries can ship such viruses to WHOCCs and WHO H5 Reference Laboratories in around 10 days, others may require up to a month or even longer. In some countries there are also ethical and other requirements when collecting and shipping original A(H5N1) clinical specimens.

In terms of the timing and frequency of shipments, WHO recommends shipping seasonal virus samples to a WHOCC at least one month prior to the twice yearly WHO vaccine composition meetings, and to aim to send four shipments a year. Additionally, all samples obtained in certain specified contexts (for example, unusual clusters of severe disease or deaths caused by suspected influenza) must be shipped immediately to WHOCCs for further investigation. To a large extent, ensuring the timeliness of shipments is the responsibility of the NIC. With the increasing use of diagnostic PCR technology, there is a need for updated WHO guidance on the selection and shipping of representative clinical specimens and/or virus isolates to WHOCCs.

NICs that participated in the WHO Global NIC Survey 2010 rated the content, clarity and usefulness of WHOCC feedback reports on forwarded clinical specimens and/or virus isolates
as either excellent or good. There are issues however with the comprehensiveness and
timeliness of feedback to NICs with significant variations in content and format depending
upon individual WHOCCs. In addition, the frequency of WHOCC reports does not always
accord with the number of shipments made to the WHOCC by individual laboratories. Other
potential areas for improvement include shortening the current report turnaround time of 1–3
months. Efforts must be made, however, to ensure that any additional demands placed upon
WHOCCs can be efficiently met without detrimental effects on the timely performance of core
GISN activities.

The range of GISN information-sharing needs is broadening. In addition to formal reporting
mechanisms such as the IHR (2005) and the WHO FluNet for virological data reporting, there
is a need for the prompt and coordinated exchange of other types of information. To promote
such exchange, a password-protected GISN Information Centre hosted on the web-based
collaborative EZcollab platform has been active since 2007, with currently over 220 registered
users. Key functions include the sharing of documents, announcements of new publications
and upcoming events, and free message posting and exchanges in dedicated discussion areas.

**Strengthening pandemic preparedness**

The development and refinement of laboratory preparedness plans in accordance with national
pandemic preparedness plans remain essential. Such plans should set out mechanisms for
mounting a rapid response and for scaling-up laboratory throughput. During the 2009 H1N1
pandemic, many NICs and other laboratories had little or no opportunity to provide advice on
the prioritizing of diagnostic activities in hospitals and clinics. Laboratory preparedness
planning must therefore address the prioritization of national-level sample testing as part of a
feasible overall strategy covering aspects such as the specimen-testing strategy of sub-national
laboratories and specimen-transport logistics. Communication channels must be maintained
between national authorities and the GISN, and in some NICs there will also be a need for
public communications capacity, for example to deal with queries from clinicians, hospitals
and the media.

Potential improvements within the GISN include streamlining, better promoting and making
available the range of WHO pandemic preparedness and response guidance. Resources
currently undergoing development include guidance on the roles of NICs during different
pandemic periods, and a practical operational framework for NICs during a pandemic. Pending
revision of the WHO pandemic phase definitions, these guidance documents will be revised
and published.

**Improving GISN communication and coordination activities**

Existing communication channels between WHO, NICs and WHOCCs are considered to work
well overall. However, notification of important meetings and other communications have on
some occasions failed to reach individual NICs. There is also a sense that NIC feedback and
suggestions are either not always received or not always responded to.

NIC communication activities with the NICs of neighbouring countries could also usefully be
intensified, while improved communication and coordination with regional influenza
laboratories is also likely to bring significant benefits. WHO teleconferences with WHOCCs,
ERLs, NICs and GISN partner organizations during the 2009 H1N1 pandemic were highly
successful in helping to coordinate activities both within the GISN and with external partners.
The efficiency of GISN activities could also be improved through strengthened coordination. For example, improved coordination between various bodies will help to prevent the unnecessary overloading of NICs when responding to multiple questionnaires, surveys and other information requests. In addition, a lack of coordination within WHO or between WHO, the United States CDC, FAO and other agencies in organizing meetings, workshops and training courses has led to timetable clashes or congestion, resulting in some NICs being unable to participate in important events.

4. Proposed action points

Highlighting the importance of the GISN and raising the profile of NICs

- WHO to continue its high-level advocacy activities at global and regional levels, and with individual Member States, highlighting the importance of the GISN in monitoring and responding to the threat of both seasonal and pandemic influenza.

- WHO, with support from an NIC working group and other parties, to complete the revision of the document currently titled *Role of National Influenza Centres (NICs) in monitoring and responding to the threat of human influenza* – pending revision of WHO pandemic guidance. If required, the WHO TORs for NICs should also be revised in order to more clearly emphasize the core activities required for NIC recognition – pending the progress of the ongoing Open-Ended Working Group of Member States on Pandemic Influenza Preparedness (OEWG/PIP): Sharing of Influenza Viruses and Access to Vaccines and Other Benefits.9

- WHO to consider issuing annual or biennial letters of recognition to NICs based upon an agreed checklist and copied to respective ministries of health reaffirming the central role of the NIC in national and global influenza surveillance and response activities. This process has already started in the WHO European Region and has received positive feedback.

- NIC and other laboratory representatives to establish contact with national decision-makers to bring to their attention the full range of services the laboratory provides throughout the year, and how these help to produce the vital information needed to guide far-reaching political decisions, particularly during an influenza pandemic.

Increasing laboratory capacity and maintaining quality standards

- WHO to finalize the collation, validation and analysis of the WHO Global NIC Survey 2010 to help inform the further development of influenza virological surveillance at national, regional and global levels.

- WHO to continue working with a range of international agencies and other partners to further the process of building sustainable regional and national laboratory surveillance capacity.

- NICs – in collaboration with their national partners and ministries of health – to evaluate their specific requirements for the surveillance of influenza and other respiratory viruses,

9 [http://apps.who.int/gb/pip/e/E_Pip_oewg.html](http://apps.who.int/gb/pip/e/E_Pip_oewg.html)
and to determine their ability to sustain the use of advanced laboratory techniques beyond the core requirements of the WHO TORs for NICs.

- NICs – particularly those either lacking expertise in basic requirements such as virus isolation or sufficiently well resourced to sustainably acquire advanced capabilities such as gene sequencing and antiviral susceptibility monitoring – are encouraged to participate in the relevant training activities organized by WHO and other agencies.

- Well-resourced and well-functioning NICs to consider, according to available resources, developing innovative approaches to support other NICs (particularly in resource-poor settings).

- NICs to continue participating in external quality assessment initiatives such as the WHO EQAP to improve and maintain laboratory diagnostic quality standards.

- WHO to consider ways of better coordinating laboratory quality-assurance activities to avoid duplication and synchronize efforts. Initiatives already under way in some regions to incorporate the quality assurance of virus isolation and antiviral susceptibility monitoring should be continued.

- WHO, through the PCR Working Group, to continue the harmonization of PCR-based testing techniques in different laboratories, including through the improved sharing of testing protocols disseminated as part of GISP information-sharing activities.

- WHO to finalize, publish and disseminate the *WHO Manual for the Laboratory Diagnosis and Virological Surveillance of Influenza*.

### Strengthening global influenza surveillance and reporting

- WHO to continue to seek inputs from NICs, WHOCCs and other GISP laboratories in the development and revision of influenza virological surveillance guidance, and to ensure that GISP members have access to the broad range of guidance available through the WHO web site and other information-sharing resources.

- Collaboration between national laboratory, epidemiological and clinical sectors could where feasible be usefully strengthened in countries where coordination is currently weak. As the primary national resource on influenza virology, NICs – with ministry of health support – should be involved in efforts to strengthen such collaboration and to promote mechanisms for integrated surveillance.

- WHO to continue to promote participation in the FluNet and FluID reporting platforms either directly or via regional platforms such as EuroFlu, and to further develop user-friendly interfaces for data collection, analyses and reports.

- WHO and veterinary organizations such as OFFLU to maintain ongoing dialogue based upon their mutual needs and interests. Efforts to establish more formal collaborative mechanisms and to share materials and information to be continued as part of ensuring that activities are complementary.

### Improving virus and information sharing

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• NICs to work with their national authorities to ensure that national legislation and regulations covering the collection, shipment and use of clinical specimens are met, while allowing for the timely forwarding of clinical specimens and virus isolates to WHOCCs for characterization. NICs should ensure that such forwarding is both regular and timely, including in relation to the twice yearly WHO vaccine composition meetings.

• WHO to continue training NIC personnel in international shipping requirements and procedures, with the re-certification of individuals made possible through online courses.

• WHO to continue to raise – with regional office support – awareness of the SFP and its procedures. This could include the updating of WHO guidance on the selection and shipping of clinical specimens and/or virus isolates. Where possible, NICs should consider securing annual shipping permits or utilizing other streamlined national mechanisms to avoid procedural delays.

• WHOCCs to consider standardizing the format and content of reports on the detailed analysis of viruses forwarded by NICs, and to train or otherwise assist NIC staff in interpreting the full range of results. WHOCCs to continue to promptly report any unusual findings to the originating NIC and to provide appropriate guidance. When required, the use of telephone, SMS alerts or other accelerated communication channels should be considered.

• GISON members to consider using the posting facility of the GISON Information Centre on the WHO EZcollab platform to informally share experiences in real-time, publish regular protocol updates, and disseminate other information of interest within the GISON community.

• WHO to consider making further improvements to its web site and other information-sharing tools to facilitate the easy location of the extensive guidelines, reports and other archived materials available – for example by improving the naming, organization and searchability of GISON documentation and other information resources.

**Strengthening pandemic preparedness**

• NICs with the assistance of WHO regional offices and headquarters to continue highlighting the need for sustained government funding for pandemic influenza preparedness, and to increase awareness that such preparedness can only be achieved through support for continual seasonal influenza surveillance and response activities.

• WHO to continue to seek inputs from NICs, WHOCCs and other GISON laboratories in further developing its guidance on contingency planning and other preparedness activities.

• NICs to continue to strengthen their pandemic contingency planning in accordance with the recently revised *Pandemic contingency planning checklist for National Influenza Centres (NICs) and other national influenza laboratories.*

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• WHO to review likely evolving GISN information needs during a pandemic, and to maintain timely, efficient and well-coordinated information-sharing platforms and tools capable of meeting such needs.

**Improving GISN communication and coordination activities**

• WHO to review current GISN communication mechanisms to identify potential improvements in light of the results of the WHO Global NIC Survey 2010.

• WHO to announce upcoming WHO-coordinated GISN events, meetings and training courses as early as possible to allow for the planning of attendance and the securing of funding where required from NIC budgets.

• WHO – in coordination with its relevant partners – to make efforts to minimize timetable clashes, and where possible to harmonize WHO and partner-organization meetings, training courses and other events. One potential solution would be the development of a harmonized calendar of events.
Annex: List of participants
(Alphabetically by country)

Vilma Savy, Instituto Nacional de Enfermedades Infecciosas, Buenos Aires, Argentina
Jorge Augusto Camara, Influenza and Respiratory Virus Laboratory, Cordoba, Argentina
Ian Barr, WHO Collaborating Centre for Reference and Research on Influenza, Victoria, Australia
Wyller Alencar de Mello, National Influenza Laboratory, Brazil
Richard Njouom, NIC Cameroon, Yaoundé, Cameroon
Rodrigo Fasce, Laboratorio de Virus Respiratorios y Exantematicos, Santiago, Chile
Xiao Donglou, Ministry of Health, China
Wilina Lim, Centre for Health Protection, Hong Kong, China S.A.R
Dayan Wang, WHO Collaborating Centre for Reference and Research on Influenza, Beijing, China
Vladimir Drazenovic, NIC Croatia, Zagreb, Croatia
Betsy Acosta Herrera, NIC Cuba, Habana, Cuba
Martina Havlickova, NIC Czech Republic, Prague, Czech Republic
Nagwa El Kholy, Egyptian Organisation for Biological Products and Vaccines (VACSERA), Cairo, Egypt
Claire A. Cornelius, NAMRU-3, Cairo, Egypt
Kaie Otsmaa, NIC Estonia, Tallinn, Estonia
Thedi Ziegler, NIC Finland, Helsinki, Finland
Keith Hamilton, OIE, Paris, France
Dominique Rousset, Institut Pasteur, Paris, France
Patricia Leung-Tack, Sanofi Pasteur SA, Marcy l'Etoile, France
Ann Machablishvili, NIC Georgia, Tbilisi, Georgia
Brunhilde Schweiger, NIC Germany, Berlin, Germany
William Kwabena Ampofo, NIC Ghana, Accra, Ghana
Angeliki Melidou, NIC Greece, Thessaloniki, Greece
Mandeep Chadha, NIC India, Pune, India
Jagvir Singh, National Centre for Disease Control, Delhi, India
Ondri Dwi Sampurno, NIC Indonesia, Jakarta, Indonesia
Novilia Sjari Bachtiar, PT. Bio Farma Bandung, Indonesia
Rini Mula Sari, PT. Bio Farma Bandung, Indonesia
Isabella Donatelli, NIC Italy, Rome, Italy
Simona Puzelli, NIC Italy, Rome, Italy
Sandra Jackson, NIC Jamaica, Kingston, Jamaica
Takato Odagiri, National Institute of Infectious Diseases, Tokyo, Japan
Masato Tashiro, WHO Collaborating Centre for Reference and Research on Influenza, Tokyo, Japan
Kaliya Kasymbekova, NIC Kirghizistan, Bishkek, Kirghizistan
Natalija Zamjatina, NIC Latvia, Riga, Latvia
Matthias Opp, NIC Luxembourg, Luxembourg, Luxembourg
Jean-Michel Heraud, NIC Madagascar, Antananarivo, Madagascar
Gisela Barrera Badillo, Instituto de Diagnostico y Referencia Epidemiologico, Mexico DF, Mexico
Pagbajab Nymadawa, NIC Mongolia, Ulaanbaatar, Mongolia
Fatima El Falaki, NIC Morocco, Rabat, Morocco
Jan De Jong, NIC Netherlands, Rotterdam, Netherlands
Bishnu Upadhyay, NIC Nepal, Kathmandu, Nepal
Said Ali Saif Al Baqlani, NIC Oman, Muscat, Oman
Marilla G. Lucero, NIC Philippines, Muntinlupa City, Philippines
Elena Burtseva, NIC Russian Federation, Moscow, Russian Federation
Ludmila Tsybalova, NIC Russian Federation, St. Petersburg, Russian Federation
Mbayame Ndiaye Niang, NIC Senegal, Dakar, Senegal
Jasmina Nedeljkovic, NIC Serbia, Belgrade, Serbia
Soo Sim Lee, Regional Emerging Disease Intervention Centre (REDI), Singapore, Singapore
Katarina Prosenc, NIC Slovenia, Ljubljana, Slovenia
Florette Treurnicht, NIC South Africa, Sandringham, South Africa
Tomàs Pumarola, NIC Spain, Barcelona, Spain
Geethani Wickramasinghe, NIC Sri Lanka, Colombo, Sri Lanka
Eeva Broberg, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
Maria Brytting, NIC Sweden, Solna, Sweden
Malinee Chittakanpitch, NIC Thailand, Nonthaburi, Thailand
Victoria Morris Glasgow, NIC Trinidad and Tobago, Port of Spain, Trinidad and Tobago
Amine Slim, NIC Tunisia, Tunis, Tunisia
Awatef El Moussi, NIC Tunisia, Tunis, Tunisia
Miriam Mantoya, NIC Tanzania, Dar es Salaam, United Republic of Tanzania
Alla Mironenko, NIC Ukraine, Kiev, Ukraine
Catherine Thompson, Health Protection Agency, London, United Kingdom
John McCauley, WHO Collaborating Centre for Reference and Research on Influenza, London, United Kingdom
Tony Colegate, IFPMA, Liverpool, United Kingdom
Rod Daniels, WHO Collaborating Centre for Reference and Research on Influenza, London, United Kingdom
Rick Bright, Biomedical Advanced Research and Development Authority, Washington DC, United States of America
Mary Hoelscher, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America
Alexander Klimov, WHO Collaborating Centre for Surveillance, Epidemiology and Control of Influenza, Atlanta, United States of America
Ann C. Moen, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America
Stacey Schultz-Cherry, WHO Collaborating Centre for Studies on the Ecology of Influenza in Animals, Memphis, United States of America
David J. Spiro, NIAID/NIH/DHHS, Bethesda, United States of America
Xiyan Xu, Centers for Disease Control and Prevention (CDC), Atlanta, United States of America
Mai Le, NIC Viet Nam, Hanoi, Viet Nam
Dang Tho Nguyen, National Centre for Veterinary Diagnostics, Hanoi, Viet Nam
Andros Theo, Virology/Immunology Lab, Lusaka, Zambia

Rapporteurs

Olav Hungnes, NIC Norway, Oslo, Norway
Anthony Waddell, Durham, United Kingdom

WHO Regional Offices

Ali Yahaya, AFRO
Otavio Oliva, AMOR
Ali Mafi, EMRO
Hassan El Bushra, EMRO
Caroline Brown, EURO
Dimitriy Pereyaslov, EURO
Rajesh Bhatia, SEARO
Jeffrey Partridge, WPRO

WHO Secretariat

Cindy Aiello, WHO/HQ/HSE/GIP
Terry Besselaar,WHO/HQ/HSE/GIP/VMV
Sylvie Briand,WHO/HQ/HSE/GIP
Tristan Chevignard,WHO/HQ/HSE/GIP/VMV
Ellah Frodeman,WHO/HQ/HSE/GIP/VMV
Christian Fuster,WHO/HQ/HSE/GIP/VMV