

PROTOCOL FOR NATIONAL INFLUENZA SENTINEL SURVEILLANCE



REGIONAL OFFICE FOR

World Health
Organization

Africa

PROTOCOL FOR NATIONAL INFLUENZA SENTINEL SURVEILLANCE

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ABBREVIATIONS

A/H5	Influenza A(H5N1)
AFRO	African Regional Office
CDC	Centers for Disease Control and Prevention
FAO	Food and Agricultural Organisation
GISN	Global Influenza Surveillance Network
GISRS	Global Influenza Surveillance and Response System
HA	Haemagglutinin
IFA	Immunofluorescence Antibody
HAI	Haemagglutination Inhibition
PCR	Polymerase Chain Reaction
IDSR	Integrated Disease Surveillance and Response
IHR	International Health Regulations
ILI	Influenza-like Illness
MOH	Ministry of Health
NA	Neuraminidase
NIC	National Influenza Centre
NIL	National Influenza Laboratory
NP	Nasopharyngeal
OIE	World Organisation for Animal Health
OP	Oropharyngeal
PHEIC	Public Health Event of International Concern
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
UTM	Universal Transport Medium
VTM	Viral Transport Medium
WHO CC	WHO Collaborating Centre
WHO	World Health Organization

GLOSSARY (SUGGESTED INCLUSION)

Sentinel site — A sentinel site, as referred to in this document, may be an ambulatory, outpatient or local community clinic, a specialist or general hospital or any setting where ILI and/or SARI data and specimens are collected for the purposes of influenza surveillance.

National Influenza Laboratory (NIL) — This term, as is used in this document, refers to any laboratory where ILI and/or SARI clinical specimens are received and **tested** for influenza according to the minimum standards (RT-PCR) as outlined in the Global Epidemiological Surveillance Standards for Influenza [1]. It may also be from where specimens and/or viral isolates are forwarded to a collaborating inter-country laboratory, a WHO Collaborating Centre for Reference and Research on Influenza (WHO CC) or an A/H5 reference laboratory for testing and characterization.

National Surveillance Unit (NSU) — In the context of this document the NSU is a generic name given to the entity assigned to coordinating influenza surveillance in a country. The NSU is the location where influenza surveillance data are received, collated and analysed and from where reports are disseminated to stakeholders.

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BACKGROUND

1.1 Influenza

Influenza is an acute viral respiratory tract disease in humans, often characterized by fever, headache, myalgia, prostration, coryza, sore throat and cough. Influenza infection is clinically indistinguishable from other respiratory viral diseases without laboratory confirmation.

Etiology: Influenza infection is caused by the influenza virus, a single-stranded RNA virus belonging to the *Orthomyxoviridae* family. Influenza viruses are classified as types A, B and C. Influenza A and B viruses can cause epidemic disease in humans and type C viruses usually cause a mild, cold-like illness. Natural reservoirs of influenza A are aquatic birds and bats; however, the virus can infect multiple species, including humans, pigs and other mammals and wild and domestic birds. Influenza A viruses can be subtyped according to the antigenic and genetic nature of their surface glycoproteins haemagglutinin (HA) and neuraminidase (NA). Eighteen haemagglutinin (HA) and 11 neuraminidase (NA) subtypes have been identified to date [2] therefore many different combinations of HA and NA surface glycoproteins are possible. Three HA subtypes regularly cause disease outbreaks in humans, namely HA subtypes H1, H2 and H3. However, non-sustained outbreaks of influenza infections, caused by other HA subtypes (H5, H6, H7, H9 and H10) have also been reported [2]. Two neuraminidase subtypes commonly cause disease in humans: N1 and N2. However, like HA, other NA subtypes (N7, N8 and N9) have caused sporadic human infections [3]. Over the past two centuries, seasonal outbreaks of influenza disease in humans have been caused by influenza A(H1N1); A(H1N2); A(H2N2); A(H3N2) subtypes and more recently a pandemic strain influenza A[H1N1]pdm09 caused significant morbidity and mortality [4].

Genes encoding the surface glycoproteins of influenza A and B viruses mutate constantly, leading to the emergence of new viruses with different antigenic characteristics, a process called 'antigenic drift'. Another process, antigenic shift, on the other hand, is characterized by an abrupt or major change in antigenicity such that very few people in a population have immunity against the newly emerged virus. Antigenic shift can occur via three possible mechanisms; (i) a non-human virus may be passed from an avian host through an intermediate host e.g. pig, to humans; (ii) a virus from another animal e.g. bird or pig can infect a human directly without undergoing genetic reassortment; or (iii) a virus with a new HA or NA can arise through genetic reassortment of HA and NA genes from non-human and human viruses [5]. Antigenic shifts sometimes result in the appearance of a novel influenza virus that can infect, and be easily transmissible among humans, potentially leading to a pandemic.

Epidemiology: The influenza virus spreads rapidly around the world in seasonal epidemics, resulting in significant morbidity and mortality. In temperate climates, influenza is seasonal, typically occurring every year in the late fall or winter, although sporadic cases of influenza can occur year-round. Although the exact reason for influenza seasonality remains unresolved, and a number of theories have been postulated, it has been shown that climatic conditions of humidity and temperature such as those experienced during winter months are strong predictors of influenza outbreaks in temperate regions [6]. Furthermore, changes in host behaviour during winter periods increase virus transmission and facilitate influenza outbreaks [6, 7]. Typically, an outbreak will reach its peak within 2-3 weeks and may last around 8 weeks in a given community, (at national level in large countries seasonal outbreaks usually last longer) although the virus may still circulate in the community for weeks before and after

the onset of outbreak. The first indication of an influenza outbreak might be signalled by an event, such as increase in school absenteeism due to acute respiratory diseases, followed by influenza-like illness in adults. Annual global attack rates for influenza are approximately 5-10% in adults, with significantly higher attack rates 20-30% in children [8].

Sporadic cases of influenza can occur year-round in tropical and subtropical regions, but the existence of seasonal patterns of influenza transmission in these regions is unknown. Notably, data describing seasonality, epidemiology, transmission patterns and disease burden from human influenza in the African Region are limited. Current data suggest that influenza transmission patterns across this Region differ with geographical location, in some countries coinciding with lower environmental temperatures and rainy seasons and in others with cooler, dry periods [9]. However, data are limited to only a small number of countries restricting extrapolation to all countries in the Region. Expansion of routine influenza surveillance and reporting in the African Region would provide comprehensive regional data, fill these knowledge gaps and enhance guidance on the selection and distribution of resources and vaccines [10].

Seasonal influenza: Seasonal influenza is an acute viral infection, caused by influenza viruses; these are easily transmitted from person to person and circulate globally causing annual epidemics. Epidemics usually occur during winter in temperate regions and can result in significant morbidity and decreased productivity due to employee absence from work. All age groups are affected by seasonal influenza; however, those most at risk of complications or severe disease are children under 2 years of age, adults over 65 years of age, pregnant women and those with co-morbidities. Influenza vaccine formulations are revised annually and new vaccines are produced each year, due to seasonal changes in antigenicity of the virus, as a result of antigenic drift.

Pandemic influenza: An influenza pandemic can occur only if there is efficient and sustained viral transmission of a pathogenic influenza subtype to which few people are immune. In the last hundred years, four global pandemics have occurred. The 1918 pandemic (influenza A/H1N1) infected an estimated 500 million and killed 50-100 million people worldwide [11]. More recent pandemics, although not quite as deadly, still resulted in significant morbidity and mortality. The 1957 Asian Flu pandemic (influenza A/H2N2) resulted in an estimated 2 million deaths globally with 1/4000 infected and the milder 1968 Hong Kong flu pandemic (influenza A/H3N2) in an estimated 1 million deaths [12]. The most recent pandemic occurred in 2009 (influenza A[H1N1]pdm09). Pandemic influenza strains often cause severe disease among younger, healthy individuals, unlike seasonal influenza strains [13].

Influenza A[H1N1]pdm09 pandemic: In late April 2009, the World Health Organization (WHO) received reports of sustained human-to-human transmission of a new influenza A[H1N1]pdm09 virus strain that was causing community-level outbreaks in Mexico and the United States. Unlike past pandemic influenza viruses, international travel facilitated the rapid geographical spread of this new pandemic virus to all the six WHO Regions in less than 9 weeks. Typically, cases were initially identified in urban centres with high intensity of transmission before spreading geographically within countries.

The majority of cases during the pandemic were mild, self-limiting infections, resolving without antiviral treatment. The highest attack rates were reported in children and young adults with hospitalization rates higher for children <5, in particular those under the age of 1 year. Mortality rates were highest among children, young adults and pregnant women with

90% of deaths occurring in those less than 65 years of age, in contrast to seasonal influenza epidemics [14]. However, although epidemiologic and serologic evidence demonstrated a lower susceptibility for infection in those >65 years of age, the case fatality rate was highest in those over 50 years old [14].

Death in severe cases was caused by severe viral pneumonia and, as with seasonal influenza, underlying conditions, which were risk factors for severe disease with influenza A[H1N1]pdm09 [14] included pregnancy; asthma or other lung disorders; cardiovascular disorders; diabetes; immune-suppression; neurological disorders and obesity.

The number of laboratory-confirmed deaths reported for the pandemic was 18 500, although this is thought to be a vast underestimate of true global mortality, which was estimated to range from 105 700 to 395 600. Significantly, the majority of estimated deaths (51%) occurred in Africa and South East Asia [4].

Avian influenza virus infections in humans

In 1997, the first human influenza A/H5N1 outbreak was reported in Hong Kong Special Administrative Region, China. Before the outbreak was brought under control, due to swift and coordinated containment, a total of 18 cases and 6 deaths were recorded. Since 2003, sixteen countries, representing all WHO regions have reported human infections of A/H5N1 with 840 cases and 447 deaths recorded [15]. To date, human cases and deaths from A/H5N1 have been associated with outbreaks of avian influenza in poultry without sustained human-to-human transmission [3].

In addition to A/H5N1, an increasing number of avian influenza A viruses are being recognized as causing sporadic infections in humans. Human disease caused by some avian viruses can be mild; however, some avian viruses may cause severe disease and mortality.

In 2013, avian influenza A/H7N9 emerged as a human pathogen in China and to date laboratory-confirmed cases have been reported from China, Hong Kong, Special Administrative Region, China and the Taipei Centres for Disease Control [16]. Unlike other H7 viruses (A/H7N7) that usually cause a mild disease in humans, A/H7N9 causes severe disease characterized by rapidly progressing severe pneumonia. Although most cases reported have some association with poultry, for instance visiting a market, a definitive link between poultry and human cases has not been established, as H7 infection in poultry is unapparent. Human infections with other H7 subtypes include A/H7N7, A/H7N3 and A/H7N2 [3].

Other avian influenza A viruses that cause disease in humans include A/H6N1, A/H9N2, which circulate endemically in poultry in many regions of the world, including Africa, and A/H10N8 which causes severe disease in humans [3].

The ability of some known avian influenza viruses, e.g. A/H5N1 and A/H7N9 to cause severe disease in humans, albeit in sporadic cases to date, is of concern. A/H5N1 has been identified in poultry in the Region, and although A/H7N9 has not been identified outside China, it is difficult to detect in the avian population as it exhibits low pathogenicity in poultry. The presence and introduction of avian influenza viruses in Africa is not surprising since large and small-scale poultry farming and trade operations exist and migratory flyways traverse Africa to central and east Asia [17].

If these viruses were to acquire the ability to transmit easily among humans, taken together with the ease of dissemination of influenza, as illustrated by the rapid spread of influenza A[H1N1]pdm09, an influenza pandemic could ensue, with the potential to cause large-scale mortality. Additionally, human activities, such as extensive legal and illegal trade of live birds and poultry products; a relative lack of biosafety in the poultry industry; and the widespread practice of keeping poultry in households increases the risk of Africa being the possible origin of a human pandemic. This stresses the need to further strengthen influenza surveillance activities in the Region, in line with the Integrated Disease Surveillance and Response (IDSR) strategy.

The contribution of zoonotic disease to the global disease burden is increasing. In a dataset analysing human disease outbreaks spanning 1980 to 2013 in 219 countries, 56% of outbreaks were caused by zoonotic agents, highlighting the fact that most new human infections will likely originate from wildlife or livestock, making animals an integral part of human disease outbreaks [18, 19].

The One-Health approach, where not only stakeholders in the area of human health are engaged, but also those in animal health, agricultural and environmental entities, is essential when considering influenza, as it is a natural infection of aquatic (migratory) birds. Extensive work has been done aligning animal and human influenza surveillance activities since controlling influenza at its animal source will not only protect animal health and maintain livelihoods, but will also prevent exposure of humans to animal pathogens and the possible emergence of a pandemic influenza strain. As such, the “Four-Way Linking Project for Assessing Health Risks at the Human-Animal Interface”, a collaboration between WHO, World Organisation for Animal Health (OIE) and UN Food and Agricultural Organisation (FAO) has been established. This project, which aims to capture epidemiological and virological data on animal and human health and to link these data in time and space, has been piloted in a small number of A/H5N1-endemic countries with reported human cases. This type of data provides a more informed picture of influenza infection at the animal-human interface and may aid in the rapid identification of locations where zoonotic infection may occur.

Other organisations and initiatives collaborating with WHO on human influenza and the animal interface include; OIE, FAO, Global Early Warning System for Major Animal Diseases Including Zoonosis and the OIE/FAO Network of Expertise on Animal Influenza (OFFLU).

1.2 Objectives of influenza surveillance

The overall objectives of influenza surveillance in the context of this document are to provide timely epidemiological and virological data so as to better inform national prevention and control activities including immunization.

More specific objectives of influenza surveillance are to:

- (a) Characterize and monitor trends of influenza-associated illnesses and deaths attributable to mild and/or severe acute respiratory illness;
- (b) Identify the start and end of the influenza season and describe seasonality of influenza where feasible;

- (c) Provide data to identify and monitor groups at high risk for severe disease and mortality;
- (d) Provide information to establish baseline levels of activity for influenza-like illness (ILI) and severe acute respiratory illness (SARI), to facilitate assessment of severity and impact of seasonal influenza, providing a context for identification of unusual outbreaks of respiratory disease or a pandemic;
- (e) Monitor antiviral resistance/sensitivity of circulating influenza viruses;
- (f) Provide information on the contribution of influenza to the burden of respiratory diseases in order to prioritize resources and plan public health interventions;
- (g) Provide virus isolates and/or candidate viruses to WHO Collaborating Centres for Influenza Reference and Research and/or A/H5 Reference Laboratories for vaccine selection and production;
- (h) Describe antigenic and genetic characteristics of circulating viruses;
- (i) Identify locally circulating influenza types and subtypes and their relationship to global and regional patterns;
- (j) Provide a platform to monitor impact of control strategies;
- (k) Provide data that will assist in understanding the relationship of virus strain to disease severity;
- (l) Detect unusual and unexpected events such as outbreaks of influenza outside the typical season, severe influenza among health-care workers or clusters of vaccine failures that may indicate the presence of a novel influenza virus event;
- (m) Detect new influenza strains.

It is recognised that all objectives may not be achieved by every system, especially when resources are limited. Member States and health planners are encouraged to identify their own specific priorities for surveillance before establishing a surveillance system or adapting an existing system, since objectives will influence configuration, activities and size of the system. However, it is crucial to establish surveillance systems to enable detection and investigation of the first evidence of sustained human-to-human transmission of an influenza virus with pandemic potential. Under the IHR (2005), a State Party is required to notify WHO of the first occurrence of human influenza caused by a new subtype. Table 1 describes public health outcomes that can be achieved by adopting and meeting related influenza surveillance goals.

Table 1: Objectives of influenza surveillance and its use in achieving public health outcomes [1].

Principal Objective	Use of surveillance data in decision-making
Determine when and where influenza activity is occurring and who is affected	Alert health-care providers to anticipate influenza disease in clinics and hospitals. Inform and target national prevention and treatment policies such as vaccination timing and the use of pharmaceutical and non-pharmaceutical interventions to control spread.
Detect changes in the antigenic and genetic characteristics and antiviral sensitivity of influenza viruses	Inform local clinician of antiviral therapies.

Principal Objective	Use of surveillance data in decision-making
	Inform choice of vaccine locally and selection of appropriate viruses globally
Determine and monitor underlying risk conditions that are associated with severe disease and use of health-care resources. Describe the clinical patterns of disease	Improve clinical management and prevention of disease in high-risk patients
	Inform national policies such as priority groups for vaccination and treatment
Assess and monitor relative severity of annual epidemics or an outbreak of a novel virus	Assist policy-makers in making decisions about public interventions
	Inform cost-benefit type decisions related to public interventions
Estimate contribution of influenza to severe respiratory illness or overall disease burden	Allow appropriate allocation of limited health resources among competing disease-related priorities
	Establish epidemic thresholds for comparison of disease severity between years and localities
	Contribute to global knowledge base regarding burden of disease attributable to influenza disease
Detection of unusual events	Rapid detection to alert international health regulation focal points about potential public health events of international concern
Measure impact of interventions	Inform choice of intervention strategies

1.3 WHO Global Influenza Surveillance and Response System (GISRS)

The World Health Organization GISRS was founded in 1952 as a surveillance system made up of laboratories and collaborating centres around the world. Formerly known as the Global Influenza Surveillance Network (GISN), the objective of the GISRS is to monitor circulating influenza viruses in order to make annual recommendations on influenza vaccine composition for the northern and southern hemispheres. It also functions as a global alert mechanism for the emergence of novel influenza viruses with pandemic potential.

The network currently comprises six WHO Collaborating Centres, four WHO Essential Regulatory Laboratories and 142 institutions in 112 WHO Member States, which are recognized by WHO as National Influenza Centres, in addition to ad hoc groups established to address specific emerging issues [20]. Since the 2009-2010 pandemic, laboratory capacity to diagnose influenza infections by RT-PCR in the African Region has grown, with 30 countries out of 47 (64%) now able to detect influenza infection.

1.4 Integrated Disease Surveillance and Response and International Health Regulations

In 1998, the Integrated Disease Surveillance (IDS) strategy was developed and subsequently adopted by Member States in the WHO African Region, in response to significant outbreaks of infectious diseases in the Region in the preceding years, to build a comprehensive public health surveillance and response system for infectious diseases, while conserving health resources. The strategy provides guidance and requirements for collecting, analysing and reporting of disease surveillance data involving all levels of the health system from community clinics to national health facilities. Initially, the IDS strategy identified and focused on 19 priority diseases. Following the 2009 influenza A[H1N1]pdm09 pandemic, IDS was expanded to include diseases or events of international concern and a framework for event-based surveillance and response. The revised strategy, renamed Integrated Disease Surveillance and Response (IDSR), aligns with and satisfies surveillance and response requirements of IHR [21].

The International Health Regulations (2005) [22] mandate that WHO Member States meet minimum core capacity requirements in regard to surveillance, reporting, notification, verification, response and collaboration activities for Public Health Events of International Concern (PHEIC). When compared, IHR and IDSR share similar functions (Figure 1) and in the WHO African Region, surveillance activities mandated in IHR are implemented in the context of IDSR.

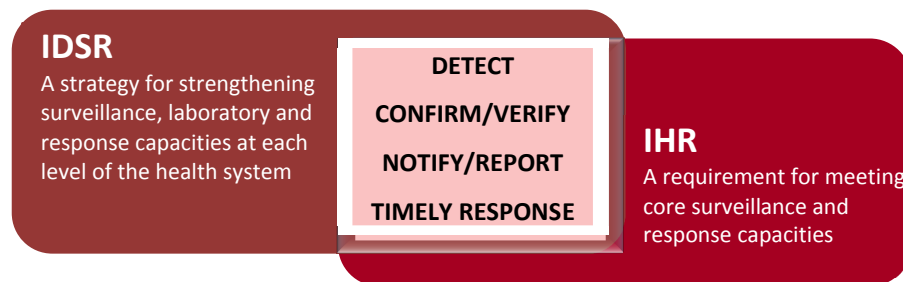


Figure 1: Relationship between IDSR and IHR [23]

The broad objective of IDSR is to strengthen the capacity of countries to conduct effective surveillance for multiple diseases by integrating and streamlining common surveillance activities and utilizing all levels of the health structure, reducing the burden on resources. Specific objectives include: to strengthen the capacity of countries to conduct effective surveillance activities; integrate multiple surveillance systems; improve use of information to detect change in order to respond rapidly; improve flow of surveillance information; strengthen laboratory capacity and involvement in pathogen detection and monitoring; increase involvement of clinicians; emphasize community participation; and trigger epidemiological investigations. In addition, IDSR incorporates the One-Health strategy, thereby promoting collaboration between national ministries of health and stakeholders in the animal health sector to identify and mitigate public health risks at the human-animal interface caused by influenza virus.

Provision is made within IDSR for surveillance of ILI, SARI and Human Influenza caused by a new subtype. Therefore, establishment of sentinel surveillance for influenza-associated ILI

and SARI should be integrated with current IDSR activities, rather than introducing another tier of surveillance activities.

2. JUSTIFICATION FOR INFLUENZA SENTINEL SURVEILLANCE

Influenza is estimated to result annually in 3 to 5 million cases of severe illness and 250 000 to 500 000 deaths worldwide, with those most at risk for severe disease being children under the age of 5, adults over 65 years of age, pregnant women and those with co-morbidities [24].

Increased mortality during influenza epidemics is caused by pneumonia and influenza, and also by cardiopulmonary and other chronic diseases (e.g. diabetes) that can be exacerbated by influenza virus infection [25-27].

There are limited data regarding the epidemiological patterns, risk factors and burden of influenza disease and the economic impact of influenza in tropical and subtropical regions in particular the WHO African Region. Although it is thought that acute respiratory infections are a major contributor to morbidity and mortality in Africa, with the burden of disease comparable to that in developed countries, the extent of its impact in the Region is still unclear. The recent pandemic highlighted that additional risk factors for severe disease and death from seasonal influenza, aside from poor nutritional status and poor access to health care (including vaccination and antibiotics), included HIV infection and active tuberculosis [28].

The establishment of influenza surveillance in countries with access to influenza virus testing would strengthen ILI and SARI surveillance and provide both epidemiological and virological data to meet current knowledge gaps. Furthermore, establishing influenza surveillance would enhance national capacities, enabling health systems to be better prepared against seasonal, zoonotic and pandemic influenza threats to populations and individuals.

A robust influenza surveillance system provides improved timely notification of unusual cases or unusual numbers of cases of influenza to health authorities and policy-makers so that informed decisions on containment, treatment and vaccination strategies can be formulated.

To help strengthen the capacity of national surveillance systems to detect influenza, the Regional Office has developed and disseminated standard operating procedures for enhancing influenza surveillance within the context of the Integrated Disease Surveillance and Response (IDSR) strategy, and countries in the Region have established epidemiological surveillance for severe acute respiratory infection (SARI) as part of IDSR.

As of May 2015, over 64% (30/47) of countries in the Region have developed laboratory capacity for influenza diagnosis using the minimum standards as recommended by WHO [1] and 45% (21/47) are implementing virological surveillance for influenza and contributing to Weekly Influenza Surveillance in the WHO African Region, in addition to FluNet. About 10 countries have been collecting and reporting both epidemiological and virological data from patients with ILI or SARI. The relative lack of linked virological and epidemiological data and information on the magnitude of disease burden has limited the Region's ability to plan and implement strategies for reducing morbidity and mortality associated with influenza.

Sentinel surveillance, which uses only selected surveillance sites, enables collection of high quality epidemiological and virological data in a timely way that is representative of a national population, with regard to demographics and geography. One of the advantages of the sentinel surveillance approach is that it requires fewer resources, since the number of sites collecting laboratory specimens for influenza testing is reduced. Also, sentinel surveillance can be integrated with current surveillance activities thereby reducing the burden on resources. A disadvantage is that, although sentinel surveillance data may be useful for documenting trends, the data may not cover the general population if sentinel sites are not selected in such a way as to provide data that are representative of the whole population.

Sentinel influenza surveillance will help inform national and regional prevention and control strategies. In addition, virus sharing through GISRS will contribute to evidence-based decisions on seasonal vaccine composition, enable assessment and monitoring of circulating viruses for antiviral susceptibility, and enhance detection of novel influenza viruses that may have pandemic potential.

The WHO ARFO Regional Office has been working with partners in supporting the establishment and functioning of influenza sentinel surveillance systems. Influenza laboratories are organized to form a regional network of laboratories, some of which are NICs. Participation of Member States in the Regional Influenza Laboratory Network enhances understanding of the epidemiology and impact of influenza and sharing of best practices in the African Region. This also facilitates detection and reporting of new strains of influenza viruses with pandemic potential.

2.1 Regional Influenza Laboratory Network

As of May 2015, the Regional Influenza Laboratory Network is composed of National Influenza Laboratories in 30 countries. All of these countries have laboratories with capacity to perform influenza PCR. However, many laboratories do not perform virus isolation. Thirteen of these countries have laboratories that are designated WHO NICs and members of the Global Influenza Surveillance and Response System (GISRS)¹. These laboratories have enhanced laboratory capacity and are able to perform virus isolation and typing/subtyping of viral isolates. From a virological surveillance perspective, using PCR and virus isolation is optimal and recommended.

The remaining countries have laboratories with capacity to perform influenza PCR. Selected laboratories in the network have enhanced laboratory capacity and are able to perform virus isolation and typing/subtyping of viral isolates.

The goals of the Regional Influenza Laboratory Network are to:

- (a) Build national laboratory capacity in African countries to conduct virological testing for influenza and other respiratory diseases;
- (b) Provide all countries with access to virological testing for influenza;
- (c) Strengthen intra and inter-country laboratory specimen collection and transport components of national laboratory networks;

¹¹ Algeria, Cameroon, Central African Republic, Cote d'Ivoire, Ghana, Kenya, Madagascar, Mauritius, Nigeria, Senegal, South Africa, Uganda and The United Republic of Tanzania.

- (d) Build the foundation for future studies on the impact of viral respiratory disease prevention and control interventions.

3. NATIONAL INFLUENZA SENTINEL SURVEILLANCE

Sentinel surveillance has the potential to provide good quality/reliable data about some of the epidemiologic characteristics of influenza-like illness (ILI) and severe acute respiratory infection (SARI) at a particular sentinel surveillance site, and also to determine proportions of ILI and SARI cases that are due to influenza.

Countries should determine their information needs and surveillance objectives when considering their National Influenza Sentinel Surveillance plan.

3.1 Objectives of national sentinel influenza surveillance

Objectives of national sentinel influenza surveillance for ILI/SARI in a national context mirror those outlined in section 1.2.

Broadly, these objectives include monitoring influenza viruses, disease trends and risk factors and estimating the burden of disease. Specifically, they are to:

- (a) Provide data on:
 - (i) Comparative virology of mild and severe disease;
 - (ii) Underlying conditions most frequently observed in individuals hospitalized or with severe disease with laboratory-confirmed influenza;
 - (iii) Demographics of influenza, in particular those hospitalized or with severe influenza (laboratory confirmed).
- (b) Provide isolates for monitoring viral genetic make-up or reassortment, which may affect vaccine efficacy, virus severity, or antiviral susceptibility.
- (c) Provide a mechanism to establish baseline thresholds of disease and trends of both mild and severe disease in humans.
- (d) Provide a platform for surveillance that includes other respiratory pathogens that may be of national interest.
- (e) Provide data that can contribute to the burden of severe respiratory disease associated with influenza and other respiratory pathogens.

3.2 Relationship to early detection of signal events

A national sentinel surveillance system can support pandemic planning by providing country-specific data, supporting laboratory and epidemiologic infrastructure for alert and response activities and by providing an established means to monitor severity, intensity and progression of pandemic cases.

A national surveillance system can also help identify early warning signs of a novel influenza or a virus that may have pandemic potential. Events such as clusters of SARI cases in people

with social connections within a 2-week period, pneumonia in health-care workers or people with an occupational or social connection and changes in the epidemiology of SARI including a shift in age distribution, increase in mortality or in the number of cases may be early warning signs of circulation of a new respiratory pathogen [29].

The surveillance methodology outlined in this protocol does **not** describe a pandemic early warning system or a system for rapid detection of emerging novel influenza strains or outbreaks. Sentinel surveillance does not recognize signal events nor does it have the reporting mechanism that accompanies this strategy.

Establishing an early-warning event-based surveillance system and methods for outbreak investigation, with a view to meeting IHR core capacities, can be found in the IDSR technical guidelines [23, 30].

3.3 Purpose of protocol

Historically, the global influenza surveillance system has focused primarily on virological surveillance, and so data collected have not included the epidemiological information needed to support influenza control strategies, such as impact of the disease and individuals at highest risk in a community. There is a need to better understand the epidemiology, seasonality and economic burden of influenza in order to better target disease interventions in countries in the AFRO Region.

The influenza A[H1N1]pdm09 2009 pandemic highlighted the need for rapid reporting of cases to assess the severity of the disease and to define risk factors for severe outcome. This pandemic also identified knowledge gaps and highlighted the need to strengthen both epidemiological and virological surveillance systems in the African Region.

The purpose of this document is to provide guidance to Member States on establishment of a sentinel influenza system or on integration of sentinel influenza surveillance into an existing framework.

The sentinel surveillance activities described in this document are intended to provide background rates and trends that will help health-care officials to assess the importance of unusual events, such as outbreaks, and will provide health-care planners with data that will help them to understand the contribution that influenza makes to the overall burden of respiratory disease and to further understand the seasonality phenomenon.

Sentinel surveillance is not intended to serve as the sole method for providing early warning of an unusual event. A sentinel surveillance system should, therefore, be complemented by a more sensitive event-based surveillance system covering all aspects of the health-care system. The detection, reporting and investigation of such unusual events are described in the IDSR guidelines which incorporate IHR [23].

This protocol **is not** intended to give guidance for setting up an early warning system or event-based surveillance, as this information is captured in the Regional IDSR guidelines. The protocol is meant to provide a platform for health-care systems to address core capacities required by Member States to satisfy the IHR.

Target audience

The target audience for this document includes, but is not limited to: National surveillance bodies; communicable disease epidemiologists; clinicians and laboratory specialists responsible for influenza surveillance; personnel at sentinel sites conducting surveillance activities as described in this document; and any other health-care professional involved in sentinel surveillance activities for influenza-like illnesses, including severe acute respiratory infections as described in this document. This document can also be used as reference for animal health sectors to promote implementation of influenza surveillance at the human-animal interface, in line with the One-Health approach.

3.4 Components and Structure of National Sentinel Surveillance System

Sentinel Site

- (a) ***Sentinel hospital for SARI surveillance:*** Sentinel surveillance for illnesses and deaths that meet the case definition for SARI is implemented in sentinel hospitals. Clinical specimen and epidemiological data from SARI patients should be collected by trained medical personnel, in accordance with national procedures. It should be noted that SARI is one of the IDSR priority diseases; it is, therefore, recommended that data be regularly collected/reported through the weekly or monthly reporting system.
- (b) ***Sentinel site for ILI surveillance:*** Ambulatory clinic-based sentinel surveillance for illnesses that meet the case definition of ILI is implemented in one or more sentinel surveillance sites, e.g. hospital outpatient clinic. Specimens from ILI patients should be collected by trained medical personnel in accordance with national procedures.

Sentinel site(s) in a country can be either public or private health facilities.

National Influenza Laboratory (NIL)

This is any laboratory that has the required capacity to perform testing for influenza, according to the minimum standards as outlined in Global Epidemiological Surveillance Standards for Influenza. It may also be from where specimens and/or viral isolates are forwarded to a collaborating inter-country laboratory, a WHO Collaborating Centre for Reference and Research on Influenza (WHO CC) or a WHO reference laboratory for the diagnosis of influenza A/H5 infection for testing and characterization.

Depending on laboratory capacity of the country, an NIL may be:

- (a) Regional hospital laboratory;
- (b) National Reference Laboratory;
- (c) National Influenza Centre (NIC);
- (d) WHO Collaborating Centre for Reference and Research on Influenza;
- (e) WHO Reference Laboratory for Diagnosis of Influenza A/H5.

Influenza surveillance also requires efficient and safe specimen collection, packaging and transportation system. Countries that do not have a NIL should consider collaborating with an

influenza laboratory in a neighbouring country (NIC or WHO CC) or plan to develop laboratory capacity for influenza.

National Surveillance Unit/Coordination Point/Focal Point:

The national surveillance unit (NSU) or structure is responsible for coordinating and monitoring data collection, reporting, analysis and feedback. It is important to promote rational use of resources by integrating influenza sentinel surveillance into the IDSR surveillance unit.

3.5 Methods and procedures

Implementation

Ideally, both ILI and SARI surveillance should be implemented within a country. Collecting information on both illnesses provides a more complete picture of the epidemiology of influenza disease. Although it is useful to monitor both ILI and SARI to identify trends in the population, it is advantageous to implement SARI surveillance so that target groups for vaccination and severe strains of influenza can be identified in a timely manner.

If a country does not have an existing surveillance mechanism for respiratory disease surveillance, a step-wise approach in the establishment of an influenza sentinel surveillance system is recommended. The principal goal is to achieve surveillance sustainability, therefore integration of ILI and SARI surveillance into existing public health systems is advocated. Countries must establish minimum standards for inpatient and outpatient respiratory disease surveillance reporting, data collection and analysis, and adopt international standard case definitions and procedures where possible.

At a minimum, a surveillance system might consist of a single site, made up of both inpatient and outpatient facilities in a district hospital. This site could cover ILI and SARI surveillance, with the latter being important for obtaining epidemiological data on severe cases. Expansion beyond the initial site would be dependent on the availability of resources and experience in running the first site. A suggested structure for organizing a sentinel influenza surveillance system is illustrated in Figure 2.

Duration of surveillance

In tropical and sub-tropical regions, where there is no well-defined influenza season and where transmission is sometimes continuous, **surveillance should be maintained all year round**. If routine surveillance activities are suspended during periods when influenza transmission is known to be low, Member States should maintain surveillance activities aimed at early identification of unusual influenza-related events or other viral respiratory pathogens during this period.

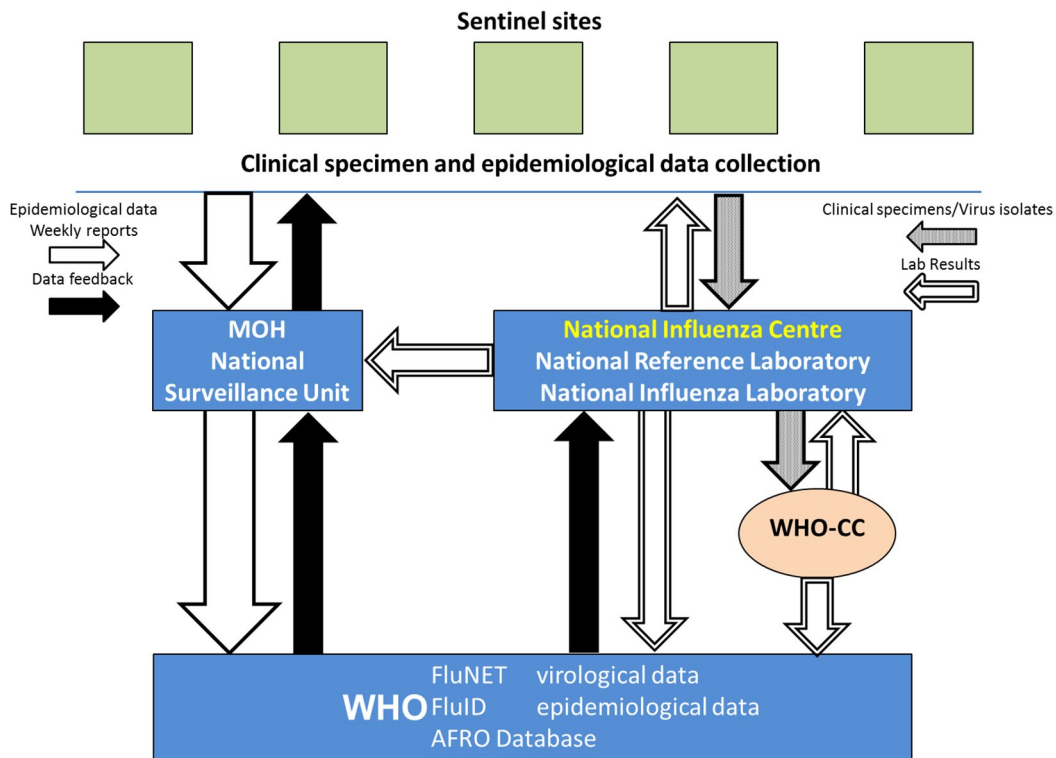


Figure 2: Suggested flow of surveillance data

3.6 Case Definitions

To maintain consistency and accuracy in international, national and local influenza surveillance data collection and reporting, the following standardized case definitions for ILI and SARI, as defined by WHO, must be used to select patients for inclusion [1].

Surveillance case definitions for ILI and SARI

ILI case definition
 An acute respiratory infection with:

- measured fever of $\geq 38\text{ C}^\circ$;
- and cough;
- with onset within the last 10 days.

SARI case definition
 An acute respiratory infection with:

- history of fever or measured fever of $\geq 38\text{ C}^\circ$;
- and cough;
- with onset within the last 10 days;
- AND requires hospitalization.

3.7 Selection and location of sentinel sites

The selection of sentinel sites will depend on multiple factors, many of which are specific to a country or location. Selection will also depend somewhat on the primary goals of surveillance for individual countries. For example, a country whose primary goal would be to estimate the incidence of severe influenza-related illness would want to select sites in areas where it may be possible to estimate the population served by the site (i.e. the "denominator" for incidence measures). On the other hand, countries that have a primary interest in risk groups may place a site in an institution that would see a broad range of patients that are not "preselected" by underlying disease or age so that results of the surveillance activity would provide an unbiased view of risk groups such as children under 5 years, but especially those under 2 years, adults 65 years of age and older and pregnant women, etc. These two objectives are not mutually exclusive, and with care it may be possible to choose a site that would provide data to meet most of the surveillance objectives.

The following factors should be considered when selecting sentinel surveillance sites:

(a) Representativeness

Ideally, sites should represent the population of interest. For ILI sentinel sites, general outpatient clinics or acute care facilities represent a wide range of patients. For SARI sentinel sites, general or community hospitals are preferred to specialty care or referral hospitals in order to provide an unbiased selection of cases. Potential sites may include paediatric and adult medical, maternity, antenatal, postnatal and intensive care units.

(b) Location

The sentinel sites should represent a wide cross-section of socioeconomic groups and the different climatic and geographic regions and any other relevant characteristics of the country and its population, to capture the epidemiological characteristics of influenza. Countries are encouraged to distribute, as best as they can, sentinel sites so as to include both urban and rural locations.

(c) Logistics

It is preferable to select sites that are easily accessible for supervision, delivery of supplies and transportation of specimens. Each site should be easily accessible for supervision, delivery of supplies and transportation of specimens.

(d) Availability of Denominators²

- (i) If possible, the sentinel site should be selected from a location where denominators are available, estimates of the service population or rates of total consultations or admissions are easy to obtain, and where the service population is representative of groups of national interest such as urban, rural or national representation.
- (ii) It is recommended that a country prioritize collection of good quality surveillance data, starting with one or two sentinel sites and then gradually expanding to other sites. Adequate piloting and evaluation should be performed before adding new sentinel sites.

² Global Influenza Programme, World Health Organization. A manual for estimating disease burden associated with seasonal influenza in a population.

(e) Patient Volume

Patient volume should be adequate to allow meaningful monitoring of respiratory disease trends and evaluation of risk factors, but not so high as to be overwhelming or unmanageable. Very low-volume facilities will likely provide too few cases to allow meaningful interpretation. On the other hand, facilities with huge, unmanageable patient volumes will make interpretation of data very difficult, due to inability to understand what fraction of the total is being captured, to systematically select cases in an unbiased way, or to understand the representativeness of data.

(f) Feasibility

The feasibility of a facility to participate in the sentinel surveillance system is of paramount importance and country ownership is crucial when selecting sites. The following criteria should be considered when assessing feasibility of a prospective site:

- (i) That sentinel site/facility staff and management be committed and motivated to implement and sustain surveillance activities;
- (ii) Commitment and motivation of local staff to follow regional and national influenza surveillance guidelines;
- (iii) A site's ability to routinely collect, manage and report surveillance data, including communication infrastructure;
- (iv) Comparative low implementation cost, in relation to other sites, and available stable, long-term funding to cover cost of maintaining surveillance at the site;
- (v) Capacity and an efficient, consistent and sustainable mechanism of site to collect, store, and transport laboratory specimens is imperative.

A checklist to help in identifying and selecting suitable sentinel sites is provided in Annex 1.

NB: It is crucial to promote innovative approaches for maintaining functionality of selected sentinel sites; these may include organization of regular training sessions, sentinel site supervision and annual meetings to evaluate activities being conducted by each site and to promote sharing of best practices.

3.8 Case selection and sampling strategy/protocol

The number of patients sampled for laboratory testing will depend on the ability of sentinel sites to process, store and ship specimens as well as the capacity of the laboratory to process, store and test specimens. A review of admission or consultation books, or discharge diagnoses is recommended to estimate the numbers of SARI and ILI patients seen by the facility throughout the year before selecting a particular site.

Consultation and coordination between the national surveillance unit, national influenza laboratory and sentinel site(s) are essential to ensure capacities are accurately estimated so as to implement an unbiased sampling method. The maximum number of specimens that theoretically could be processed weekly by a laboratory should correlate with the maximum number of patients sampled. An appropriate sampling strategy should be determined for each disease.

Selection of SARI cases for laboratory testing and epi data collection

Ideally, every SARI patient or most SARI cases should be sampled, and all specimens tested. Where it is not possible to test all SARI cases, a non-biased sampling strategy should be defined.

Sampling strategies

Sampling should be based on a systematic selection scheme (interval sampling). For example, the testing of **every n th case of ILI or SARI**, with n being equal to the number of weekly ILI or SARI seen by the facility divided by the maximum number of specimens that can be processed by the laboratory in a week. For example, if a hospital admits 80 SARI patients weekly during the peak of the influenza season, and if the maximum number of specimens that the laboratory can process every week is 20, then a suitable systematic sampling would be every fourth (4th) SARI case.

In case neither the random selection nor the systematic selection approach is feasible, it may be more appropriate to use another method. A reasonable alternative would be to collect specimens and data from **all SARI and ILI cases on a specific day or days of the week**. In order to avoid bias, different days of the week should be used during consecutive weeks. For example, a site might sample and test every case that comes in on a Tuesday and Thursday of a given week, then Monday and Saturday of the subsequent week, and Wednesday and Friday of the week after.

The method, which is most likely to introduce bias, and therefore not recommended, is to collect specimens from **the first x patients each day**. Health-seeking behaviour patterns differ in different groups and so working adults, for example, are less likely to come to seek care during normal office hours.

Inclusion criteria

To be tested for influenza, patients should meet the following criteria:

- (a) **The clinical case definition for SARI or ILI;**
- (b) The onset of symptoms falls within 10 days of specimen collection;
- (c) The patient is systematically chosen for testing (see above);
- (d) Patient or guardian consent (verbal/written) to specimens being collected.

If a patient does not meet all the criteria, declines testing or is not tested for any other reason, the next patient with SARI or ILI should be tested.

Assigning unique ID numbers

Each case will be assigned a unique identifier so that laboratory and epidemiological data may be linked. The protocol for assigning unique identifiers should be standardized throughout the country so that identifiers are not repeated. This identifier will be assigned to cases at the time of specimen collection and the associated epidemiological forms completed. This number will be written on any forms or specimens from that case sent to the national surveillance centre and the laboratory.

An example of assigning unique identification numbers is as follows:

- (a) The first three numbers specify the sentinel site code. *In this example, the site is 034*
 - Each sentinel site in the country will be assigned a number by the national coordinating authority.
- (b) The next two-digit number indicates the year of symptom onset. *In this example the year is 2009.*
- (c) This is followed by one number that indicates whether the case is SARI or ILI (e.g. 1=SARI, 2=ILI). *In this example it is an ILI case.*
- (d) The last four-digit number is the case number. *In this example, it is the 23rd case identified at this site.*
 - This is assigned as SARI and/or ILI case as found at each sentinel site. The case number should begin with the number 1 at the beginning of each influenza season, and at each sentinel site.

(Sentinel Site) (Year) (SARI or ILI) (Case Number)
034 /09/ 2 /0023

3.9 Specimen collection

Successful diagnosis of influenza in clinical specimens depends mainly on the quality of the specimen, how it is stored and transported prior to processing. It is recommended that clinical specimens be taken as soon as possible following onset of symptoms, preferably within three (3) days but up to seven days of symptom onset. Specimen collection for hospitalized SARI cases may occur when patients are being assessed for admission in an emergency room or after their admission to the ward. Ambulatory cases that meet the case and inclusion criteria should have clinical specimens taken at the time of assessment at the sentinel site.

Preferred clinical specimens for upper respiratory infections and influenza testing for ILI and/or SARI cases include:

- (a) Nasal (from the anterior turbinate area) or nasopharyngeal swab;
- (b) Nasopharyngeal aspirate;
Nasal and nasopharyngeal (NP) specimens have a higher yield for influenza virus detection in ILI cases than do oropharyngeal (OP) specimens.
- (c) Throat swab;
- (d) Combined nasal and throat swab;
- (e) Nasal wash;
- (f) Throat wash.

For SARI cases, the relative sensitivity of NP and OP swabs to detect influenza virus infections is unknown. If both specimens are collected, they can be placed in the same tube of viral transport media for processing. If patients are intubated, the following specimens can be collected where clinically indicated:

- (a) Endotracheal aspirate;
- (b) Bronchoalveolar lavage.

Serum can also be collected for diagnosis by serology; however, this method is not frequently used for influenza diagnosis as it requires paired serum specimens collected weeks apart.

Clinical specimens from SARI and ILI cases should be collected in accordance with the procedures outlined in Annex 2 and the WHO Global Influenza Surveillance Network: Manual for the laboratory diagnosis and virological surveillance of influenza, using appropriate biosafety procedures [31, 32].

Individuals at sentinel sites collecting and shipping infectious material should be trained in biosafety procedures and shipping of infectious substances [31-33]. WHO supports Member States to participate in the Infectious Substances Shipping Training (ISST).³ This training enables health workers to be certified as a “Shipper of Dangerous Goods Specialization in Infectious Substances”.

3.10 Storage and Transport of Specimen (Processing at Sentinel Site)

The successful detection of influenza virus in patient specimens not only depends on the quality and timing of patient specimen but also on the use of appropriate storage and transport conditions (Annexes 3 and 4). Specimens should be stored in viral/universal transport medium (VTM/UTM) or a suitable medium before transport to a laboratory[5]. If specimens are to be transported within 48 hours, they can be stored at 4°C before and during transportation. If specimens cannot be transported to the laboratory within 48 hours, it is recommended to store them at -70 °C or keep them on ice or in the refrigerator (4°C), for as long as necessary, until they are transported to the laboratory. **Do not subject specimens to freeze and thaw cycles** as this destroys virus viability. Specimens should not be stored in a standard -20°C freezer because of freeze-thaw cycles. It is preferable to keep specimens on ice, even for a week, than to allow them to freeze and thaw multiple times.

Ideally, specimens should be sent as soon as possible to the laboratory accompanied by a copy of the data collection and investigation form. Commercial transport media or media developed at the laboratory can be used in accordance with WHO guidelines (see Annex 3 [5]).

Clinical specimens should be packaged and transported to the National Influenza Laboratory in accordance with current WHO guidance on transportation of infectious substances ([33] and summarized in Annex 4).

The WHO Shipping Fund Project provides logistic support for sharing of viruses with GISRS by means of providing shipping and transport of specimens from National Influenza laboratories to WHO CC or A/H5 Reference laboratories. For detailed information, contact WHO Headquarters: girs-who@who.int

3.11 Laboratory testing

The NIL is responsible for testing clinical specimens for diagnosis of influenza. The minimum recommended laboratory test for detection of influenza in specimens is reverse transcriptase polymerase chain reaction (RT-PCR) and/or virus isolation [5, 34]. If possible,

³ http://www.who.int/ihr/i_s_shipping_training/en/

influenza virus isolation and preliminary antigenic and genetic characterization of the virus may be performed if appropriate laboratory capacity is available.

The NIL should immediately forward to a WHO CC:

- (a) Clinical specimens or viral isolates from influenza viruses that cannot be readily identified using reagents or protocols provided through the WHO GISRS;
- (b) Representative viral isolates from:
 - (i) Beginning, peak and end of the season;
 - (ii) Outbreak investigations;
 - (iii) Severe or unusual cases;
 - (iv) Any low reacting viruses in the haemagglutination inhibition test.

The laboratory should record frequency and percentage of positive viruses by type and subtype. Results should be reported to the sentinel site that submitted the specimen and collated data reported to the NSU using standardized data reporting forms (Annexes 7, 8 and 9). The National Influenza Laboratory or NSU should also report virological results to WHO via the FluNet (www.who.int/flunet) web portal. If a regional reporting system that is linked to FluNet is available, data may be entered through this system.

If influenza A(H7N9) is suspected, and the laboratory has the required biosafety infrastructure to perform diagnostic testing of H7N9 specimens, technical guidance on the detection of avian influenza A(H7N9) virus is available from WHO and should be consulted prior to specimen manipulations [35]. If the required laboratory infrastructure is not available, suspected H7N9 specimens should be shipped to a WHO CC for testing.

Any specimens suspected of being positive for avian influenza A(H5N1) [A/H5] virus or any highly pathogenic influenza viruses should be handled and tested using appropriate biosafety protocols. If the required level of biosafety for analysis of A/H5 specimens is not met, specimens should be shipped to a WHO Reference Laboratory for Diagnosis of Influenza A/H5.

3.12 Data Collection

Epidemiological data collection

Surveillance for severe acute respiratory infection

The following data, as minimum information from each SARI case from whom a specimen is collected*, should be recorded using a standardized data form (see following page(s) for examples of a standardized reporting form(s):

- (a) Unique identifier (to link laboratory and epidemiological data, and for tracking patients if necessary);
- (b) Sex;
- (c) Age;
- (d) History of fever and body temperature at presentation;

- (e) Date of onset of symptoms;
- (f) Date of hospitalization (SARI patients only);
- (g) Date of specimen collection;
- (h) Antiviral use for present illness at the time of specimen collection;
- (i) Seasonal influenza vaccine status; date of administration;
- (j) Pregnancy status (for women in reproductive age);
- (k) Presence of chronic pre-existing medical illness(es):**
 - (i) Chronic respiratory disease;
 - (ii) Asthma;
 - (iii) Diabetes;
 - (iv) Chronic cardiac disease;
 - (v) Chronic neurological or neuromuscular disease;
 - (vi) Immunodeficiency, including HIV;
 - (vii) Chronic haematological disorders;
 - (viii) Chronic liver disease (optional);
 - (ix) Chronic renal disease (optional).

The inclusion of additional epidemiological indicators can be considered in specific circumstances, depending on country surveillance priorities, and may include:

- (a) Signs and symptoms of illness;
- (b) Smoking history;
- (c) Infection with tuberculosis and status of infection (i.e. latent or active);
- (d) Specific haematological disorders e.g. sickle cell disease or thalassemia major;
- (e) Height and weight (to determine body mass index);
- (f) Patient outcome (death, survival).

*If specimens are not collected from all SARI cases, due to limitations in laboratory capacity and/or the sampling strategy selected, it is recommended that a line list of all SARI patients, which includes the following information: Unique ID (if assigned), name, age and gender, be recorded.

**The WHO standardized list of pre-existing medical illnesses or co-morbid conditions includes both known and suspected risk factors for severe influenza disease. The list is based on available data from seasonal and pandemic influenza. For definitions of pre-existing medical conditions, see Appendix 5.

A copy of the SARI/ILI data collection form must accompany each SARI patient specimen sent to the laboratory for testing.

The following SARI epidemiological data should be collated by age-group (Annex 6) and reported **weekly**, using a standardized data reporting form (an example of a form is provided on the following page):

- (a) Number of total hospital admissions for that week (The number of total admissions can often be calculated from the log book of the hospital admissions/discharges);
- (b) Number of new SARI case admissions;
- (c) Number of new SARI cases for whom specimens and epidemiological data have been collected;
- (d) Proportion of sampled SARI cases that are positive for influenza;
- (e) Number of SARI deaths;
- (f) Catchment population.

SARI Data Collection Form

Sentinel site # _____ **Date form completed:** _____

CASE DEFINITION: Acute respiratory infection

with:

fever or measured fever of $\geq 38\text{ C}^\circ$

cough

onset within the last 10 days

AND hospitalization

DATA COLLECTION FORM FOR SAMPLED CASES

ID number:	Date of symptom onset:	Date of hospitalization:	Date of specimen collection:
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IDENTIFICATION

Patient's name: (family name), (given name(s))

Age: Years _____ Months _____

Address: _____ **Contact Telephone Number(s):** _____

PRE-EXISTING MEDICAL CONDITIONS

<input type="checkbox"/> Heart Disease <input type="checkbox"/> Asthma <input type="checkbox"/> Chronic Lung Disease <input type="checkbox"/> Liver Disease <input type="checkbox"/> Diabetes <input type="checkbox"/> Chronic haematological disorder	<input type="checkbox"/> Chronic neurological disease <input type="checkbox"/> Chronic renal disease, <input type="checkbox"/> Neuromuscular Dysfunction <input type="checkbox"/> Immune compromised <input type="checkbox"/> Other _____ <input type="checkbox"/> Unknown	Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female If Female: <input type="checkbox"/> Pregnant: _____ trimester
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VACCINES AND ANTIVIRALS

Exposure to influenza antiviral drugs during the last 14 days? None
 Yes, patient
 Yes, household contact
 Unknown

If Yes, name of antiviral: _____

Vaccination for influenza in current season? Yes No Unknown Date: _____

PATIENT OUTCOME - SARI

Patient outcome: Discharged alive Died Unknown

Was the patient admitted to the ICU? Yes No Unknown No ICU in hospital

Did the patient require mechanical ventilation during this hospitalization? Yes No Unknown

LABORATORY RESULTS – to be completed by laboratory staff

Type of specimen collected: nasal swab throat swab other _____

Laboratory confirmation method: PCR/RT-PCR Viral Culture Immunofluorescence (IFA) other _____

Test result: Influenza A/H1
 Influenza A/(H1N1)pdm09
 Influenza A (not subtyped)
 Other influenza subtype _____

Influenza A (H3)
 Influenza A (H5)
 Influenza B
 Other respiratory pathogen _____

Date of testing: _____ Name/ID of person collecting specimen: _____

REPORTING INFORMATION

Name of Reporting Doctor: _____ Telephone Number(s): _____

Name of Person Completing Form: _____ Signature: _____

Send one copy of this form to the confirmatory laboratory with the specimen and one copy to the national surveillance unit. The original form should be kept at the surveillance site.

Weekly Aggregated Data form for SARI

Sentinel Site ID
Number: _____

Reporting week # _____ From(date) _____ to _____

	Age Distribution (years)						Total
	0-<2	2-<5	5-<15	15-<50	50-<65	≥65	
Number of total hospital admissions*							
Number of new SARI case admissions							
Number of new SARI cases from whom specimens and epidemiological data have been collected							
Number of SARI specimens tested							
Proportion of specimens tested that are positive for influenza							
Number of SARI deaths							
Catchment population**							

*Excluding labour and delivery and elective surgery

** Likely to be the same for several weeks.

Surveillance of influenza-like illness in sentinel sites

Procedures for ILI surveillance data collection are similar to those for SARI surveillance. ILI data must be reported independently of SARI data.

Minimum case-based data, as described above for SARI cases (except date of hospitalization), should be collected for every sampled ILI case from whom a specimen is collected, using a standardized data collection form. An example is provided on the following page.

Clinical specimens collected from ILI patients are to be collected, packaged and transported to the NIC or the National Influenza Laboratory for testing. A copy of the SARI/ILI data collection form must accompany each ILI patient specimen sent to the laboratory.

The following epidemiological data from ILI cases should be collated by age group (Annex 6) and reported **weekly** using a standardized data collection form (see below):

- (a) Total number of ambulatory clinic/outpatient consultations for that week;
- (b) Number of new ILI case visits;
- (c) Number of new ILI cases for whom specimens and epidemiological data have been collected;

- (d) Proportion of sampled ILI cases that are positive for influenza;
- (e) Catchment population.

ILI Data Collection Form			
Sentinel site # _____		Date form completed _____	
CASE DEFINITION: Acute respiratory infection with:			
<input type="checkbox"/> measured fever of $\geq 38\text{ C}^\circ$ <input type="checkbox"/> cough <input type="checkbox"/> onset within the last 10 days		NO hospitalization	
DATA COLLECTION FORM FOR SAMPLED CASES			
ID number: _____	Date of symptom onset: _____	Date of consultation: _____	Date of specimen collection: _____
IDENTIFICATION			
Patient's name: (family name), (given name(s)) _____			
Age: Years _____ Months _____			
Address: _____		Contact Telephone Number(s): _____	
PRE-EXISTING MEDICAL CONDITIONS			
<input type="checkbox"/> Heart Disease <input type="checkbox"/> Asthma <input type="checkbox"/> Chronic Lung Disease <input type="checkbox"/> Liver Disease <input type="checkbox"/> Diabetes <input type="checkbox"/> Chronic haematological disorder	<input type="checkbox"/> Chronic neurological disease <input type="checkbox"/> Chronic renal disease, <input type="checkbox"/> Neuromuscular Dysfunction <input type="checkbox"/> Immune compromised <input type="checkbox"/> Other _____ <input type="checkbox"/> Unknown	Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female If Female: <input type="checkbox"/> Pregnant: _____ trimester	
VACCINES AND ANTIVIRALS			
Exposure to influenza antiviral drugs during the last 14 days? <input type="checkbox"/> None <input type="checkbox"/> Yes, patient <input type="checkbox"/> Yes, household contact <input type="checkbox"/> Unknown			
If Yes, name of antiviral: _____			
Vaccination for influenza in current season? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown Date: _____			
LABORATORY RESULTS - to be completed by laboratory staff			
Type of specimen collected: <input type="checkbox"/> nasal swab <input type="checkbox"/> throat swab <input type="checkbox"/> other _____			
Laboratory confirmation method: <input type="checkbox"/> PCR/RT-PCR <input type="checkbox"/> Viral Culture <input type="checkbox"/> Immunofluorescence (IFA) <input type="checkbox"/> other _____			
Test result: <input type="checkbox"/> Influenza A/H1 <input type="checkbox"/> Influenza A/(H1N1)pdm09 <input type="checkbox"/> Influenza A (not subtyped) <input type="checkbox"/> Other influenza subtype _____ <input type="checkbox"/> Influenza A (H3) <input type="checkbox"/> Influenza A (H5) <input type="checkbox"/> Influenza B <input type="checkbox"/> Other respiratory pathogen _____			
Date of testing: _____		Name/ID of person collecting specimen: _____	
REPORTING INFORMATION			
Name of Reporting Doctor: _____		Telephone Number(s): _____	
Name of Person Completing Form: _____		Signature: _____	
<i>Send one copy of this form to the confirmatory laboratory with the specimen and one copy to the national surveillance unit. The original form should be kept at the surveillance site.</i>			

Weekly Aggregated Data form for ILI

Sentinel Site ID Number:

Reporting week # **From (date)** **to**

	Age Distribution (years)						Total
	0-<2	2-<5	5-<15	15-<50	50-<65	≥65	
Total number of outpatient consultations (all causes)							
Number of new ILI case visits/consultations							
Number of new ILI cases from whom a specimen was collected and epidemiological data recorded.							
Number of ILI specimens tested							
Proportion of specimens tested that are positive for influenza							
Proportion of ILI (%)							
Catchment population*							

* Likely to be the same for several weeks.

Laboratory data collection

Following is the recommended minimum laboratory-based data (results) that should be collected **weekly** by the National Surveillance Unit from the National Influenza Laboratory. If an external laboratory (i.e. outside the country) is used for virological testing, results should be forwarded to the original referring laboratory that will report results to both the sentinel site and the NSU.

- (a) The number of samples tested for influenza during the week;
- (b) The proportion of samples that were positive for influenza for ILI and SARI (reported separately);
- (c) Types and subtypes of viruses detected during the week (if applicable);
- (d) Results from antiviral resistance testing (if applicable).

Annexes 7, 8 and 9 are examples of weekly laboratory data reporting forms.

Specimen and data handling and their flow through the surveillance system are illustrated in Figure 3.

3.13 Data analysis and reporting

Effective data management is integral to collection, processing and dissemination of information in a surveillance system. The establishment of a data management system or integration of influenza surveillance data processing with an existing data management system is recommended. Guidelines on setting up a data management system are detailed in Global Epidemiological Surveillance Standards for Influenza (Annex 9) [1].

Laboratory

Laboratory results should be communicated as quickly as possible to the originating sentinel site, local surveillance office and NSU. Virological data should also be reported to the WHO Global reporting network tool FluNet (<http://www.who.int/flunet>) by the National Influenza Laboratory.

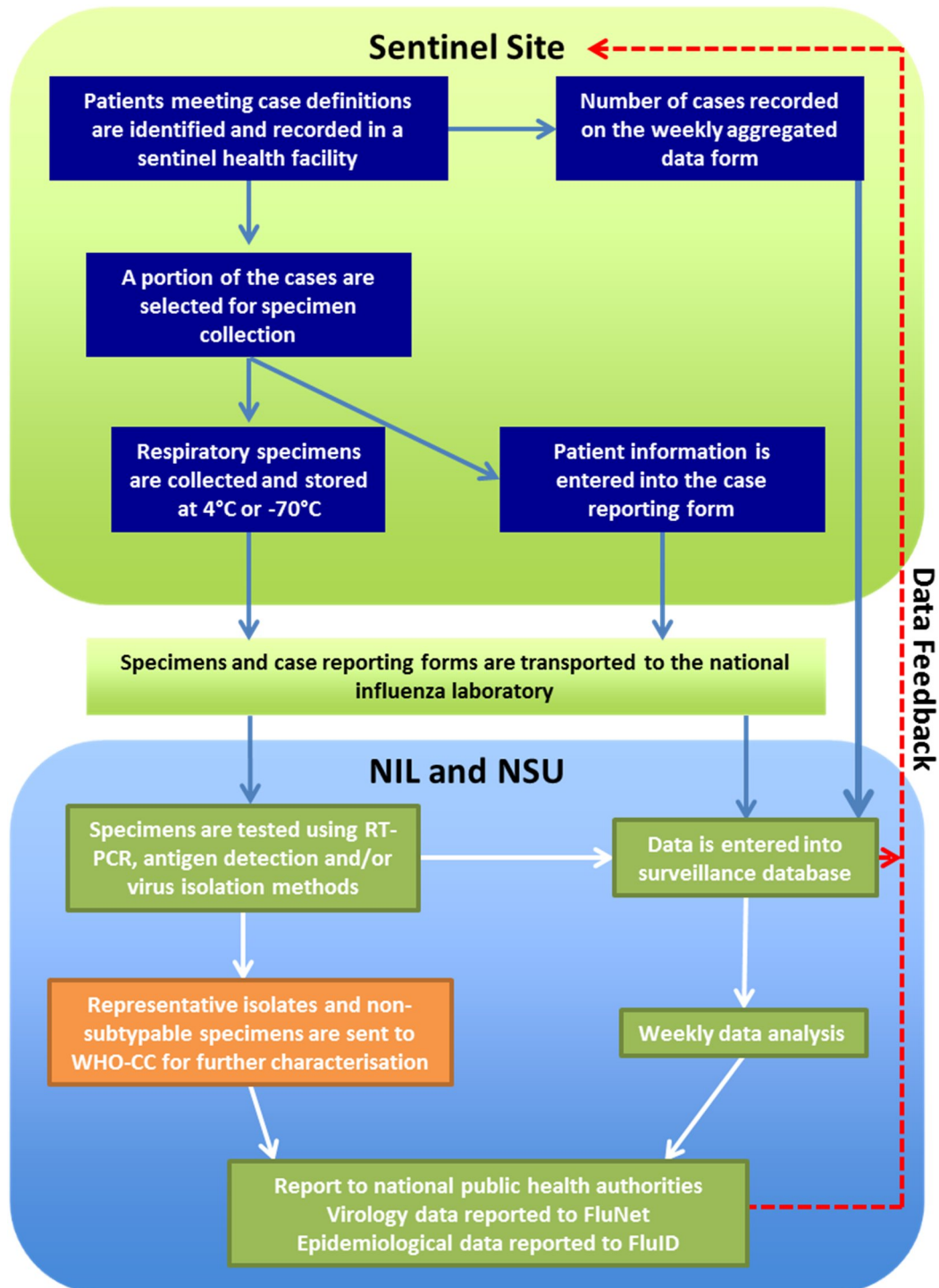


Figure 3: Flow of specimens and data in sentinel surveillance process (modified from [36]).

Sentinel sites are to report SARI and ILI data on a weekly basis to the NSU using standardized data forms. Reporting forms should be sent to the NSU at the beginning of the subsequent week and qualitative indicators (Annex 10) reported to WHO/FluNet.

The following epidemiological data on ILI/SARI and mortality, by age groups, should be reported to FluID (http://www.who.int/influenza/surveillance_monitoring/fluid/en):

- (a) Number of new influenza-positive ILI and SARI cases during the week being reported;
- (b) Number of total new outpatient visits in outpatient clinics where ILI surveillance is being conducted and/or the catchment population to the sentinel site during the week being reported;
- (c) Number of total new hospital admissions in wards where SARI surveillance is being conducted during the week being reported.

Sentinel site

Virological and epidemiological data should be analyzed weekly as reports from sentinel sites and laboratories are generated on a weekly basis. Influenza data can be inserted in the IDSR weekly bulletins.

The minimum analysis should include:

- (a) Number of sentinel sites reporting;
- (b) Graph of weekly SARI cases at the sentinel site by age group (where possible in comparison with previous years);
- (c) Graph of weekly ILI cases at the sentinel site by age group (where possible in comparison with previous years);
- (d) Number of SARI/ILI patients tested;
- (e) Number of SARI/ILI patients positive, by influenza type and subtype.

If possible, data should be presented with gender breakdown.

The NSU will conduct additional analysis, such as burden of disease, for influenza and other infectious respiratory diseases⁴. The NSU should also forward influenza data to WHO AFRO to be included in regional publications and influenza surveillance updates.⁵

At the conclusion of each epidemiological week, an influenza surveillance report should be generated by the NSU. An example of a weekly influenza surveillance report is provided in Global Epidemiological Surveillance Standards for Influenza (Annex 6) [1].

Annually, case-based information on risk factors and other data should be collated and analyzed. An example of data requirements for an annual influenza sentinel surveillance report is provided in Annex 11. Collection of data over multiple years will enable a better understanding of groups at risk for severe outcomes and guide control strategies for subsequent influenza seasons.

⁴ Global Influenza Programme, World Health Organization. A manual for estimating disease burden associated with seasonal influenza in a population.

⁵ Influenza Surveillance in the WHO African Region.

3.14 Organization and functions of National Surveillance Structure/System

The organization, roles and responsibilities of national influenza sentinel surveillance will, as much as possible, be aligned to existing surveillance system(s) in the host country. Detailed consultation would be undertaken between partners and the national government before deciding on where sites will be located and how they will operate. Access to the influenza laboratory will also be discussed and agreed upon during this consultation.

Roles and responsibilities

Sentinel site(s): Hospital and/or Ambulatory Clinic

Sentinel site staff will be responsible for:

- (a) Collecting epidemiologic data on any SARI related deaths, SARI and ILI using standardized data collection forms.
- (b) Reporting data to the local and national disease surveillance unit(s) on a weekly basis.
- (c) Collection and transport of patient respiratory specimens to the NIC or National Influenza Laboratory or designated laboratory for testing according to established WHO protocols.

Local sentinel laboratory (if present)

- (a) Process respiratory specimens for influenza A and B and other respiratory viruses (adenovirus, parainfluenza, and respiratory syncytial virus), using designated testing procedure(s) according to the etiology of the virus and appropriate biosafety conditions, as defined by WHO.
- (b) Communicate laboratory results in a timely manner to the originating practitioner.
- (c) Compile weekly laboratory results and report to the Epidemiology Office (local or intermediate depending on the organization of the sentinel unit) and to the National Reference Laboratory.
- (d) Send all influenza-positive specimens and a proportion of negative specimens to the NIC/National Influenza Laboratory according to shipping protocols [33] for further testing.

National Influenza Centre/National Influenza Laboratory

The primary responsibilities of the NIC/National Influenza Laboratory are to:

- (a) Perform detection/diagnosis of influenza infection and identify virus type and subtype from specimens submitted by the sentinel sites*;
- (b) Test a proportion of negative samples submitted by the sentinel sites;
- (c) Forward any clinical specimens that cannot be identified using standard reagents and any low reacting viruses to a WHO CC for further characterization;
- (d) Isolate (depending on laboratory capacity) and characterize circulating influenza viruses and novel viruses from positive samples, according to WHO-defined protocols under

WHO-defined biosafety conditions, and/or transport virus isolates or specimens to WHO-CC for further characterization;

- (e) Report laboratory surveillance results to sentinel sites and other stakeholders (states or provinces, and to the Ministry of Health);
- (f) Enter laboratory data into FluNET;
- (g) Consolidate and analyze national laboratory data and prepare reports on a weekly basis;
- (h) Train and supervise hospital and laboratory staff involved in surveillance on biosafety practices with specimen handling and shipping.

*This may depend on infrastructure and capacity at the sentinel site, i.e. if a laboratory with the capacity to perform PCR on influenza, and typing and subtyping of specimens is located at the sentinel site, then confirmation at the NIC is not necessary.

National Surveillance Unit

This is a universal term, in the context of this protocol, given to the entity coordinating influenza surveillance in the country. This unit is normally located in a ministry of health, or national institute for public health and is closely affiliated with the National Influenza Laboratory. The unit should contain a national surveillance focal point, a person or persons responsible for implementation and coordination of a national influenza surveillance system.

Generally, this unit is also the national disease surveillance unit responsible for IDSR within the ministry of health.

General roles and responsibilities of the NSU include, but are not limited to the following:

- (a) Providing support to the surveillance system under its responsibility;
- (b) Coordinating training of hospital and outpatient health-care staff in specimen collection methods;
- (c) Consolidating and analyzing data provided by Sentinel sites under its responsibility;
- (d) Ensuring proper collection of patient information and clinical samples at Sentinel Sites and ensuring samples are properly transported to the NIC/National Influenza Laboratory;
- (e) Coordinating implementation of the surveillance system;
- (f) Consolidating information forwarded from other levels in the structure/system;
- (g) Analyzing information on the weekly epidemiologic situation;
- (h) Setting up national and international public health alerts in the event of influenza outbreaks or other situations of concern;
- (i) Disseminating information and results via periodic reports (e.g., e-mail, website, periodic epidemiologic bulletins) to the public, the surveillance system, and stakeholders;
- (j) Promoting collaboration with the animal health sector through sharing of virological and epidemiological information on avian influenza in animals and humans.

Ministry of Health

The national disease surveillance unit within the ministry of health will be responsible for analyzing data to i) inform public health guidelines and policy decisions and ii) provide feedback to sentinel site staff and other stakeholders. In addition, they will be responsible for supervision and provision of supplies to sentinel sites and the influenza laboratory. National

authorities will also be responsible for facilitating sharing of seasonal, untypable and newly emerging influenza virus isolates and/or clinical samples with WCCs.

Resources

The responsibility for providing resources to all components of the influenza surveillance structure lies with national governments. Ministries of health within existing collaboration may request partners' support in operationalizing sentinel sites, including necessary training, evaluation, supervision, provision of supplies and operation costs. Several mechanisms may be used to fund influenza sentinel surveillance services such as government or public health insurance and donations. However, the government should remain the key source of funding for improving the capacity of national influenza sentinel services. Countries should use existing national surveillance structures and resources such as the IDSR infrastructure to develop their influenza surveillance capacity.

3.15 Monitoring, review and evaluation of the surveillance system

Feedback

Feedback is an essential component of any surveillance system. By providing feedback to all participants in the surveillance system (e.g. clinicians, sentinel site, laboratory, MOH), each participant will have a better understanding of the usefulness of data. Feedback could include analysis results (e.g. trends in SARI and ILI cases) and other information. It is recommended that weekly epidemiological and laboratory reports be sent to all stakeholders, including other critical sectors.

Monitoring and evaluation

Indicators will be used to measure quality of influenza sentinel surveillance (see Annex 12).

Additionally, at least a yearly local surveillance review is recommended to ensure high quality data, protocol adherence and standardization over time.

Surveillance meetings at the sites, laboratory, and at district and national levels are encouraged to ensure understanding and coordination of influenza sentinel surveillance.

In addition, WHO will continue to organize Global and Regional NIC meetings to contribute to further strengthening of regional surveillance and response capacity for seasonal and pandemic influenza viruses.

3.16 Outbreak investigation

As previously noted, a national sentinel surveillance system can support outbreak/pandemic planning by providing country-specific data such as baselines and thresholds; establishing infrastructure such as transporting specimen and testing systems; data reporting and analysis systems and a means to monitor severity, intensity and progression of pandemic cases, further highlighting the need for routine surveillance activities in Member States.

More importantly, a sentinel surveillance system can be instrumental in identifying early warning signs or events of a novel influenza or a virus that may have pandemic potential including clusters of SARI cases in people with social connections within a 2-week period, pneumonia in health-care workers or people with an occupational or social connection and changes in the epidemiology of SARI including a shift in age distribution; increase in mortality or increase in the number of cases, which, in turn trigger the initiation of an outbreak investigation [29].

Event-based surveillance systems rely on unstructured descriptions and reports from a variety of sources such as rumours, ad-hoc reports or notifications communicated through formal (health-facility based and routine reporting) or informal (media, health workers, general public) channels on events related to the occurrence of human disease or events related to potential exposures for humans to disease sources such as infected livestock or domestic animals [36].

Human influenza due to a new subtype, which may be indicated by some of the events listed above, is specified as a disease or event of international concern, and as such, requires immediate notification as indicated by IDSR and IHR (2005) [22, 23].

An outbreak investigation should also be initiated within 48 hours of notification to:

Purpose	Action
Verify outbreak and risk.	Review clinical and epidemiological history to verify that suspected cases satisfy the parameters of the case definition.
Identify and treat cases, and additional cases that have not been reported or recognized.	Actively search for suspected cases and deaths in health facility records and search for contact persons and suspected deaths in the community.
Collect information and laboratory specimens for confirming diagnosis.	Specimens should be collected from patients, animals and the environment (if suspected as the cause of the outbreak) and forwarded to the National laboratory so that the etiology of the outbreak can be confirmed.
Identify sources of infection or causes of outbreak Describe how the disease is transmitted and the populations at risk.	Define time, place person for the outbreak by investigation and analysis of data compiled from the activities listed above.
Select an appropriate response to control the outbreak.	As required

The establishment of an early-warning event-based surveillance system and methods for outbreak investigation, can be found in the IDSR guidelines and the following documents - Public health events of initially unknown etiology: A framework for preparedness and response in the African Region and A Guide to Establishing Event-based Surveillance [23, 30, 37].

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5. WHO SUPPORTING DOCUMENTATION

- WHO information for molecular diagnosis of influenza virus – update March 2014.
http://www.who.int/influenza/gisrs_laboratory/molecular_diagnosis/en/
- Manual for the laboratory diagnosis and virological surveillance of influenza
http://www.who.int/influenza/gisrs_laboratory/manual_diagnosis_surveillance_influenza/en/
- WHO External Quality Assessment Project for the detection of influenza virus type A by PCR
http://www.who.int/influenza/gisrs_laboratory/external_quality_assessment_project/en/
- WHO laboratory biosafety guidelines for handling specimens suspected of containing avian influenza A virus
http://www.who.int/influenza/resources/documents/guidelines_handling_specimens/en/
- WHO guidelines for the storage and transport of human and animal specimens for laboratory diagnosis of suspected avian influenza A infection
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- Recommendations and laboratory procedures for detection of avian influenza A(H5N1) virus in specimens from suspected human cases. Revised August 2007
http://www.who.int/influenza/resources/documents/h5n1_laboratory_procedures/en/
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- WHO guidelines for the storage and transport of human and animal specimens for laboratory diagnosis of suspected avian influenza A infection
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http://www.who.int/influenza/resources/documents/guidelines_handling_specimens/en/

H7N9

Avian influenza A(H7N9) virus: Publications

http://www.who.int/influenza/human_animal_interface/influenza_h7n9/publication/en/

- Serological detection of avian influenza A(H7N9) virus infections by modified horse red blood cells haemagglutination-inhibition assay. 20 December 2013
- Serological detection of avian influenza A(H7N9) infections by microneutralization assay. 23 May 2013
- Real-time RT-PCR Protocol for the Detection of Avian Influenza A(H7N9) Virus. 8 April 2013, *Updated on 15 April 2013*
- Laboratory biorisk management for laboratories handling human specimens suspected or confirmed to contain avian influenza A(H7N9) virus causing human disease Interim recommendations Current as of 10 May 2013

National Influenza Centre Publications

http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/en/

- How to become a National Influenza Centre
- Terms of reference for National Influenza Centres

ANNEXES

ANNEX1: SENTINEL SURVEILLANCE SITE CHECKLIST[1]

SITE DESCRIPTION	
Is hospital/clinic management agreeable to implementing influenza surveillance?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Are staff members willing to work on influenza surveillance?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site offer outpatient services?(ILI cases)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site offer inpatient services? (SARI cases)	<input type="checkbox"/> Yes <input type="checkbox"/> No
Are the patients attending the clinic from all age groups?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Are the patients attending the clinic from all socioeconomic strata and ethnic groups?	<input type="checkbox"/> Yes <input type="checkbox"/> No
What is the 3-month average number of outpatient consultations?	<input type="checkbox"/> Yes <input type="checkbox"/> No
What is the 3-month average number of in-patient medical admissions?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Can the catchment population be estimated?	<input type="checkbox"/> Yes <input type="checkbox"/> No
HUMAN RESOURCE CAPACITY	
Does the site have at least permanent clinical staff that can be trained in the identification of ILI and SARI and in respiratory sample collection?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site have at least one permanent lab worker who can be trained in the collection, storage, testing and transportation of respiratory samples/specimens?	<input type="checkbox"/> Yes <input type="checkbox"/> No
INFRASTRUCTURE	
Does the site have a laboratory?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site have access to a NIC or <i>National Influenza Laboratory</i> ?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Do surveillance staffs have access to computers?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Do the surveillance staff have access to the internet	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site have reliable power supply and fridge/freezer where samples/specimens can be stored?	<input type="checkbox"/> Yes <input type="checkbox"/> No
Does the site have access to transport/shipping	<input type="checkbox"/> Yes <input type="checkbox"/> No

ANNEX 2: TECHNIQUES FOR RESPIRATORY SAMPLING

Standard precautions should always be followed and barrier protection applied during sampling.

Nasal swabs with nasal secretions (from the anterior turbinate area) or NP aspirates or swabs are appropriate for detecting human influenza A and B.

If Influenza A/H5N1 is suspected, use appropriate PPE for sample collection[38]. Posterior-pharyngeal (throat) swabs are currently the highest yield upper respiratory tract specimen for detecting A (H5N1) (unlike human influenza)[38]. Naso-pharyngeal swabs may be collected if necessary.

Swabs used for RT-PCR testing must be Dacron or rayon. DO NOT use cotton swabs or calcium alginate swabs, or swabs that have wooden shafts since these may contain substances that inhibit PCR testing.

(a) Nasal swabs

Insert a **dry polyester or Dacron swab** into the nostril in line with the palate. Advance the swab tip past the vestibule (anterior nares) to the nasal mucosa (approximately 2–3 cm from the nostrils in adults) and gently rotate (5 to 10 seconds) to collect nasal secretions from the anterior portions of the turbinate and septal mucosa. Specimens from both nostrils are obtained with the same swab.

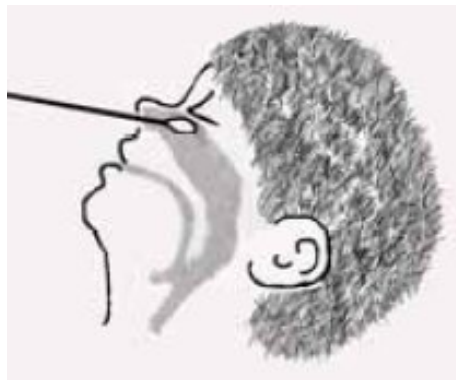


Figure 4. Illustration of collection of a nasal swab.

Introduce the swab into the tube that contains the transport medium: If a commercial medium is used, place the swab in the transportation tube and press the bottom of the tube in order to liberate the medium or put pressure on the padding at the bottom.

If a laboratory-prepared medium is used, cut any leftover rod off the swab so that only the part that adheres to the swab remains in the tube. Close the tube with the cover. Swabs should always be kept moist during shipping.

(b) *Nasopharyngeal swabs*

Insert a dry rayon or polyester swab into the nostril and back to the nasopharynx. The swab should be slid straight into the nostril with the patient's head held slightly back. The swab is inserted following the base of the nostril towards the auditory pit and will need to be inserted at least 5–6 cm in adults to ensure that it reaches the posterior pharynx. Do NOT use rigid shafted swabs for this sampling method—a flexible shafted swab is essential.

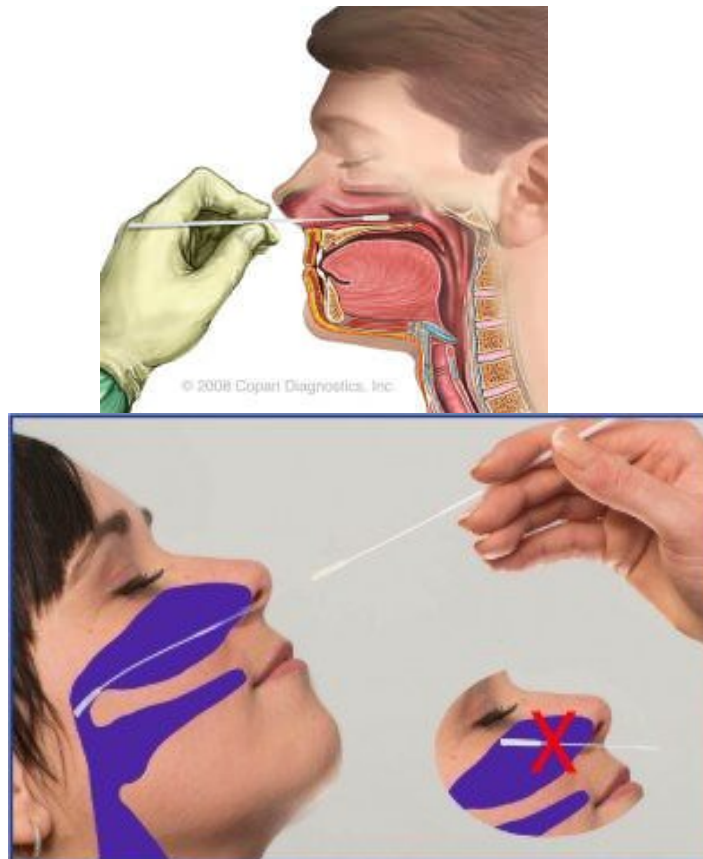


Figure 5. Illustrations of collection of naso-pharyngeal swabs.

- (i) Leave the swab in place for a few seconds.
- (ii) Slowly remove the swab while slightly rotating it.
- (iii) Put tip of swab into vial containing VTM, breaking applicator's stick.
- (iv) A second swab should be used for the other nostril and put into a second tube. This can serve as the second sample from the patient.

Note: Nasopharyngeal sampling is an invasive process that can cause considerable distress to the patient.

(c) *Posterior pharyngeal swabs (throat swabs)*

- (i) Hold the tongue down with a tongue depressor.
- (ii) Use a sweeping motion to swab the posterior pharyngeal wall and tonsil pillars. Have the patient say “aahh” to elevate the uvula. Avoid swabbing the soft palate and do not touch the tongue with the swab tip. (**Note:** This procedure can induce the gag reflex).

- (iii) Put the swab into VTM.
- (v) Combined nasal and throat swab: nasal and throat swabs are taken as described above and then placed into the same vial or tube containing transport medium.

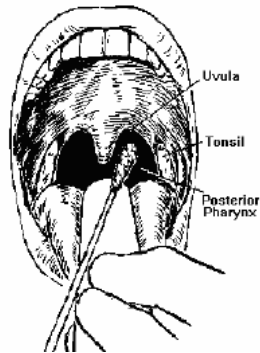


Figure 6: Illustration of collection of a throat swab

ANNEX 3: VIRAL TRANSPORT MEDIA

Viral transport medium, abbreviated as VTM, is used in the collection of samples for viral isolation and testing. VTM prevents the specimen from drying out, and it also prevents bacteria and fungi from growing.

VTM can be made in a lab (see recipe below[38]) or purchased commercially. There are several different types of viral transport media. The choice of which VTM to use depends on whether the samples are being collected from animals or humans and the type of testing to be performed with the sample. There is VTM for collection of animal specimens, VTM for viral isolation from human specimens, and VTM for molecular testing. Each has slightly different recipes, and it is important **NOT** to use phosphate-based media when VTM is used for molecular testing. If VTM is not available, 100% ethanol can be used for collection of swabs for molecular testing.

Virus transport medium

Virus transportation medium for use in collecting throat and nasal swabs (human):

- (a) Add 10 g veal infusion broth and 2 g bovine albumin fraction V to sterile distilled water (to 400 ml).
- (b) Add 0.8 ml gentamicin sulfate solution (50 mg/ml) and 3.2 ml amphotericin B (250 µg/ml).
- (c) Sterilize by filtration.

It is important to correctly store VTM. If VTM is made in the laboratory, place 2–3 millilitres of VTM into sterile collection vials. The vials can be stored at –20 °C until use. The vials can be stored for short periods of time at 4–6°C.

Keep records of when the VTM was made, and **do not use** vials if the liquid becomes cloudy, as this is a sign of contamination.

Universal transport medium (UTM) is also available commercially and typically can be stored at room temperature until sample collection. UTM is an acceptable alternative to VTM.

For specimens in VTM/UTM

- (a) Transport to laboratory as soon as possible.
- (b) Store specimens at 4°C before and during transportation within 48 hours.
- (c) Store specimens at –70°C beyond 48 hours.
- (d) **Do not** store in standard freezer—keep on ice or in refrigerator.
- (e) **In order to prevent loss of virus viability, avoid freeze-thaw cycles.** It is better to keep on ice for a week than to have repeat freezing and thawing.

ANNEX 4: SPECIMEN PACKAGING AND TRANSPORT

For the detection of influenza virus by isolation, PCR or antibody testing, inadequate or inappropriate specimen storage and transport can result in false negative results.

Specimens should be sent to the laboratory in viral transport medium (VTM) as soon as possible. Optimally, storage of specimens at -70°C is strongly recommended, particularly for virus isolation, if specimens cannot be processed within 48 hours of collection. However, if this is not possible, specimens can be stored as recommended (Table 1) for laboratory analysis[39-41].

If VTM is not available, influenza virus can be detected by PCR from either swabs stored in sterile saline or dry as indicated in Table 1[39, 40].

Table 1: Suitability of various storage and shipment conditions for different specimen types[#]

Storage/ shipment conditions	Manipulation							
	Virus Isolation			PCR				Antibody testing
	Swabs or other specimens in VTM	Blood serum	Swabs or other specimens in VTM/UT M	Swabs or other specimens in saline	Swabs in ethanol*	Dry swabs	Blood serum	Blood serum for antibodies
-70°C OR dry ice OR Liquid N_2	SR	SR	SR	NA	R	NA	SR	SR
-20°C	NR	NR	21	NA	21	21	A	SR
$+4^{\circ}\text{C}$	4	4	5-21	7	21	21	7	5-7
Room temperatur e	NR	NR	14	7	14	7	A	NR
Dried blood spot on filter paper	NA	NA	NA	NA	NA	NA	A	A

[#]Storage suitability, where represented by a number, indicates the number of days post-collection sample can be stored under the conditions indicated.

- * where refrigeration is not available
- SR = strongly recommended method
- A = adequate method
- NR = not recommended
- NA = not applicable

If specimens are to be transported within 48 hours, it is recommended to store them at 4°C both before and during transportation.

If specimens cannot be transported to the laboratory within 48 hours (2 days), it is recommended to aliquot specimens and store them at -70°C. If this cannot be done, specimens should be kept on ice or in the refrigerator as long as necessary until they are shipped.

For virus isolation **DO NOT** put specimens in a standard (-20°C) freezer (particularly frost-free type), as the virus does not survive well at this temperature. It is also very important to avoid freeze-thaw cycles as this destroys virus viability. It is strongly recommended to keep a sample on ice, even for a week, than to allow it to freeze and thaw several times.

When the specimens are ready to be packed for transportation from the field or sentinel site to the laboratory, it is necessary to follow “Guidance on regulations for the Transport of Infectious Substances 2015-2016”

http://www.who.int/ihr/publications/who_hse_ihr_2015.2/en/.

Primary container: The primary container, which contains the specimen, must be leak-proof (watertight). Examples: Vacutainer with adhesive tape around cap, conical screw-cap tubes with parafilm around the cap or cryovials. Do not use Eppendorf tubes, with tape or parafilm around cap.

Secondary container: The secondary container may contain several primary containers. The secondary container must also be leak-proof (watertight).

Examples of watertight secondary containers include ziplock plastic bags, conical 50ml test tubes and screw-cap containers.

Absorbent material must be placed between the primary and secondary container. The quantity should be sufficient to absorb all liquid in the shipment.

Examples include paper towels, cotton balls, filter paper, etc.

If dry ice is needed to keep samples frozen, it should be put between the secondary and tertiary/outer packaging. Styrofoam and cardboard both allow dry ice vapour to escape, so dry ice must be placed **OUTSIDE** the secondary packaging, never within the secondary container. Packaging dry ice inside impermeable, screw-cap secondary containers may cause the container to explode. Additionally, specimens should be in an airtight container as carbon dioxide from dry ice can inactivate the virus.

Tertiary or Outer shipping container: The tertiary packaging (outside) must protect the inside packaging to avoid breakage or perforation under normal transport conditions. Corrugated cardboard is the usual choice. Styrofoam boxes, plastic bags, or paper envelopes are unacceptable outer containers for shipping biological materials.

Just as it is important to keep specimens cold during storage, it is equally important to keep specimens cold during *transportation*. Try to keep specimens at 4°C. A cooler filled with ice packs can be used for this purpose.

Be sure to coordinate shipment with the laboratory. An itemized list of specimens, with specimen identification numbers and instructions for the laboratory, must be included with all specimen shipments.

ANNEX 5: PRE-EXISTING CONDITIONS ASSOCIATED WITH SEVERE INFLUENZA OR DEATH[1].

Pre-existing conditions associated with increased risk of severe influenza or death.

Risk Condition	Examples, definitions:
Chronic respiratory disease	Chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD)
Asthma	Asthma that requires continuous or repeated use of bronchodilators, inhaled or systemic corticosteroids, or with previous exacerbation required hospital admission.
Diabetes	Type 1 diabetes Type 2 diabetes requiring insulin or oral hypoglycemic drugs
Chronic cardiac disease	Conditions that require regular medications and/or follow-up including: Congenital heart disease Cardiomyopathy as the result of prolonged hypertension(hypertension alone in the absence of associated heart disease is not considered a risk factor for severe outcome) Chronic heart failure Ischaemic heart disease
Chronic renal disease	Chronic renal failure Nephrotic syndrome Renal transplantation
Chronic liver disease	Cirrhosis Biliary atresia Chronic hepatitis
Chronic neurological impairment	Stroke with persistent neurological deficit Neuromuscular diseases associated with impaired respiratory function or aspiration risk such as cerebral palsy or myasthenia gravis Severe development disorder in children
Chronic haematological disorder Immune compromise (as a result of disease or treatment)	Sickle cell disease, Thalassemia major Aplastic anaemia Immunodeficiency's related to use of immunosuppressive drugs (e.g. chemotherapy or drugs used to suppress transplant rejection) or systemic steroids Asplenia or splenic dysfunction (sickle cell anaemia) Human Immunodeficiency Virus infection or Acquired Immuno-Deficiency Syndrome (HIV/AIDS).
Obesity parameter, Body Mass Index (BMI)	BMI is calculated as body weight in kilograms divided by the square of the height in meters (kg/m ²). WHO defines obesity as a BMI of > 30 kg/m ² . A commonly used definition for extreme or morbid obesity is a BMI > 40 kg/m ²
Tuberculosis	History of current symptomatic tuberculosis requiring treatment

ANNEX 6: WHO GISRS AGE GROUPS FOR DATA REPORTING

WHO GISRS Age Groups for Data Reporting and Analysis

0 to <2
2 to <5
5 to <15
15 to <50
50 to <65
≥ 65

ANNEX 8: WEEKLY LABORATORY RESULTS-ILI

Weekly Laboratory Results Weekly Influenza Sentinel Surveillance Report-ILI

Ambulatory Patient with ILI							
Sentinel Site:				Epidemiological Week #:			
				Report Date:			
Number of ILI Cases Tested for Viral Respiratory Infection							
Etiological Agent	Total	0-<2	2-<5	5-<15	15-<50	50-<65	≤65
	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>
Influenza A							
Influenza B							
RSV							
Adenovirus							
Parainfluenza							
Negative							
Total							

ANNEX 9: WEEKLY LABORATORY RESULTS-SARI

Weekly Laboratory Results Weekly Influenza Sentinel Surveillance Report-SARI

Hospitalized Patients with SARI							
Sentinel Site:		Epidemiological Week #:					
		Report Date:					
Number of SARI Cases Tested for Viral Respiratory Infection							
Etiological Agent	Total	0-<2	2-<5	5-<15	15-<50	50-<65	≤65
	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>	<i>ILI</i>
Influenza A							
Influenza B							
RSV							
Adenovirus							
Parainfluenza							
Negative							
Total							

ANNEX 10: QUALITATIVE INDICATORS TO BE REPORTED TO WHO/FLUNET

Geographical spread

Geographical spread refers to the number and distribution of sites reporting influenza activity.

- (a) No activity: No laboratory-confirmed case(s) of influenza, or evidence of increased or unusual respiratory disease activity;
- (b) Localized: Limited to one administrative unit of the country (or reporting site) only;
- (c) Regional: Appearing in multiple but <50% of the administrative units of the country (or reporting sites);
- (d) Widespread: Appearing in $\geq 50\%$ of the administrative units of the country (or reporting sites);
- (e) No information available: No information available for the previous 1-week period.

Trend

Trend refers to changes in the level of respiratory disease activity compared with the previous week.

- (a) Increasing: Evidence that the level of respiratory disease activity is increasing compared with the previous week;
- (b) Unchanged: Evidence that the level of respiratory disease activity is unchanged compared with the previous week;
- (c) Decreasing: Evidence that the level of respiratory disease activity is decreasing compared with the previous week;
- (d) No information available.

Intensity

The intensity indicator is an estimate of the proportion of the population with acute respiratory disease, covering the spectrum of disease from influenza-like illness to pneumonia.

- (a) Low or moderate: A normal or slightly increased proportion of the population is currently affected by respiratory illness;
- (b) High: A large proportion of the population is currently affected by respiratory illness;
- (c) Very High: A very large proportion of the population is currently affected by respiratory illness;
- (d) No information available.

Impact

Impact refers to the degree of disruption of health-care services as a result of acute respiratory disease.

- (a) Low: Demands on health-care services are not above usual levels;
- (b) Moderate: Demands on health-care services are above the usual demand levels but still below the maximum capacity of those services.
- (c) Severe: Demands on health-care services exceed the capacity of those services.
- (d) No information available.

ANNEX 11: EXAMPLE OF COMPONENTS OF ANNUAL INFLUENZA SURVEILLANCE REPORT[1]

Summary

- Brief summary description of the epidemiological virological ILI and SARI data

Description of the surveillance system

- Brief description of how data are collected and how the surveillance system is organized
- Reporting procedures

Epidemiological surveillance

- Present the epidemiological data graphically
- Describe the season in terms of starting date, duration of outbreak, intensity, and criteria for defining the start and end of season
- Age groups most affected
- Differences in regions, if applicable
- Comparison of current season to previous seasons

SARI data

- Description and summary of influenza-associated SARI data collected every week admitted, age and gender
- Co-morbidity among cases
- Vaccine coverage among SARI patients
- Fatal cases (if available)

Virological surveillance

- Present virological data graphically
- Description of how many influenza detections were done, as well as the type and subtypes of influenza viruses
- Describe differences in the distribution of viruses, by age or severity
- Summarize any notable changes from previous years

Vaccine data

- Match between circulating viruses and strains covered by the vaccine
- Vaccination coverage, if possible, by age and/or risk group

Antiviral resistance data (if available)

- Number of viruses tested for antiviral resistance
- Result from testing
- Number of viruses sent to WHO CCs for further testing

Performance of the surveillance system

- Brief description of the system and its operations
- Proportion of sentinel sites reporting weekly to national level
- Proportion of sentinel sites regularly submitting specimens for laboratory testing
- Number of specimens sent from sentinel sites

NB: This report can be inserted in the annual report of the disease surveillance unit within the Ministry of Health.

ANNEX 12: MONITORING AND EVALUATION INDICATORS

Key performance indicators	Target	Purpose
Influenza laboratory		
Percentage of received specimens that are tested	95%	Evaluate efficiency of the influenza laboratory
Timely laboratory results shared with stakeholders	90%	Evaluate timelines of virological surveillance reporting
Surveillance unit		
Percentage of sentinel that report according to the agreed timelines	80%	Evaluate timelines of reporting by sites
Number of sentinel site supervision visits conducted.	80%	Evaluate monitoring of sentinel sites
Proportion of sentinel site that received at least one supervisory visit from national level during the last year		
Timely epidemiology results shared to stakeholders	90%	Evaluate timelines of epidemiological surveillance reporting