

SELF-ASSESSMENT OF THE
WHO GLOBAL INFLUENZA SURVEILLANCE AND RESPONSE
SYSTEM (GISRS)

Report to the PIP Advisory Group

October 2014

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ACRONYMS

BSL-2 or 3	Biosafety level 2 or 3
CVV	Candidate Vaccine Virus
GISRS	Global Influenza Surveillance and Response System
GISRS-SA	GISRS self - assessment
HI	Hemagglutination inhibition test
ILI	Influenza-like illness
IVTM	Influenza Virus Traceability Mechanism
MERS-CoV	Middle East respiratory syndrome coronavirus
MNT	Microneutralization test
NIC	WHO-recognized National Influenza Centre
PCR	Polymerase chain reaction
PIP	Pandemic influenza preparedness
PIP-AG	PIP Advisory Group
PIP-BM	PIP Biological Material
PIPF	PIP Framework for the sharing of influenza viruses and access to vaccines and other benefits
RSV	Respiratory syncytial virus
SARI	Severe acute respiratory infection
SARS	Severe acute respiratory syndrome
SMTA	Standard Material Transfer Agreement
TORs	Terms of Reference
VWG	Virtual Working Group
WHO CC	WHO Collaborating Centre for Influenza
WHO ERL	WHO Essential Regulatory Laboratory
WHO H5 RL	WHO H5 Reference laboratory
WHO HQ	WHO Headquarters
WHO AFRO	Africa Regional Office
WHO AMRO	Americas Regional Office
WHO EMRO	Eastern Mediterranean Regional Office
WHO Europe	Regional Office for Europe
WHO SEARO	South-East Asia Regional Office
WHO WPRO	Western-Pacific Regional Office

EXECUTIVE SUMMARY

During its second meeting (February, 2012), the Advisory Group (AG) of *Pandemic Influenza Preparedness (PIP) Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits* consulted with Global Influenza Surveillance and Response System (GISRS) laboratories to discuss the role, function and capacities of GISRS in relation to implementation of the PIP Framework. As a result, the PIP-AG recommended to the Director-General that GISRS laboratories conduct a self-assessment along these lines.¹ The PIP-AG further recommended that the PIP Framework Secretariat facilitate this by working with relevant GISRS laboratories to conduct the self-assessment in an efficient and practical manner.

The Secretariat interviewed the following persons by telephone: the 6 directors of WHO Collaborating Centres (WHO CCs); the 4 heads of Essential Regulatory Laboratories (WHO ERLs), and 4 directors of H5 Reference Laboratories (WHO H5 RLs). The Secretariat also interviewed 26 WHO-recognized National Influenza Centres (NICs)². In advance of such interviews, a structured questionnaire was developed and sent to each interviewee. The interview covered broad areas related to the laboratory's role and capacity, rapid response to new threats, support and resources, and understanding of the PIP Framework.

The main findings show that GISRS is generally seen as a robust network with strong technical foundations, fulfilling its aim to provide real-time information on risk assessment and response to influenza in the world. GISRS generates essential data required to support recommendations on the composition of seasonal and pandemic influenza vaccines. Through efficient collaboration and exchange of information, GISRS undertakes rapid and focused response to threats from novel influenza and other respiratory viruses. GISRS is also a well-established network for the exchange of information, viruses, reagents and training.

Although many new NICs have joined GISRS in the past 10 years, geographical gaps remain in several areas of the world. Several GISRS laboratories maintain contacts with veterinary laboratories and occasionally exchange services with those. Although some NICs lack the ability to isolate influenza viruses, polymerase-chain reaction (PCR) technology has given them the opportunity to identify influenza viruses in clinical specimens, which they can share with WHO CCs for further analyses. Only through active surveillance of influenza by NICs and other laboratories of GISRS will the Network maintain and further develop the capacity and skills to rapidly react to new threats.

In many interviews, strong concerns were expressed about funding cuts and travel restrictions. GISRS entities have had to reduce staff, some struggle with rapid staff turnover, or experience difficulties in recruiting suitable individuals into senior positions.

The understanding of the PIP Framework is generally good, although NICs as a whole would benefit from more information. The PIP Framework creates additional work, particularly for directors of WHO CCs and WHO ERLs, as the PIP Framework needs to be explained to staff and to prospective recipients of PIP Biological Material (PIP-BM).

In general, the Influenza Virus Traceability Mechanism (IVTM) is considered useful. For many laboratories it is essential to continue using their own databases as part of their laboratory information management system and for regulatory compliance.

¹ http://www.who.int/influenza/pip/pip_meetings_consultations/en/

² See Annex 2 for a full list of interviewees as well as the criteria for the selection of the NICs that were interviewed.

Based on information extracted from the telephone interviews, seven questions covering different aspects of the PIPF were included in the NIC Survey conducted in spring 2014. Analyses of the answers received to these questions revealed that most NICs know how to proceed if an unusual influenza virus is detected. The majority of NICs seems to have an adequate understanding of the PIPF and many NICs have received PIP-BM from GISRS laboratories. A minority of NICs detected or isolated influenza viruses with pandemic potential in their own laboratory, and when they did, most of these viruses were sent to WHO CCs or to WHO H5 RLs. Not all of these shipments have been registered in the IVTM. Only a few NICs have shared PIP-BM with entities outside the GISRS.

Combining information received through telephone interviews and the NIC Survey, a SWOTT analysis (Strengths, Weaknesses, Opportunities, Threats, Trends) has been undertaken and a summary is presented in Annex 1 of this document.

1 OBJECTIVES OF THE GISRS SELF-ASSESSMENT

In February 2012, the Advisory Group (AG) of *Pandemic Influenza Preparedness (PIP) Framework for the Sharing of Influenza Viruses and Access to Vaccines and other Benefits* recommended to the Director-General that the PIP Framework Secretariat facilitate a self-assessment of the Global Influenza Surveillance and Response System (GISRS) with respect to its role, function and capacities in connection with the PIP-Framework³. The PIP-AG advised the Secretariat to work with relevant GISRS laboratories to implement this self-assessment in an efficient and practical manner.

2 METHODOLOGY

To facilitate the self-assessment, an informal Virtual Working Group (VWG) was established consisting of members from WHO Headquarters (HQ), WHO Regional Offices, and members of GISRS (see Annex 6 for the list of members of the VWG). Criteria were defined to select NICs to be interviewed in each of the 6 Regions (See Annex 2 for further details).

Questions to guide structured interviews were developed by the VWG; two sets of questions were developed: one for WHO Collaborating Centres (CC) and WHO Essential Regulatory Laboratories (ERL) directors (see Annex 3 for the text of the questionnaire), and the other for directors of WHO H5 Reference Laboratories (H5 RLs) and National Influenza Centres (NICs) (see Annex 4). The questions covered the following areas:

- Role of the laboratory within the GISRS
- Laboratory capacity
- Ability to respond to an emergency
- Laboratory's national role in an emergency
- Support of the laboratory and sustainability of this support
- Awareness and understanding of the PIPF and the Influenza Virus Traceability Mechanism (IVTM)
- Contact with the animal health sector
- Opinion of GISRS and future role of Network

All interviews were conducted by telephone.

³ http://www.who.int/influenza/pip/pip_meetings_consultations/en/

Using the preliminary findings from the interviews, seven questions were included in the NIC Survey⁴ conducted in spring 2014 in order to obtain a better grasp of NICs' understanding of the PIPF, their Terms of Reference (TORs), and the Standard Material Transfer Agreements (SMTAs). These PIPF-specific questions are presented in Annex 5.

The preliminary report presented to the PIP Advisory Group for their meeting in April 2014 was shared with the VWG and all persons interviewed. Comments received from the PIP Advisory Group, members of the VWG, and some interviewees are reflected in this final report.

3 THE GLOBAL INFLUENZA SURVEILLANCE AND RESPONSE SYSTEM

The need for international coordination of research in the field of influenza led to the establishment of the WHO global influenza surveillance network (GISN⁵) in the early 1950s. The objectives of the Network were to monitor the evolution of influenza viruses and to provide recommendations on which candidate vaccine viruses should be included in seasonal and pandemic vaccines.

3.1 Structure of GISRS

Currently, the Network comprises six WHO CCs (five for human and one for animal influenza), four WHO ERLs, 141 institutions recognized by WHO as NICs, and 12 WHO H5 RLs, in a total of 111 WHO Member States. Some laboratories act in more than one capacity; thus, for instance, a WHO CC may also be a NIC, WHO H5 RL and/or WHO ERL for its host country.

3.1.1 National Influenza Centres

All NICs interviewed collect clinical specimens for the detection of influenza viruses through national surveillance networks. Some of the laboratories also collect syndromic and epidemiological influenza data. Surveillance is performed in primary health care centres and in hospitals, and many countries also include severe acute respiratory infection (SARI) patients in their investigations. While the surveillance network is dense and well developed in many countries, some NICs collaborate only with a small number of surveillance sites. Because of year-round circulation of influenza viruses in areas with different climatic zones, surveillance is considered complex.

Most NICs surveyed have the capacity to identify different subtypes of influenza A viruses, including seasonal influenza, H5 and H7, and have indicated that viruses for which the subtype cannot be identified would be sent to a WHO CC. Many NICs serve as national reference laboratory for other diagnostic laboratories in the country.

Some NICs do not have the capacity to isolate influenza viruses but can identify influenza viruses using polymerase chain reaction (PCR) techniques and send selected influenza-positive clinical specimens to a WHO CC. Other NICs have biosafety level (BSL) -2 and even BSL-3 laboratory facilities available and can thus culture seasonal influenza viruses and eventually also viruses with pandemic potential. In addition to adequate laboratory facilities, virus isolation requires know-how and well-established logistics for specimen transport from the primary care site to the NIC and adequate specimen handling in the NIC. This explains why not all NICs are able to perform virus isolation.

While PCR technology belongs to the primary repertoire of all NICs, some NICs also have other molecular techniques at hand. These techniques allow them to determine the nucleotide sequence of certain influenza virus genes and to identify mutations

⁴ <http://who.int/wer/2014/wer8934/en/>

⁵ The name 'GISN' was changed to 'GISRS' following the adoption of the PIP Framework in May 2011, by the World Health Assembly resolution 64.5

altering the properties of influenza viruses or rendering them resistant to commonly used antiviral medicines. Many NICs test for different respiratory and non-respiratory viruses. Timely feedback from WHO CCs concerning characteristics of viruses submitted is highly appreciated by NICs. The majority of NICs work with reagents and kits provided through GISRS, which for some laboratories is the only source of reagents.

3.1.2 WHO H5 Reference Laboratories

WHO H5 RLs are equipped to rapidly identify and characterize influenza viruses at the human-animal interface, including handling of viruses under BSL-3 conditions. They serve as reference laboratory in their respective countries or in a larger region.

3.1.3 WHO Essential Regulatory Laboratories

WHO ERLs are formally associated with the national regulatory authority in their respective countries and play a critical role in developing, regulating and standardizing influenza vaccines.

They develop candidate vaccine viruses (CVVs) for the inclusion in seasonal and pandemic influenza vaccines, and they prepare and supply the reagents needed by manufacturers to quantify and standardize the antigen content of each vaccine lot.

3.1.4 WHO Collaborating Centres

Of the 6 WHO CCs, 5 focus primarily on human influenza and one is working on studies on the ecology of influenza in animals. The primary function of WHO CCs is to perform detailed analyses of viruses submitted by NICs and other laboratories in order to follow closely the evolution of circulating influenza viruses and the risks they pose. WHO CCs are able to provide WHO with a global assessment through a timely exchange of viruses and information. In addition to standard techniques such as virus isolation in cell cultures and in embryonated eggs, antigenic characterization using specialized tests (e.g. HI and MNT), WHO CCs employ sophisticated molecular techniques in order to understand the detailed properties of viruses under investigation, and they develop and characterize CVVs. WHO CCs provide risk assessment for seasonal influenza as well as for viruses with pandemic potential, and they provide a rapid response when emergencies arise. All six WHO CCs serve also as WHO H5 RLs. In addition, the WHO CC in Memphis focuses on the ecology of influenza and on the characterization of influenza viruses at the animal-human interface.

3.1.5 The role and tasks of different laboratories

NICs conduct year-round surveillance and collect influenza viruses circulating in their respective countries. After primary identification and characterization, NICs send selected viruses to one of the five WHO CCs for human influenza for thorough analyses of their antigenic and genetic characteristics. Serological studies, conducted particularly by some ERLs and WHO CCs, determine whether immunity derived from previous infection or immunization still provides protective immunity to currently circulating viruses. Based on results from these virological and serological investigations, WHO twice annually makes recommendations on influenza viruses for inclusion in seasonal influenza vaccines for the Northern and Southern Hemisphere. A similar process was used to develop the recommendation for the 2009 H1N1 pandemic vaccine.

Genetic sequencing of certain influenza virus genes nowadays forms a central part in the characterization of seasonal influenza viruses and of viruses with pandemic potential. Genetic sequences can provide information about evolutionary trends, possible reassortment in nature, geographic distribution, pathogenic properties and antiviral susceptibility of influenza viruses. All WHO CCs perform extensive sequence analyses and also an increasing number of NICs can provide sequence information to WHO CCs. NICs are encouraged to send available sequence data together with

virus isolates or clinical specimens to the WHO CC of their choice. A considerable part of genetic information produced by the GISRS is submitted to publicly accessible databanks. In emergencies, genetic information from WHO CCs is shared immediately when it becomes available, often within hours. In the weeks leading up to the VCM, sequences are uploaded within days. Uploading of genetic information produced by NICs occasionally takes a little longer⁶.

WHO CC and WHO ERL directors regularly exchange information with each other and with WHO using multiple communication channels. This information exchange is enhanced ahead of the Vaccine Composition Meeting each February and September, and whenever an emergency arises.

WHO CC, WHO ERL, WHO H5 RL and NIC directors have worked for many years as influenza experts in public health and in academic research and they contribute to the strong scientific backbone of GISRS, its immense wealth of knowledge, and its experience. Providing training is a core function of WHO CCs; that said, other laboratories and networks also provide training to visiting scientists either at the trainer's laboratory, or at times, in the receiving laboratory.

WHO CCs, WHO ERLs, and some of the WHO H5 RLs prepare reagents and kits to be distributed to other laboratories. Also laboratory protocols are regularly updated as new information about circulating influenza viruses accumulates. WHO HQ and some Regional Offices maintain electronic platforms e.g. EZCollab, for the rapid dissemination of essential information.

Another important role of GISRS is to rapidly detect influenza viruses with human pandemic potential or other viruses that could have public health significance. With the threat of A(H5N1) avian influenza viruses re-emerging in 2003, WHO designated, on an *ad hoc* basis, twelve WHO H5 RLs that have the capacity to detect and thoroughly characterize influenza viruses with pandemic potential.

4 INTERVIEW FINDINGS

4.1 Emergency response and the role of laboratories

GISRS has a proven track record for rapidly responding to new threats. With the emergence of the H7N9 virus in China in March 2013, essential information about the virus was shared within days, which gave GISRS the possibility to conduct risk assessments, design laboratory tests for the specific identification of the novel virus, develop diagnostic reagents and kits to be distributed to GISRS laboratories and other entities, and prepare CVVs for distribution to vaccine manufacturers. Although GISRS was able to promptly respond to the threat of H7N9, many NICs lack the capacity to develop assays for the detection of new influenza viruses, and depend on the distribution of diagnostic protocols and reagent kits through GISRS.

GISRS rapidly responded to the emergence of the H1N1 pandemic virus in 2009 and several other zoonotic influenza viruses such as H5N1, H3N2v, and H9N2. During the severe acute respiratory syndrome (SARS) epidemic in 2003, GISRS laboratories were at the forefront of the global response to diagnose the new pathogen. NICs rapidly received essential information and specific reagents through GISRS that allowed for the timely set-up of diagnostic capabilities and response.

Also with the sudden emergence of the Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012, GISRS proved its capacity to respond to threats caused by other viruses than influenza. In fact, interviews revealed that a number of

⁶ The 5 WHO CCs for human influenza and many NICs upload their sequence data to GISAID.

NICs and WHO H5 RLs routinely identify also other viruses, including respiratory syncytial virus (RSV), measles, polio, and viruses causing hemorrhagic fever.

WHO CCs play a central role in the response to novel threats due to influenza. They have the technical know-how to perform detailed characterization of unusual influenza virus subtypes. Based on these studies, diagnostic assays are designed and validated, and protocols and control reagents are shared within GISRS. Some Network laboratories routinely monitor drug-susceptibility of circulating influenza viruses, providing public health officials with essential data. It is essential to sustain active surveillance of influenza by NICs and other laboratories of GISRS to ensure the Network has the capacity and skills to ramp-up activities and react swiftly to new threats.

During public health alerts and emergencies, WHO CCs, WHO ERLs, WHO H5 RLs, and NICs play a pre-eminent role in the primary virological response to the threat. NICs are on the front line to detect the new virus in clinical specimens. In some countries, NICs have the capacity to develop national testing algorithms and laboratory protocols, and lead the development of diagnostic capacities in the public health and diagnostic laboratory network(s) of a country. GISRS laboratories perform specialized analyses of clinical specimens sent from other laboratories, and share control reagents with diagnostic laboratories, prepare and distribute CVVs, and provide training.

In general, laboratory directors interviewed for this self-assessment agree that GISRS could and should play a leading role in emergencies caused by respiratory viruses.

4.2 Laboratory funding and sustainability

As may be expected from a network comprised of laboratories in over 100 countries around the globe, funding and resource levels vary greatly, from cutting-edge laboratories with highly trained staff and state-of-the-art equipment and reagents, to laboratories working with minimal resources. Insufficient funding, lack of long-term government commitment, insufficient number of well-trained staff, and rapid staff turnover were identified as significant challenges by many NICs. In some countries, particularly in tropical areas, influenza is not considered a priority public health problem.

Inadequate or decreasing financial and human resources were highlighted as significant problems by all laboratory categories. However, several WHO CCs and WHO ERLs indicated that they have good relations with their governments and thus are able to underline the public health importance of influenza.

Directing a laboratory at any level, but in particular, a laboratory that has reference functions such as a WHO CC, WHO ERL, and WHO H5 RL, requires significant training and abundant experience, as well as strong links to colleagues nationally and internationally within the Network and beyond. The current directors of these laboratories uniformly indicated that heightened attention should be given to ensuring that trained and experienced persons are prepared to assume, in due course, the functions of laboratory director.

Many of the interviewees indicated that they participate in national committees for pandemic preparedness, which provides them the opportunity to strengthen their links with government and to draw attention to the lack of sufficient support for their laboratories, as appropriate.

4.3 Awareness and understanding of the PIPF and the IVTM

Directors of WHO CCs, WHO ERLs, and WHO H5 RLs indicated that they have a sound understanding of the PIPF. Many of these directors participated in the negotiations of the Framework and thus gained knowledge about the Framework and their respective laboratory TORs.

At the NIC level, awareness and understanding of the PIPF is more heterogeneous. While some NIC directors indicated they had an excellent understanding, some admitted that they needed to take a closer look, while others indicated that they had little insight into it.

It is well understood that transfers of PIP-BM within GISRS and to entities outside the Network are regulated through SMTAs. It was mentioned that at the beginning of implementation of the PIP Framework, a non-GISRS prospective recipient of PIP-BM that was unable to handle the PIPF obligations chose not to accept the PIP-BM. Several interviewees mentioned that it is impossible to monitor whether recipients of PIP-BM comply with the terms of onward sharing contained in the PIPF.

WHO CC directors indicated that the PIPF has caused additional work because they need to inform their staff of its meaning and intent, and to explain the Framework to potential recipients of PIP-BM. They also underscored the importance of the use of the “Operational Exemption”⁷ in the sharing of PIP-BM. The “Operational Exemption” was first used during the emergence of the H7N9 virus in spring 2013, and enabled the swift distribution of PIP-BM within GISRS and to laboratories providing diagnostic services for a non-commercial, public health use. The “Operational Exemption” is considered crucial for the smooth operation of GISRS in responding to public health threats. Without the careful definition of PIP BM and without the Operational Exemption the response of GISRS in an emergency situation might be delayed.

In general, the IVTM is regarded as a useful platform that enhances the transparency of the sharing of PIP-BM. Shipments are recorded in the IVTM and can then be monitored. It was also mentioned that the IVTM helps laboratories determine from where they can obtain certain viruses. However, the IVTM has created additional work for all GISRS laboratories that had their own databases into which they have entered virus shipments for many years and must continue to do so due to institutional requirements. The IVTM is not seen as a replacement for institutional databases. It is understood as an additional public database for transfer of PIP-BM, which by necessity duplicates efforts. Particularly during emergencies, this can add extra burden to laboratories.

Several NIC directors indicated that it would be useful to receive more direct information from the WHO HQ about new developments such as the PIPF and the IVTM and how these developments would affect their work. Some NIC directors suggested that exchange of information within the GISRS could be further improved if more NICs subscribed to the EZCollab platform and used it regularly.

4.4 Contacts with the animal health sector

In general, WHO CCs maintain good contacts with the veterinary sector through regular meetings, participation in joint working groups, common research projects, and exchange of viruses. The ‘One World – One Health’ concept is regarded as

⁷ PIP Framework Section 4.1 footnote 1 states: “OPERATIONAL EXEMPTION: materials shared within the WHO GISRS or with other laboratories specifically for non-commercial public health uses including surveillance activities, diagnostic applications, and quality assurance, are not handled as PIP Biological Materials. Their onward transfer for purposes other than those specified in the terms of reference of National Influenza Centres, WHO Collaborating Centres, Essential Regulatory Laboratories and H5 Reference Laboratories is not allowed under this operational exemption.

important, and there is a general effort towards active involvement in OFFLU. Contacts between the two sectors are both formal and informal. WHO H5 RLs have strong links to the animal health sector, serving as reference laboratories at the human-animal interface. Finally, some NICs maintain contacts with the veterinary sector and occasionally participate in activities on the surveillance of influenza in animals, particularly birds. Several laboratory directors intend to intensify their contacts with the animal health sector. The WHO CC Memphis studies the ecology of influenza in animals, further strengthening collaboration of GISRS with the animal health sector.

4.5 Opinion of GISRS and its future role

General Comments

In general, the interviews revealed a positive opinion of GISRS, which is considered to be a successful network that fulfills its role in the virological surveillance of influenza and provides sound, scientific information needed for making recommendations such as influenza vaccine composition. Interviewees indicated that they believed the Network is well coordinated through the WHO HQ. Several NIC directors indicated that they would like the dialogue between WHO HQ, WHO Regional Offices, WHO Country offices and NICs to be intensified. NIC directors indicated that the links with WHO Regional Offices vary greatly – from non-existent to quite close. While some WHO Regions hold annual NIC meetings, several NIC directors voiced their hope that WHO could more often organize global NIC meetings. Past global meetings have been considered very useful to build contacts with other GISRS members, exchange information, and establish partnerships. These meetings also provide an opportunity to further strengthen the link between human and animal health sectors.

Geographical coverage of GISRS

GISRS has clear geographical gaps particularly with respect to the presence of NICs. In order to fill these gaps, building capacity in regions and countries that do not yet have a NIC is essential.

GISRS substantive focus

Currently, GISRS focuses on influenza virological surveillance. Several interviewees noted that GISRS should also be in the position to conduct epidemiological surveillance and that field-epidemiology activities of GISRS could be developed.

Additionally, some GISRS laboratories have rapid response teams available for deployment to outbreak investigations while others do not. Several interviewees indicated that rapid response training could be established in more laboratories.

Finally, as mentioned earlier, several NICs routinely perform surveillance for respiratory viruses other than influenza. This provides the Network with the potential to rapidly respond to various respiratory threats as was seen during the SARS epidemic and with the emergence of the MERS-CoV. Integrating this broader focus more officially into the GISRS responsibilities would widen its activities beyond influenza. However, several laboratory directors raised the concern that taking on additional routine surveillance activities should not jeopardize the current, high-quality influenza surveillance that exists. It was also noted that if GISRS should broaden its responsibilities, additional funds would need to be made available to the laboratories. With currently available funding, many GISRS laboratories are already working to their limit.

GISRS Structure

There were divergent opinions as to whether the current structure of GISRS is sufficient. Some laboratories are seeking to achieve recognition or designation of

their laboratory at a different or more specialized level. It was mentioned that additional laboratories in new sectors, such as the human-animal interface, might strengthen the Network. It was also recognized that the relatively small number of WHO CCs and ERLs enables efficiency in the consolidation of data from many countries, synthesis and exchange of information, and rapidity of reaching consensus on recommendations.

4.6 Perception and understanding of the PIPF by NICs

The following information is summarized from responses to the PIPF-related questions in the NIC survey conducted in spring 2014.

- Most responding NICs have guidelines on what to do in case an unusual influenza virus is detected, and these guidelines include informing the national IHR Focal point.
- The majority of laboratories and their staff are familiar with the TORs for NICs found in the PIPF.
- Many NICs report that the PIPF is causing additional administrative and laboratory work as well as extra costs.
- One third of the NICs have received PIP-BM since 2010, and most of these laboratories clearly identified the material as PIP-BM.
- Twenty-four of the responding NICs have detected influenza viruses with human pandemic potential and most of these viruses were sent to a WHO CC or to a WHO H5 RL.
 - Registration of these shipments in the IVTM was inconsistent.
- Four laboratories report having shared PIP-BM with an entity outside the GISRS.
 - Two of these transfers were registered in the IVTM, and one of the recipients was instructed to contact WHO in order to conclude an SMTA2.
- Sharing of PIP-BM within GISRS has led to scientific collaboration, which in some instances also resulted in joint scientific publications.

4.7 SWOTT analysis of the GISRS

Information received through the telephone interviews and from answers to the PIPF-related questions in the NIC Survey conducted in spring 2014 was carefully reviewed in order to identify strengths and weaknesses of the GISRS, opportunities that the Network holds within or which may come from outside, threats that may weaken the function of the Network, and general trends. Results from this SWOTT analysis are presented in Annex 1.

5 CONCLUSIONS

Since 2007, GISRS has grown considerably: one new WHO CC has been established, and 29 new NICs have been recognized by WHO. GISRS has proved to be an essential network for global public health. It is a sound global mechanism for response to emergencies, including influenza outbreaks. The Network demonstrates excellence across the globe, though this excellence is not evenly spread, particularly across NICs.

Regarding global coverage of NICs, some gaps still exist in Eastern Europe and South-East Asia, and significant gaps remain in Africa and the Middle East. GISRS should therefore continue to grow in order to fill these gaps.

To overcome challenges associated with imbalances in NIC capacities, strengthening of existing national and regional systems will be instrumental and should be a priority. Through better integration of clinical and epidemiological data with the virological data, a more comprehensive knowledge of influenza can be obtained. This would enhance the value of GISRS contributions to global seasonal and pandemic risk-assessments.

In order to maintain and enhance the quality and relevance of GISRS activities, the Network should continue to strengthen its collaboration with its stakeholders (e.g., public health laboratories, animal health laboratories, vaccine industry laboratories, research institutions) at national, regional and international levels.

The emergence and spread of influenza H5N1, H7N9, and other zoonotic viruses such as SARS-CoV and MERS-CoV highlight the pressing need to continuously strengthen and broaden current GISRS capacity at the human-animal interface.

In order to continue implementation of their responsibilities under the PIPF, GISRS laboratories require regular updates on the Framework and its implications. To this end, a bi-monthly PIP newsletter⁸ has been launched, and the EZCollab platform continues to be another valuable source for relevant information.

Based on evidence of the significant morbidity and mortality associated with the disease, Member States should be encouraged to reinforce their support of GISRS, which, in turn, provides significant value to global public health and global health security.

The PIP Framework has created both opportunities and challenges to the work of GISRS laboratories. To ensure continued implementation of the Framework, the PIP Secretariat should continue to work closely with GISRS and its stakeholders to improve the level of understanding and compliance with TORs in the PIP Framework.

⁸ To subscribe to the PIP newsletter, please contact pipframework@who.int

GISRS SWOTT analysis based on responses from telephone interviews

Strengths	<ul style="list-style-type: none"> - GISRS is a global influenza surveillance network established more than 60 years ago and well-coordinated by WHO HQ - GISRS provides a timely picture of the global influenza situation - GISRS comprises a wealth of technical expertise - GISRS delivers the scientific base for the composition of seasonal and pandemic vaccines - Strong trust among members of GISRS has been built through long collaboration - Many GISRS laboratories have highly devoted staff and cutting-edge technology - GISRS members have good communications using different channels - Many GISRS laboratories have the ability to provide surveillance of other respiratory viruses - GISRS took the lead in the virological response to the 2003 epidemic of SARS and rapidly reacted to the emergence of the threat caused by MERS-CoV - Many GISRS laboratories participate in national pandemic planning
Weaknesses	<ul style="list-style-type: none"> - GISRS laboratories are not equally distributed over the globe; geographical gaps exist in Africa, the Middle East, and in South-East Asia - Virological surveillance provided by GISRS is sensitive enough to pick up unusual, serious events; however, clinically mild cases caused by a virus with pandemic potential may go undetected for a lengthy period - In some countries influenza surveillance and response has to compete for funds with other important public health issues - Many GISRS laboratories, especially NICs are not sufficiently funded, which has a direct impact on a laboratory's ability to perform essential services - Many NICs do not have resources to isolate influenza viruses, which may put additional burden on WHO CCs - Limited funds and national or international regulations may limit abilities to timely send viruses from NICs to WHO CCs - On a global level, surveillance of animal influenza is weak - Implementation of the PIPF and the IVTM have created additional workloads particularly for WHO CCs
Opportunities	<ul style="list-style-type: none"> - GISRS has remarkable expertise, which can be used for the surveillance of non-influenza infectious diseases and for response to non-influenza threats - Highly trained, motivated, and dedicated staff are available at GISRS laboratories of different levels - Some GISRS laboratories can deploy specifically trained outbreak investigation teams to the field - GISRS laboratories have developed training capacity and deliver training to staff of other laboratories - Many GISRS laboratories maintain contacts with national animal health authorities - GISRS consists of well-established structures with good

	channels for exchange of information
Threats	<ul style="list-style-type: none"> - Due to the global economic crisis and various levels of “flu fatigue”, many GISRS laboratories have experienced budget cuts and have had to reduce staff - Travel restrictions have resulted in limited training opportunities - Rapid staff turnover is common in some GISRS laboratories, which can affect quality of performance - Reduction of staff at the WHO HQ has been perceived to reduce its ability to provide leadership to GISRS and lead the Network into the future - Some governments are not committed to providing long-term support to GISRS laboratories in their respective country - Being responsible for a GISRS laboratory requires knowledge, skills, experience, and national and international contacts. It can be difficult to keep possible successors on that track - Due to geographical and technical gaps, new threats may emerge in an area where it may go undetected for a lengthy period before being recognized
Trends	<ul style="list-style-type: none"> - An increasing number of NICs only use PCR for the detection of influenza viruses. This may create extra work-load to WHO CCs because they need to culture viruses directly from the submitted clinical specimen - Strengthened global surveillance of influenza may reveal an increasing number of zoonotic transmissions of influenza viruses and eventually of other animal viruses

List of GISRS laboratories interviewed for the Self-Assessment

WHO Collaborating Centres (all WHO CCs serve also as WHO H5 RL)

Australia: Victorian Infectious Diseases Reference Laboratory
Melbourne
China: Chinese Centre for Disease Control and Prevention
Beijing
Japan: National Institute of Infectious Diseases
Tokyo
United Kingdom: National Institute for Medical Research
London
United States of America: Centers for Disease Control and Prevention
Atlanta, GA
United States of America: St. Jude Children's Research Hospital
Memphis, TN

WHO Essential Regulatory Laboratories

Australia: Therapeutic Goods Administration
Woden ACT
Japan: National Institute of Infectious Diseases
Tokyo
United Kingdom: National Institute for Biological Standards
and Control
Hertfordshire
United States of America: Food and Drug Administration/Centre
for Biologics Evaluation and Research
Rockville, MD

WHO H5 Reference Laboratories

China, Special Administrative Region of: Centre of Influenza
Research, The University of Hong Kong
Hong Kong
Egypt: U.S. Naval Medical Research Unit No.3 (NAMRU-3)
Cairo
France: Institute Pasteur
Paris
India: National Institute of Virology
Pune
Russian Federation: Federal State Research Institution VECTOR
Koltsovo

WHO-recognized National Influenza Centres

There are 141 WHO-recognized National Influenza Centres in 111 countries or territories. Given the limited time and resources available to the Secretariat, a selection among the many NICs was made. In order to ensure the breadth of viewpoints provided, NICs were selected for an interview based on the following criteria that were developed and reviewed by the VWG:

- 1) Geographical representation: Four to five NICs per WHO Region;
- 2) Laboratory capacity: NICs to be interviewed should reflect a broad range of laboratory capacities;

- 3) Participation in GISRS activities: NICs to be interviewed should reflect a broad range of participation (regular, rare and at unpredictable intervals);
- 4) Data reporting: NICs to be interviewed should reflect a broad range of reporting practices (regular, rare, and no reporting).

Using the above criteria, the following NICS were selected for interview:

AFRO	Cameroon, Mauritius, South Africa, Uganda
AMRO	Brazil, Jamaica, Mexico, Paraguay
EMRO	Afghanistan, Iran, Kuwait, Sudan
EURO	Germany, Kazakhstan, Russia, Turkey, United Kingdom
SEARO	Bangladesh, India, Indonesia, Nepal, Thailand
WPRO	Cambodia, Fiji, Laos, Mongolia

Interview questions for Directors of WHO Collaborating Centres and WHO Essential Regulatory Laboratories

Type of lab and function

- Please outline the role you and your laboratory/institute play in the network, routinely and during an influenza emergency (e.g. emergence of novel influenza virus with human pandemic potential).

Opinion of GISRS

- During an influenza emergency does GISRS facilitate your laboratory's ability to respond to the emergency?
- What are the strengths of GISRS?
- For instance: technical capacity/expertise, platform for sharing of laboratory findings, collaborative efforts, etc.
- What are its weaknesses? For instance: funding, human resources, laboratory capacity
- Do you think GISRS fulfills its role to conduct global influenza virological surveillance?
- Which areas (in priority order) should be improved?
- Do you think GISRS's current components and structure are sufficient for it to carry out this responsibility?
 - If not, what (in priority order) should be improved?
- For broad global influenza surveillance, preparedness and response, what additional functions, if any, should GISRS take on board?
- For response to global respiratory emergencies e.g. SARS, MERS-CoV, do you think GISRS should have a role?
 - If so, what should it be?

PIPF

- Since implementation of the PIPF began in 2011, do you have a better understanding of what PIPF is trying to achieve?
- Has the adoption of the PIPF affected your routine laboratory activities? If yes, how?
 - Provide examples if possible.
- How has this affected your activities during an influenza emergency?
- What are the most challenging issues about implementing your PIP Terms of References?
- When you ship PIP Biological Materials (PIPBm) what are the most common questions or requests related to these shipments and how are you handling them?
- Has IVTM been helpful in tracking PIPBM shipments?
- What has been your experience (if any) of shipping PIPBM under the 'Operational Exemption'?
- Has there been any downstream impact on the use of IVTM under these conditions? By your institute or by laboratories received your shipment?
 - Have you put in place any long-term measures to ensure your lab's ability to continue contributing to global influenza surveillance?
 - If yes, what are some of those measures?

Human-animal interface

- Is there an existing collaboration between your institute and animal health sector?
 - If yes in what capacity?

Interview questions for directors of WHO H5 Reference Laboratories and WHO-recognized National Influenza Centres

Type of lab and function

- How long has your laboratory been involved with the GISRS network?
- What are your principal activities?
- How often do you share viruses with GISRS WHO CC's?
- How often do you use the guidelines, recommendations and other materials provided by GISRS in your routine activities?

Influenza surveillance program

- Please describe the influenza surveillance network, if there is one, in your country. If appropriate specify if surveillance carried-out is community and/or hospital-based.
- What specific measures are in place to detect unsubtypable (i.e. novel, non-seasonal, e.g., H7N9) influenza viruses infecting humans in your country?

Laboratory capacity

- What are the strengths of your laboratory in responding to an influenza emergency (e.g. emergence of novel influenza virus with human pandemic potential)?
 - For instance: active surveillance, technical expertise, access to technology, etc.
- What are the gaps faced by your laboratory to respond to an influenza emergency?
 - For instance: funding, human resources/high staff turnover, technical expertise, lack of equipment/supplies, national procurement regulations and permits, shipping capacity, etc.
- What are the strengths of your laboratory in routine influenza surveillance and preparing for next pandemic?
 - For instance: active surveillance, technical expertise, laboratory capacity, etc.
- What are the gaps faced by your laboratory in conducting routine influenza surveillance and preparing for the next pandemic?
 - For instance: human resources, funding, technical capacity, shipping capacity, training, etc.
- What would be your laboratory's national role in responding to an influenza emergency?
- What other responsibilities does your laboratory have that are not related to influenza?

Sustainability

- Have you put in place any long-term measures to ensure your lab's ability to continue contributing to global influenza surveillance?
 - If yes, what are some of those measures?

PIPF

- Since implementation of the PIPF began in 2011, do you have a better understanding of what it is trying to achieve?

IVTM

- Do you use the IVTM? Yes/No
- In your opinion, has IVTM achieved its function of showing transparency of shipment of PIPBMs within and outside GISRS?

Opinion of GISRS

- Why did your laboratory join GISRS?
- What are your expectations of GISRS?
- Have the expectations been met?
- Have your expectations changed?
- For response to global respiratory emergencies e.g. SARS, MERS- CoV, do you think GISRS should have a role? If so, what should it be?

Human-animal interface

- Is there an existing collaboration between your institute and the animal health sector and in what capacity?

Future role for GISRS

- Do you think GISRS fulfills its role to conduct global influenza virological surveillance?
- Do you think GISRS's current components and structure are sufficient for it to carry out this responsibility?
 - If not, what (in priority orders) should be improved?
- Do you think WHO and Regional Offices should be playing a greater role?
 - If yes, please provide examples?

PIP Framework Questions included in the 2014 NIC Survey 2014

Introduction

The following section and questions are related to your laboratory's work with non-seasonal influenza viruses under the *Pandemic Influenza Preparedness Framework for the sharing of influenza viruses and access to vaccines and other benefits (the PIP Framework)*. More information on the PIP Framework may be found at: http://www.who.int/influenza/resources/pip_framework/en/index.html

Background

In May 2011, the 194 Member States of WHO adopted the PIP Framework that aims to improve global pandemic influenza preparedness and response. This is to be achieved in several ways, including through the timely sharing, with a GISRS Collaborating Centre or H5 Reference laboratory, of specimens or isolates from all cases of infection due to an influenza virus with human pandemic potential. Under the PIP Framework, these materials are part of a broader set of materials known as "PIP Biological Materials" or "PIP BM" (see PIP Framework page 8 for more information). The PIP Framework does not cover seasonal influenza viruses.

To support achievement of the PIP Framework objective, Terms of Reference (TORs) were developed for all categories of laboratories in GISRS (see PIP Framework, Annex 5). Those PIP Framework TORs cover work carried out by GISRS laboratories with PIP Biological Materials. The TORs include terms and conditions on the handling or transferring of PIP Biological Materials to laboratories or institutions either in GISRS or outside GISRS (see PIP Framework, Annex 1, "Standard Material Transfer Agreement-1").

In order to maintain transparency in the movement of PIP Biological Materials, all transfers of such materials must be recorded in the Influenza Virus Traceability Mechanism ("IVTM") (see <https://extranet.who.int/ivtm>).

Finally, the Framework also requires that non-GISRS recipients of PIP Biological Materials conclude a Standard Material Transfer Agreement-2 (SMTA2) with WHO (see PIP Framework Annex 2 for more information). To ensure that such recipients are aware of this requirement, shipments of PIP BM to entities outside GISRS must contain a notice advising the recipient that acceptance of the PIP Biological Materials constitutes agreement to conclude an SMTA2 with WHO.

Questions

2. Does your laboratory have standard procedures on what to do if you identify an influenza virus of an unusual or new subtype?

Yes	No
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 - a) If so, do these procedures include informing the national International Health Regulation (IHR) Focal Point?

Yes	No
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3. Had you heard of the PIP Framework prior to this questionnaire?

Yes	No
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4. As a National Influenza Centre (NIC) in GISRS, your laboratory agreed to implement the PIP Terms of Reference described in the Background section above. Are you and your laboratory's staff familiar with these TORs?
- Yes No
5. Has implementation of the PIP Framework affected the work of your laboratory?
- Yes No
- a) If yes, in what respect?
- i. Additional administrative work
- Yes No
- ii. Additional expenses
- Yes No
- iii. Additional laboratory work
- Yes No
- iv. Other, please specify briefly:
-
6. Has your laboratory received PIP BM from a GISRS laboratory since 2010?
(The following materials are PIP BM: isolates of wild type human H5N1 and other influenza viruses with human pandemic potential, human clinical specimens containing such viruses, candidate vaccine viruses prepared by high growth re-assortment and/or reverse genetics from H5N1 and/or other influenza viruses with human pandemic potential, RNA extracted from wild type H5N1 and other human influenza viruses with human pandemic potential and cDNA encompassing the entire coding region of one or more viral genes).
- Yes No
- a) If Yes, when you received them, were you aware that they were PIP biological materials?
- Yes No
7. Since 2010 has your laboratory detected and/or isolated any influenza viruses with human pandemic potential?
- Yes No
- a) If No, please proceed to question 7.
- b) If Yes:
- i. Did you send this virus/these viruses to a WHO Collaborating Centre or an H5 Reference Laboratory or to any other GISRS laboratory?
- Yes No
- If No, please briefly explain why:
-
- ii. Was sharing of this virus/these viruses with a GISRS laboratory recorded in the IVTM either by:
- a) your laboratory
- Yes No
- b) WHO Collaborating Centre
- Yes No
- iii. Was this virus/these viruses shared with a non-GISRS laboratory or institution?
- Yes No
- a) If yes, was sharing of this virus/these viruses with a non-GISRS

laboratory or institution recorded in the IVTM?

Yes

No

b) If yes, did you inform the recipient that, in time, WHO would contact it to conclude an SMTA2?

Yes

No

8. Did your sharing of PIP BM with another laboratory result in scientific projects associated with research on clinical specimens and/ or influenza viruses?

Yes

No

a) If yes, was your laboratory actively engaged in preparation of manuscripts for presentation or publication(s)?

Yes

No

Annex 6

Members of the Virtual Working Group for GISRS Self - Assessment

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	France - Sylvie van der Werf, Paris
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