GLOBAL INFLUENZA PROGRAMME

Protocol to INVESTIGATE non-seasonal influenza and other emerging acute respiratory diseases

World Health Organization

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Abbreviations and acronyms

ARDS	acute respiratory distress syndrome
ARI	acute respiratory infection
BSL	biosafety level
FAO	Food and Agriculture Organization of the United Nations
HPAI	highly pathogenic avian influenza
ILI	influenza-like illness
IHR	International Health Regulations
IPC	infection prevention and control
MERS-CoV	Middle East respiratory syndrome coronavirus
OIE	World Organisation for Animal Health
PPE	personal protective equipment
RT-PCR	reverse transcription polymerase chain reaction
SARI	severe acute respiratory infection
SARS	severe acute respiratory syndrome
TIPRA	tool for influenza pandemic risk assessment
WHO	World Health Organization
WHO CC	WHO collaborating centre

CONTENTS

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

INTRODUCTION

Outbreaks such as those of highly pathogenic avian influenza (HPAI) A(H5N1) and severe acute respiratory syndrome (SARS) increased awareness about the global vulnerability to novel respiratory pathogens (*1, 2*). The pathogens responsible for these outbreaks spread rapidly across several countries, causing significant social and economic disruption. Public health systems continue to face human infections with non-seasonal influenza viruses such A(H7N9), A(H5N6) and A(H3N2)v, and with other emerging pathogens such as Middle East respiratory syndrome coronavirus (MERS-CoV) (*3*). With ongoing animal–human interaction, more new pathogens will cross the species line and cause human infections (*4, 5*).

Timely investigation is key to reducing the morbidity and mortality associated with events of non-seasonal influenza or other emerging respiratory disease pathogens. Investigations identify cases, and determine the cause of disease, the source and the most probable mode(s) of transmission, as well as the at-risk populations and exposures that may predispose individuals to infection (*6*). The findings are then used to assess the risk posed by the event, and to develop and implement interventions that stop transmission. Strong linkages between human and animal health sectors are needed for investigations at the human–animal interface, and risk assessments are critical to guide control and prevention measures throughout the investigation and response process.

1.1 Scope of the protocol and target users

This protocol provides an approach for public health authorities and investigators at all levels to plan for and conduct investigations of non-seasonal influenza and other emerging respiratory diseases. The disease etiology is not always known at the onset of the event; therefore, this protocol focuses on important but broadly applicable steps that should be undertaken in the investigation of an acute respiratory disease event. Similarly, the source of the illness, associated exposures and modes of transmission may not be immediately known; hence, this protocol provides guidance for the investigation of different sources, exposures and transmission patterns. Since many recent non-seasonal influenza and other emerging respiratory pathogens are zoonotic, the protocol emphasizes investigation at the animal–human interface.

The protocol reflects and incorporates the practical field experience gained by investigators working at international, national and subnational levels during investigations of non-seasonal influenza, SARS and MERS-CoV outbreaks. It is not intended to be a comprehensive compendium of all the measures that need to be instituted in response to an event, but should be read in conjunction with other guidance (e.g. for clinical management, infection prevention and control [IPC] and animal disease control) and new information about the disease as it becomes available from operational research or the investigation process. This protocol and its tools can serve as a basis for national and local authorities to develop their own procedures, tailored to their specific needs.

Throughout this protocol, general investigation tips and reminders for linkages with risk assessment are provided using the icons shown below:

TIPS AND CONSIDERATIONS

DATA AND INVESTIGATION FINDINGS that can be used to inform risk assessment as well as opportunities to conduct a risk assessment

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INVESTIGATION AND RISK ASSESSMENT

This protocol explicitly links the investigation process and findings with risk assessment. In the context of acute public health events with respiratory disease pathogens, risk assessment expresses the likelihood that the pathogen will spread further (human-to-human, animal-to-human or fomite-to-human) and what the impact of that spread would be.

Risk assessments should be conducted iteratively as new information is gathered. Risk assessors will do the following:

1. Decide on the scope of the risk assessment (e.g. by stating a risk question to be answered).

2. Reach consensus on the level of risk (based on exposure or transmission, severity, and capacity and control measures).

3. Decide on limitations or further information that could change the level of risk.

4. Determine the confidence (or uncertainty) in the risk characterized, based on the breadth and quality of data available at the time of the assessment.

Risk assessment outputs will guide the response required, as well as further data collection and monitoring needs. Because the level of risk may change as more information is obtained, risk assessments reflect a snapshot in time and should be done iteratively until the event is resolved and potentially beyond, to prevent its reoccurrence. Detailed guidance on conducting risk assessments is available *(7)*.

2.1 Triggers for investigation

A trigger is a "signal" or a series of events or cases that calls for an investigation. A trigger can arise from indicator-based (*8*) or event-based surveillance systems (*9*). For non-seasonal influenza and other emerging acute respiratory diseases, trigger criteria are designed to be sensitive and sourced from a variety of health-care, occupational and community settings (*10, 11*).

Examples of triggers include:

- respiratory disease in humans that is associated with recent exposure to animals;
- clusters[1] of severe acute respiratory infection[2] (SARI) or pneumonia in families, workplaces or social networks;
- SARI occurring in a health-care worker who cares for patients with respiratory diseases;
- SARI or pneumonia in travellers from countries or areas affected by emerging acute respiratory infections;
- SARI occurring in a laboratory worker or researcher handling novel influenza and other emerging respiratory pathogens;
- number of respiratory disease hospitalizations or deaths greater than expected;
- laboratory detection of human infection with a non-seasonal influenza virus or a novel respiratory pathogen;
- abrupt, unexplained changes in the trends of respiratory disease occurrence or clinical outcomes observed in routine surveillance activities; and
- unusually high levels of sales of pharmaceuticals used for respiratory illness that cannot be explained by known or expected disease trends.

Examples of triggers suggestive of specific etiologies include:

- for countries affected by influenza outbreaks in birds or other animals, unexplained SARI, pneumonia or deaths in workers in the poultry or livestock industry, or others with occupational exposure such as veterinarians or those working in live animal markets;
- unexplained SARI or pneumonia in a person with a history of travel to areas with animal influenza or MERS-CoV circulation; and
- new respiratory disease cases among patients hospitalized at a facility with recent nosocomial transmission of an emerging respiratory disease.

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[1] A "cluster" is defined as two or more people with onset of symptoms within the same 14-day period and who are associated with a specific setting, such as a classroom, workplace, household, extended family, hospital, other residential institution, military barracks or recreational camp.

[2] SARI is an acute respiratory infection with history of fever or measured fever of ≥38 C^0 and cough, with onset within the past 10 days, that requires hospitalization.

Verifying the trigger will determine whether the event is true or represents misinformation, and whether a field investigation is needed. Event verification with relevant local health authorities, hospitals, affected households or community leaders includes collection of the following information (*9*):

- symptoms and signs of cases (to verify the diagnosis and consider differential diagnoses);
- number of cases with similar symptoms;
- any laboratory findings;
- date of onset of symptoms of the first and the most recently detected cases;
- age and sex of cases;
- community and administrative location of cases;
- geographical, personal and time relationships between cases (e.g. residence, family setting, place of work or school, district, attendance at a common event or occurrence in a specific health facility where treating health staff also become ill);
- case management details;
- outcomes including deaths; and
- health-care staff affected.

A field investigation is warranted if the verification process and risk assessment confirms that an event exists and the disease presentation is aligned with notifiable diseases or cannot be explained by expected disease activity.

Use the information collected to ask the preliminary risk assessment question "What is the public health risk of the event?"

Consider questions such as "Is the event serious? ", "Is it unusual? ", "Can further spread be expected? " and "Is there a risk of travel or trade restrictions? ". If the answer to any of these questions is "Yes" or "Don't know ", start a field investigation.

Document the rationale for starting or not pursuing a field investigation. Based on the breadth and quality of information available, document the team's confidence in the risk characterized.

If an event may constitute a public health emergency of international concern according to defined criteria in the International Health Regulations (2005) (12), notify WHO. For more details, see Section 7.2.

2.2 Objectives of the investigation

When setting up an investigation, it is critical to clearly define the objectives. The objectives may be to:

- identify the etiological agent causing the event;
- determine the geographical area where the pathogen is transmitting;
- determine epidemiological characteristics for cases including the most probable mode or modes of transmission, incubation period and period of transmissibility;
- identify other cases and detect chains of human-to-human or animal-to-human disease transmission;
- determine the efficiency of disease transmission, and whether this transmissibility has changed;
- assess options for case management based on clinical characteristics for cases including symptoms, presentation, disease severity and fatality proportions;
- reduce onward transmission, morbidity and mortality through rapid identification, isolation, treatment and clinical management of cases and follow-up of contacts;
- prevent future cases through identification of potential human, animal or environmental sources of exposure; risk factors for infection; and implementation of appropriate prevention and control measures;
- characterize the pathogen based on microbiological findings from studies of sequencing, anti-microbial resistance, transmission and severity assessment; and
- enable timely exchange of information among clinicians, investigators of public health and other sectors (e.g. animal, wildlife or environmental authorities, and government officials) to facilitate critical and informed decision-making at subnational, national and international levels during the investigation.

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KEY STEPS FOR AN INVESTIGATION

Various activities are undertaken as part of every investigation. The order in which they are done will depend on local circumstances, and it is often the case that multiple activities are undertaken in parallel. Regardless of the sequence of investigation activities, the investigation activities and findings should feed into risk assessments, so that decisions on control measures and further data collection needs are well informed.

3.1 Prepare for the investigation

3.1.1 Assemble a multidisciplinary investigation team

The team may include expertise in field epidemiology, clinical management, laboratory specimen collection, infection control and risk communication. Animal health specialists may also be required if a zoonotic disease event is suspected. Additional team members may include logisticians, laboratory experts, database experts, statisticians, modellers, anthropologists and environmental health specialists. The size and composition of the initial investigation team may vary, depending partly on the size and complexity of the anticipated investigation. The preliminary risk assessment findings can be used to decide on expertise needed. Designation of a team leader and attribution of roles and responsibilities is critical to the success of the investigation. Examples of team terms of reference, expected skill sets and responsibilities are available (*13*). All members of the team should meet and be briefed about their role, tasks and responsibilities, and the knowledge of personal protection and use of personal protective equipment (PPE) where needed. Team members should be medically fit to be deployed, including updated vaccinations.

3.1.2 Inform relevant authorities

Relevant authorities – for example, government officials, health offices, hospitals and veterinary health authorities in the affected area – should be informed about the investigation. The team should alert and liaise with the laboratories and clinicians that will handle the animal, human and environmental specimens collected, and inform the local communities that an investigation will take place. Communities should be informed through their local leaders or others such as community elders, traditional or religious leaders or women's groups, to request their cooperation.

3.1.3 Gather information and supplies

Before deploying, the team should gather preliminary background information, and assemble the necessary materials and supplies. Sample contents of an investigation tool kit can be seen in Annex 1. Supplies to protect team members should be provided; for example, PPE, antiviral drugs, first aid kits, bed nets, disinfectants and antimalarial drugs if indicated and if availability in the affected region is limited. The team should consider whether there are any safety or security concerns, and request support or a briefing from relevant authorities.

3.2 Investigate initial cases reported

An early step in the investigation process is laboratory confirmation of the diagnosis of initial cases. However, collection, shipment and testing of specimens often requires several days or longer, and collection of specimens from these cases may not be feasible. Therefore, collection of epidemiological, laboratory and clinical data may need to begin before the diagnosis is known.

3.2.1 Case data

Information gathered about initial cases in terms of person, place and time will help the investigation team to develop case definitions for additional case finding and enhanced surveillance. The clinical and epidemiological information may also help focus attention on likely etiologies, sources of infection, modes of transmission and populations at risk – all of which can be rapidly used to apply precautionary measures for managing cases and preventing transmission.

A sample generic case investigation form can be seen in Annex 2. Questions or subsections in the form should be adjusted according to the event context and investigation objectives. If a specific pathogen is suspected to be the source of the event, or if there is a need to address specific questions and hypotheses (e.g. for MERS-CoV), then other respiratory disease-specific guidance or case forms should be used (14). Data to be collected in case investigation forms include the following:

- ***Essential basic information*** – demographic data and personal history to enable characterization of the populations at risk. This includes reporter and interviewee data, to enable follow-up for collection of additional information or feedback of results of the investigation.

- ***Clinical information*** – on the illness course and outcome, to characterize the spectrum of illness and verify that the case definition has been met. This includes health-seeking behaviour to identify likely contacts and exposures for the case as well as potential for nosocomial transmission.

- ***Exposure information and travel history*** – information that can be used to identify sources and probable mode or modes of transmission. This includes patient occupational, animal and food exposures.

- ***Laboratory information*** – to determine the etiology and course of illness.

For initial cases, specimens should be collected as quickly as possible. Samples should also be collected from animals, the environment or any foods suspected to be sources of infection. See Section 3.7 for more information

3.2.2 Information sources

Data about initial cases should be collected from a variety of sources, including from the patients themselves if feasible, their families or caregivers, health workers who provided care to the patients, neighbours or community leaders, and staff at the workplace or other locations suspected of being sources of infection. In particular, it is important to inspect the cases' households and the health facilities the individual visited during the course of illness, to verify first-hand as much information as possible.

Household data

At the household level:

- confirm the household composition over the past 2 weeks, household size and genealogical relationships between the case or cases and their household contacts;
- examine the house and its surroundings for evidence of animals or wildlife, and note whether animals have access to household water and food storage areas, and whether individuals were exposed to surfaces contaminated by animal excrement;
- create a map of the house and its surroundings, indicating the house's location in relation to neighbours or other relatives, backyard animal housing and commercial sector farms, markets and nearby bodies of water that animals could inhabit; and
- document locations of food and water sources for affected households.

This information will assist in identifying possible sources of infection, modes of transmission and populations at risk.

Health-care facilities

At the health-care facilities visited by cases during the course of their illness:

- check for other possible cases with special attention to health-care workers; this includes reviewing consultation, admission or laboratory registers and logs to identify patients with similar respiratory disease presentation;
- document acute respiratory disease activity and surveillance trends, including (if known):
  - influenza vaccination coverage and population age structure;
  - "baseline" weekly or monthly rates of influenza-like illness (ILI), SARI or pneumonia admissions or visits, by reviewing patient registers for extended periods of time (e.g. 1 year, if feasible) – see Annex 3 for an example of a report summarizing surveillance systems and respiratory disease activity;
- document procedures used to triage and manage the cases, including the infection control and case management practices applied;
- document patient flow and areas where the cases were located during their visit or admission, and the likely intensity of exposure to patients, staff and visitors during that time frame; and
- check for the availability of drugs such as antiviral drugs; supportive therapies such as antipyretics and antibiotics; and supplies for specimen collection, cold chain storage and transport packaging.

This information will help to identify cases, assess the potential for further disease spread including nosocomial transmission, provide early guidance on infection control and medical management, and initiate support for the facilities' preparedness for new additional cases by provision of technical support or supplies.

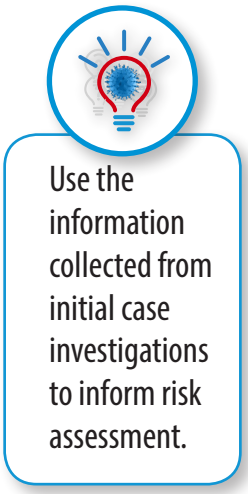
3.3 Protect the investigators

Standard IPC procedures and standard precautions[3] should always be applied, and PPE used according to risk, to protect the health of the investigators (*15*). Appropriate PPE – according to the most probable modes of transmission – should be used when in contact with symptomatic persons and in situations where human-to-human transmission is suspected. Decisions

[3] Standard precautions include hand hygiene and use of relevant PPE, depending on risk of direct contact with patients' blood, body fluids, secretions (including respiratory secretions) and non-intact skin. Standard precautions also include prevention of needle-stick or sharps injury; safe waste management; cleaning, disinfection and, where applicable, sterilization of patient-care equipment and linen; and cleaning and disinfection of the environment. Use of respiratory hygiene in anyone with respiratory symptoms should be encouraged.

on transmission-based precautions to be applied can be guided by the location of the investigation, cultural considerations, health status of interview respondents and surrounding persons, and the type of activity undertaken (e.g. specimen collection, interview or inspection of facility). Basic social distancing, hand hygiene and respiratory hygiene practices should always be emphasized. As PPE can be perceived negatively by communities not familiar with its use, investigators may elect to interview people outdoors rather than in closed interior settings, and to avoid close contact with respondents. Examples of close contact include touching, speaking with, providing care or being less than 1 m away from the other person.

All individuals investigating the event (including support team members such as logisticians or drivers) should have access to sufficient amounts of PPE, hand hygiene supplies and respiratory hygiene supplies such as disposable tissues. Further guidance on the use of PPE in health-care and other settings during case investigation and clinical management is available (*15-17*). Examples of hand hygiene posters and leaflets developed by WHO can be printed and distributed to health-care facilities or to other sites visited where there is risk of contamination or infection (*18*).



3.4 Develop case definitions

Case definitions standardize the investigation by setting out clear criteria for who should be considered as a case and who should not. Case definitions are applied systematically and without bias to all persons under investigation. Working case definitions should be developed using information obtained from the initial interview and home visit of the case patient, along with known information about the pathogen and its epidemiological characteristics. The case definitions should be sensitive enough during the initial stages of the investigation to capture most cases. As the investigation evolves and more information is obtained, it may be desirable to refine the definition to increase its sensitivity and specificity.

Typically, case definitions are divided into three categories: suspect, probable and confirmed. This allows differentiation of cases using clinical, epidemiological and laboratory findings. The definition for suspect cases is usually based on clinical signs and symptoms. The definition for probable cases commonly refers to suspect cases with the addition of an epidemiological link to a confirmed or probable case, a preliminary laboratory test result, chest X-ray finding or fatal outcome. The definition for confirmed cases refers to cases where diagnostic laboratory results have confirmed the infection.

For avian influenza A(H5N1), A(H7N9) and MERS-CoV, WHO has recommended case definitions primarily for standardized international reporting of cases (*19-21*). These definitions can be modified for the purpose of a local investigation, to incorporate time periods, localities, illness characteristics, exposure and other features relevant to the event.

Time, place and person features to consider in a case definition are outlined below:

- ***Time*** **–** for retrospective case-finding purposes, the time period should cover at least 2 weeks before the onset of symptoms of the case with the earliest onset date. Prospectively, the time period should cover twice the incubation period if known, or 2–4 weeks after the last case recovered or died if unknown. If necessary, the time periods in the definition can be revised once the incubation period and period of infectivity become clear.

- ***Place*** **–** this is the local community where the case occurred, and it should include an area that incorporates other individuals who may have exposures to the same source of illness as the initial cases. If the relevant exposures are unknown, the place should instead include the population area that the cases may have recently visited, which generally includes local markets, places of worship, farms and health facilities.

- ***Person*** **–** this refers to patients' characteristics, including the list of key symptoms observed in cases. If the characteristics of the patients are not well known, it is possible to also consider broader syndromes and characteristics such as:
  - a patient with SARI who presents with fever and cough, requires admission to hospital, and whose disease is not completely explained by another pathogen;
  - a patient with SARI whose clinical course is unexpectedly severe and who did not respond to treatment for another suspected pathogen;
  - a patient with SARI with recent exposure to animals;
  - an immunocompromised patient who presents with an acute illness that is not fully explained by another pathogen; and
  - a health worker with SARI treating patients with respiratory disease.

- ***Exposures*** **–** for pathogens with well-defined risk factors or in events where a point-source of infection is likely, the case definition may include exposure to the relevant events, environment, animals, behaviours or persons.

3.5 Find additional cases

Intensive efforts are required to identify additional cases and understand the size of the disease event. Additional cases may be detected among contacts and in the community. Activities include identifying and monitoring contacts of identified cases, and actively searching for other cases among persons with similar exposures or illness.

3.5.1 Identify and monitor contacts of cases

The purpose of contact monitoring is to find new suspected cases, document potential human-to-human transmission, and provide targeted interventions to decrease the risk of illness and interrupt further transmission. Contacts of cases should be identified and monitored for the appearance of symptoms for a designated number of days after last exposure to the case. For the event under investigation, it is necessary to define a contact, decide on the number of days for monitoring and establish procedures for monitoring, reporting and triage. Some of these aspects are addressed below. Once the definitions have been finalized, the procedures presented in Annex 4 should be used to streamline the contact tracing and monitoring process.

Who is a contact?

Contacts are persons who had contact with individuals fitting the case definition during the presumptive incubation period (*6*). For respiratory disease pathogens for which modes of transmission, periods of infectivity and incubation periods are not known, a contact may be defined as a person who came within 1 m distance from the case without PPE in the 1 day before the onset of the case's illness until 14 days after the onset of the illness (*10*). It may be necessary to trace contacts for suspect cases if the capacity to determine probable or confirmed case status is limited.

How long is the contact-monitoring period?

The number of days for monitoring contact health status depends on the incubation period of the pathogen. Contacts of cases infected with avian influenza A(H5N1) virus should be monitored for 7 days from the last unprotected contact, whereas contacts of cases infected with avian influenza A(H7N9) virus or MERS-CoV should be monitored for 14 days. If the incubation period and period of infectivity are unknown, an alternative approach is to monitor contacts for up to 14 days, until information about these epidemiological features is determined and the contact follow-up period can be revised.

Use the initial risk assessment conducted for this event to guide decisions on the scope of contact tracing and monitoring.

If an event may constitute a public health emergency of international concern according to defined criteria in the International Health Regulations (2005) (*12*), notify WHO. For more details, see Section 7.2.

How will contacts be monitored?

Monitoring of contacts can be done through household or virtual visits to check for symptoms, or by telephone, with the request that the contact self-reports if symptomatic. Factors influencing this choice include the feasibility of telecommunication, availability of human and logistical resources to conduct physical visits daily, likelihood of contacts recognizing and self-reporting illness, likelihood of symptomatic contacts fleeing from health authorities and consequences of missing cases.

Should chemoprophylaxis be provided to contacts?

The use of chemoprophylaxis, if available, depends on the event context. As per guidance for outbreaks of avian influenza A(H5N1) virus infection, use of chemoprophylaxis should be guided by an exposure risk assessment (*22*).

How will symptomatic contacts be managed?

Any contact who becomes ill in the designated monitoring time frame should be tested, isolated and provided with the available clinical care needed. Isolation can be at health facilities or at home while awaiting test results, but this depends on the severity of illness, feasibility and availability of hospital beds. Any newly identified cases should have their own contacts identified and monitored.

What if there is asymptomatic transmission?

If asymptomatic transmission is suspected in the event, as has been seen in outbreaks of MERS-CoV, consider testing asymptomatic contacts, such as household contacts, health-care workers or other inpatient hospital contacts. Guidance on MERS-CoV is available (*23*). Asymptomatic cases may be advised to self-isolate until repeat specimens test negative or until they are deemed unlikely to infect others.

3.5.2 Active case finding

Active case finding can be used to find additional cases beyond those identified from case contacts. Such case finding supports efforts to determine the magnitude of transmission in the community, ensure that all possible patients receive treatment, identify the source and mode of transmission, and document case characteristics.

In the event-affected areas, efforts for case finding and laboratory testing should be focused on the following groups:

- symptomatic individuals who may have been exposed to the same pathogen source as the case patient, individuals with animal or wildlife exposures, and individuals presenting with or who died of unexplained SARI;

- patients with unexplained SARI or unexplained illness consistent with the case definition who are currently hospitalized in the same health facilities where another case was admitted; and

- health-care workers who cared for suspected, probable or confirmed cases and who developed acute respiratory disease.

The location and context of the event, as well as risk assessments, will guide the process for active case finding. The team should consider interviewing community leaders, schools, workplaces, community health providers (including private or traditional practitioners), hospital clinicians and laboratories to identify cases. If the event appears localized, they should consider conducting house-to-house searches, or engage traditional healers and community groups (e.g. women's groups) to identify cases and encourage reporting prospectively. All stakeholders interviewed should be encouraged to immediately report any patients who have signs, symptoms and exposures aligned with the disease under investigation.

Another approach is to search for cases by reviewing patient registers or logbooks at health facilities where cases have been reported or in the event location. The aim is to look for other patients listed in the past 2–4 weeks who may have presented with similar signs and symptoms as the disease being investigated. It is important to follow up any patient whose illness appears compatible with the disease but who has already been discharged. Annex 5 explains the process for conducting a health facility register review as part of active case-finding efforts.

3.6 Enhance surveillance

In addition to case-finding and contact-monitoring activities, it may be helpful to enhance existing surveillance systems in the locations where cases reside, where animal outbreaks are occurring or where the source of infection is suspected. The main purpose is to detect cases that might arise subsequent to the discovery of the initial cases. The geographical area targeted will depend on the event context, especially the suspected exposures.

Conduct a risk assessment to support decisions on need and scale of enhanced surveillance activities. For example, ask risk questions such as:

- What is the public health risk of further exposure to the pathogen?
- What is the public health risk of spread beyond the currently known geographical regions affected by the event?

The duration of the enhanced surveillance will depend on the findings of the investigation, the pathogen causing the event and whether there is evidence indicating that sustained transmission may be occurring in the area. For example, for outbreaks of avian influenza A(H5N1) infection, surveillance should be enhanced for 2 weeks after the recovery or death of the last human case. For MERS-CoV, surveillance should be enhanced for 1 month after the last case. However, ongoing circulation of these viruses in animals in the affected area will require enhanced surveillance periods to be prolonged, because of the potential for zoonotic transmission.

The scope of the enhanced surveillance activities depends on the health-care seeking behaviour of the population, and a range of options should be considered (e.g. active and passive approaches that are health-care based and community based). In hospital settings, clinicians should consider testing patients with unexplained SARI or with signs and symptoms aligned with the current disease under investigation. Testing should be emphasized for patients who, within the 2 weeks before onset of illness, had travelled to or been exposed to humans or animals from the affected area, or had been exposed to other patients who had recently been diagnosed with SARI.

It may be necessary to consider enhancing surveillance activities at other health-care facilities such as private practitioners, laboratories and traditional healers. If needed, target surveillance at groups with greater occupational risk of exposure (e.g. health-care workers and those exposed to live or dead animals). Enhanced surveillance can be built on existing systems using supplementary measures such as telephone hotlines, rumour tracking and verification, and radio or other emergency networks, as needed. Also, it is possible to increase the timeliness of enhanced surveillance by increasing the frequency of reporting (e.g. from weekly to daily).

The success of enhanced surveillance efforts will depend on training of health professionals, local public health investigators and volunteers, and education of the community-at-large to be alert for possible cases. In particular, early self-reporting of illness and consultation with public health facilities should be encouraged (e.g. by initiating fever clinics), so that prompt and appropriate testing and clinical care can be provided. The affected community should be provided with appropriate education, prevention and intervention measures, to reduce the risk of acquiring infection from human and animal sources.

3.7 Collect specimens

Rapid collection and testing of appropriate specimens from cases and symptomatic contacts is a priority, and should be guided by a laboratory expert. Investigators need to be familiar with the type and the recommended number of specimens to be collected, optimal timing of specimen collection, correct collection techniques (including the appropriate use of PPE for different types of specimens collected), and the safety standards for specimen storage, packaging and transport *(24, 25)*. Collection of specimens from cases under investigation should be carried out in line with the established infection control guidelines *(16)*.

Table 1 provides a list of specimens that should be collected, as well as their storage and transport requirements in the context of SARI. The order of specimen priority depends on the pathogen. For example, lower respiratory tract specimens are preferred for detection of MERS-CoV (*11*), whereas upper and lower respiratory tract specimens as well as serum are preferred for influenza virus detection (*19, 25*). When the event etiology is unknown, it is useful to collect various specimens when feasible, to maximize opportunities for detection and characterization.

Specimens should be labelled with a unique identifier that can be linked to case patient demographic and epidemiological data, and identifiers should be assigned that can distinguish multiple specimens obtained from the same patient.

Adequate laboratory capacity for processing and testing of specimens must also be identified, and performed in accordance with relevant national biological safety regulations. If the capacity or biosafety facilities of a laboratory are not adequate to undertake activities to characterize potential dangerous pathogens, specimens should be shipped to a national or international laboratory with adequate biosafety facilities. Various laboratory-based techniques can be used to test for a range of viral, bacterial or mycotic pathogens or toxins.

For novel pathogens, partial and whole genome sequencing can be used to provide information on the origin and source of exposure. Relevant laboratory manuals and WHO guidance for specific pathogen diagnostic procedures should be consulted.

If influenza is suspected as the causative agent, Fig. 1 provides a suggested laboratory-testing algorithm. Manipulation of samples from patients meeting clinical and epidemiological risk factors that suggest infection with non-seasonal influenza viruses should be performed at a minimum of biosafety level 2 (BSL-2) containment and BSL-3 practices. All manipulations of live virus samples must be performed within a class-II (or higher) biosafety cabinet. The manual for the laboratory diagnosis of influenza provides more information *(26)*. A designated WHO collaborating centre (WHO CC) should be consulted on appropriate procedures and biosafety needs *(27)*. For influenza viruses, especially non-seasonal influenza viruses, detailed genetic and antigenic characterization by designated WHO CCs is critical to inform pandemic influenza global risk assessments. All influenza A virus-positive samples that cannot be subtyped should be sent immediately to a WHO CC for further analysis *(27)*. Laboratory-testing algorithms are available if other causative agents are suspected, including for MERS-CoV (*28*) or SARS *(29)*.

Table 1. – Type of specimens for testing for the presence of respiratory disease pathogens and advice on handling

SPECIMEN TYPE	TRANSPORT MEDIUM	TRANSPORT TO LABORATORY[a]	STORAGE TILL TESTING	COMMENT
Sputum	NA	4 °C	≤48 hours: 4 °C >48 hours: –70 °C	Ensure the material is from the lower respiratory tract
Bronchoalveolar lavage	NA	4 °C	≤48 hours: 4 °C >48 hours: –70 °C	There may be some dilution of pathogen, but still a worthwhile specimen
Tracheal aspirate	NA	4 °C	≤48 hours: 4 °C >48 hours: –70 °C	
Nasopharyngeal aspirate	NA	4 °C	≤48 hours: 4 °C >48 hours: –70 °C	
Nasal wash	NA	4 °C	≤48 hours: 4 °C >48 hours: –70 °C	
Nose or throat swab	VTM	4 °C	≤5 days: 4 °C >5 days: -70 °C	
Nasopharyngeal swab	VTM	4 °C	≤5 days: 4 °C >5 days: –70 °C	
Tissue from biopsy or autopsy including from lung	VTM or saline	4 °C	≤24 hours: 4 °C >24 hours: –70 °C	
Serum	NA	4 °C	≤5 days: 4 °C >5 days: –70 °C	Collect paired samples: • acute – first week of illness • convalescent – 2 to 3 weeks later
Whole blood	EDTA tube	4 °C	≤5 days: 4 °C >5 days: –70 °C	For antigen detection particularly in the first week of illness
Urine	NA	4 °C	≤5 days: 4 °C >5 days: –70 °C	

EDTA, ethylene diamine tetra acetic acid anticoagulant; NA, not applicable; VTM, viral transport medium

[a] Infectious substances are generally under Class 6.2 and can be transported as Category A or Category B. Category A refers to infectious substances that are transported in a form that, when exposure occurs, may cause permanent disability, life-threatening illness or fatal disease to humans or animals. Category B refers to infectious substances that do not pose a risk of causing permanent disability, life-threatening illness or fatal disease to humans or animals. Check with the laboratory, shipping unit and courier for advice on appropriate categorization and packaging instructions required. See WHO Guidance on regulations for the transport of infectious substances (*24*).

If laboratory capacity or biosafety facilities are not adequate to undertake activities to identify an unknown respiratory pathogen or for any step in this process, specimens should be shipped to a WHO CC for processing.

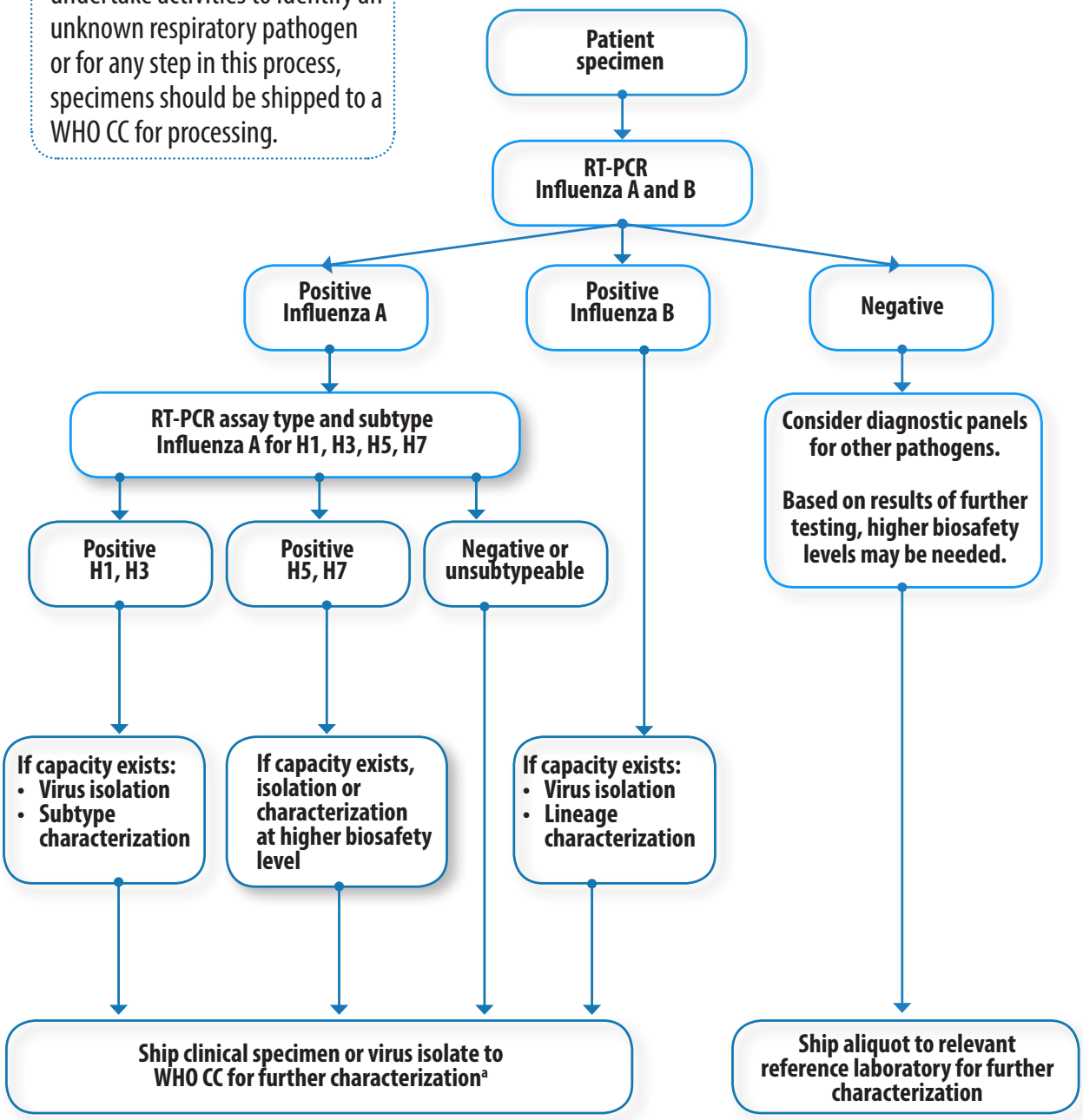


Fig. 1. – Laboratory algorithm if influenza is suspected in the event

CC, collaborating centre (WHO); RT-PCR, reverse transcription polymerase chain reaction

[a] See WHO Operational guidance on sharing seasonal influenza viruses with WHO Collaborating Centres (CCs) under the Global Influenza Surveillance and Response System (GISRS) (*30*), and WHO Operational guidance on sharing influenza viruses with human pandemic potential (IVPP) under the Pandemic Influenza Preparedness (PIP) Framework (*31*).

3.8 Undertake animal health and environmental investigations

Investigators in public health and animal health need to work together to assess the role of animals as sources of human exposure and infection. Field visits to investigate the occurrence of illness among animals or the circulation of the pathogen in animals can include visits to:

- the case's home and surroundings;
- farms and live animal markets;
- local areas where food is produced to be consumed raw or unpasteurized; and
- places frequented by wild animals (e.g. caves or watering holes).

Information should be collected on animal illnesses and deaths, as well as animal housing, feeding and handling practices. Investigators should coordinate their activities so that human and animal specimens can be linked and compared. Guidance from the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) should be consulted regarding technical issues related to surveillance, prevention and control of disease in animals.

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

DATA ANALYSIS

When setting up the record system procedures, ask the following questions:

- *Where will the records be kept?*
- *How will the records be kept?*
- *Who will be assigned to record-keeping?*
- *How will the records be backed up?*
- *How will the confidentiality of the records be maintained to protect personal information?*

4.1 Manage the data

Investigations generate a large volume of data about cases, contacts and individuals being investigated. Investigators should use a line list and establish procedures for record-keeping and data validation to facilitate the analyses.

The line list organizes data collected from investigation forms, clinical records and laboratory test results for different categories of cases, contacts and people under investigation. It should be used as the starting point for analysing data descriptively. To ensure high-quality line-list data, an electronic record-keeping system should be established; this system should be easily accessible, stable and organized. This will minimize duplication of effort, risk of data loss and errors in data entry.

To maintain high-quality data in an event information management database, the following should be considered: daily entry of records; cross-checking of the information gathered with other sources of the same information; and routine cleaning of the data, including range checks and logic checks for each variable. When possible, automatic data checks should be built in.

4.2 Analyse the data

The data analysis plan will depend on the objectives of the investigation. Basic steps include analysing the data by time, place and person to characterize trends over time, geographical distribution and the populations affected by the disease. The results of this analysis can be used to identify or infer the population at risk for the disease; raise hypotheses about the etiology, source and modes of transmission; and provide insight into potential intervention or prevention measures. The data can also underpin risk assessments, and the availability or lack of data will affect the level of confidence for the risk assessed.

4.2.1 Time

An epidemic curve should be constructed, with the number of cases on the y-axis, and their date or time of illness onset on the x-axis. An example of an epidemic curve is shown in Fig. 2. This curve can provide information on the magnitude and various epidemiological characteristics of the event, as well as the impact of control interventions, including:

- ***patterns of spread and exposure*** – the shape of the curve can indicate whether it is a common source (point, continuous or intermittent), propagated (human-to-human, vehicle-borne or vector-borne), a combination of the two, or neither pattern (suggestive of some zoonotic or vector-borne diseases, where sufficient infection in the host or reservoir species, sufficient presence of vectors and sufficient human–reservoir or human–vector interaction leads to cases); the pattern of spread can best be assessed if the disease incubation period is known;

- ***time trend of the event*** – whether it is starting, peaking or waning; this may indicate whether to expect a large or a small number of new cases;

- ***disease incubation period*** – in situations where the time frame of exposure is known but the disease etiology and features are unknown;

- ***type of exposure*** – the shape of the epidemic curve can provide clues about whether there is a possibility of propagated human-to-human transmission;

- ***outliers*** – the timing and number of cases that do not fit into the body of the curve may provide clues to other exposures or clusters of illness; and

- ***impact of interventions implemented*** – to evaluate whether the number of cases and their characteristics have shifted since measures were introduced by public health or other authorities.

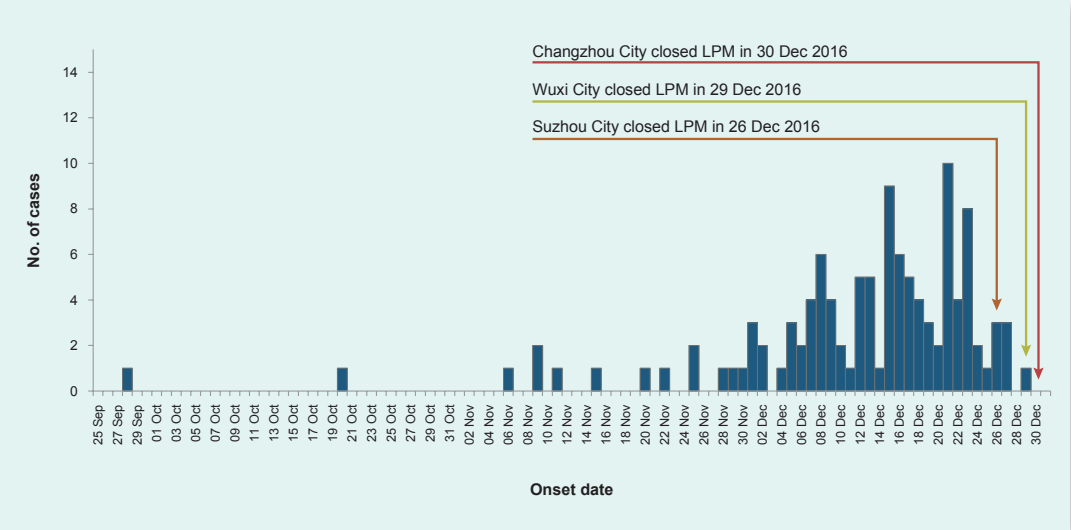


Fig. 2. – Example of epidemic curve showing cases of avian influenza A(H7N9) in China [excluding Hong Kong SAR (China), Macao SAR (China) and Taiwan, China] by day, September 2016–December 2016 (*32*)

4.2.2 Place

Cases should be mapped by geographical location; for example, by village, by home or by location in a health-care facility. The maps may be local, regional or national, depending on the geographical spread of the event. An example of an event map can be seen in Fig. 3. The visual interpretation of the data can provide important etiological clues, identify clustering and provide details on the geographical extent of disease spread:

- ***Spot map*** – use spot maps to assess the likely mode of spread. For example, cases clustered in one hospital ward would be consistent with a common source or propagated human-to-human spread, whereas scattering of cases in that facility across several wards would be more consistent with a widely disseminated vehicle, a mobile patient who is spreading disease or a source that is not associated with a particular room (e.g. air-flow patterns in the building).

- ***Area map*** – use area maps to take into consideration the underlying population in that location. This allows for direct comparison of incidence rates between sites, regions or countries.

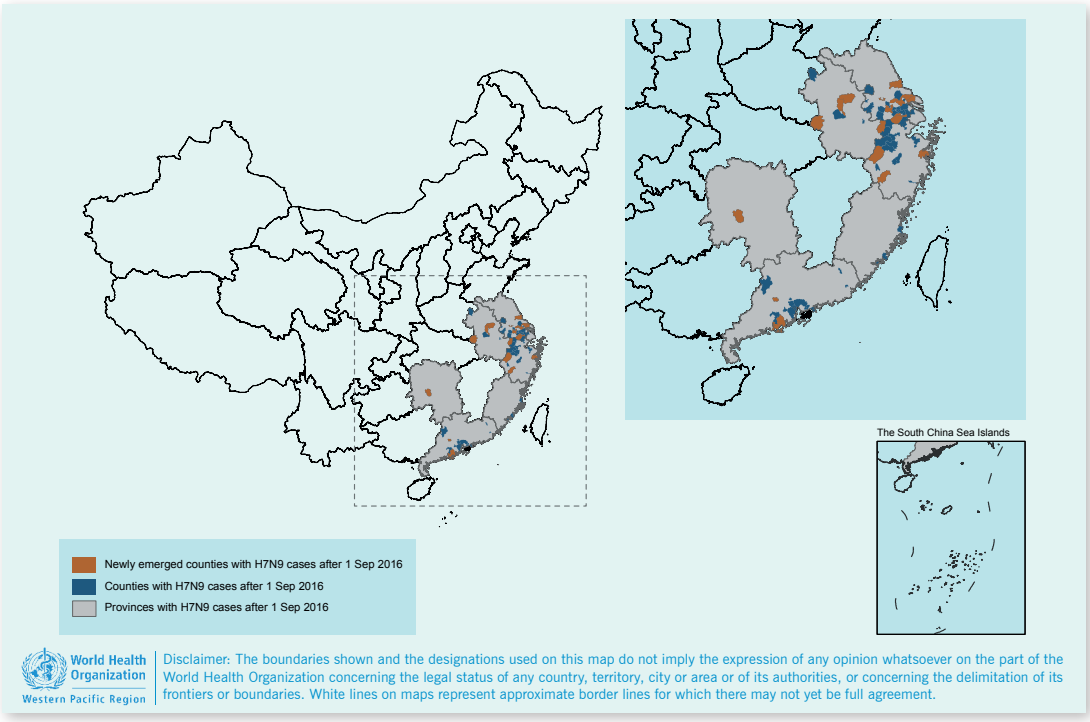


Fig. 3. – Example of map showing geographic distribution of human infection with A(H7N9) virus in China [excluding Hong Kong SAR (China), Macao SAR (China) and Taiwan, China], September 2016–December 2016 (*32*)

4.2.3 Person

To understand the clinical spectrum and disease dynamics, it is necessary to analyse:

- epidemiological and clinical parameters of the cases;
- attack rates by age, sex, occupation and exposure history; and
- for clinical parameters, the spectrum of illness severity, including proportion of cases with pneumonia, those requiring hospitalization, intensive care unit admission and the proportion that were fatal.

A summary table example of demographic, exposure and clinical features is shown in Table 2.

Table 2.– Example of demographic and clinical characteristics of 186 cases of laboratory-confirmed MERS-CoV infection, the Republic of Korea, 2015 (*33*)

CHARACTERISTICS	NO. OF PATIENTS
Sex, *n* (%)	
Male	111(59.7)
Female	75 (40.3)
Age (y), median (IRQ)	**55.(42.3)**
≥65y, *n* (%)	55 (29.6)
Case classification, *n* (%)	
Healthcare personnel	25 (13.4)
Patient	82 (44.1)
Caregiver	61 (32.8)
Others*	18 (9.7)
Symptoms at presentation, *n* (%)	
Fever/chills	138 (74.2)
Cough	33 (17.7)
Dyspnea	10 (5.4)
Myalgia	47 (25.3)
Headache	16 (8.6)
Gastrointestinal symptoms †	24 (12.9)
Sputum	14 (7.5)
Sore throat	8 (4.3)
Cormorbidities, *n* (%)	
Any ‡	102 (54.8)
Respiratory disease §	23 (12.4)
Diabetes mellitus	52 (28.0)
Cardiac disease¶	42 (22.6)
Chronic kidney disease	9 (4.8)
Malignancy	43 (23.1)
Known setting of contact, *n* (%) ¤	
Healthcare facility	178 (98.0)
Household	1 (.0.5)
Ambulance	3 (1.5)
Time from symptom onset to laboratory confirmation in days, median (IQR)	**5 (3-9)**
Time from symptom onset to death in days, median (IQR)	**15 (10-20)**
Outcome as of July 13, 2015, *n* (%)	
Recovered	131 (70.4)
Ongoing treatment in hospital	19 (10.4)
Died	36 (19.4)

* Includes visitors, hospital security agents etc; †Any one or more amouing the following symptoms: nausea, vomiting, diarrhea, gastric discomfort, loss of appetite: ‡ Any one or more among respiratory dieseases, including chronic obstructive pulmonary disease and asthma, diabetes mellitus, cardiac disease, chronic kidney disease, and malignacy; § Includes chronic obstructive pulmonary disease and asthma; ¶ Includes ischemic heart disease, arrhythmia and heart failure; ¤With exclusion of the index patient and three cases of which the precise setting of contact is unidentified. IQR = interquartile range.

Individual case timelines can be constructed, showing the timing between exposure, disease onset and disease outcome; timelines can then be compared to those of other cases in the event. An example of an individual case timeline is shown in Fig. 4.

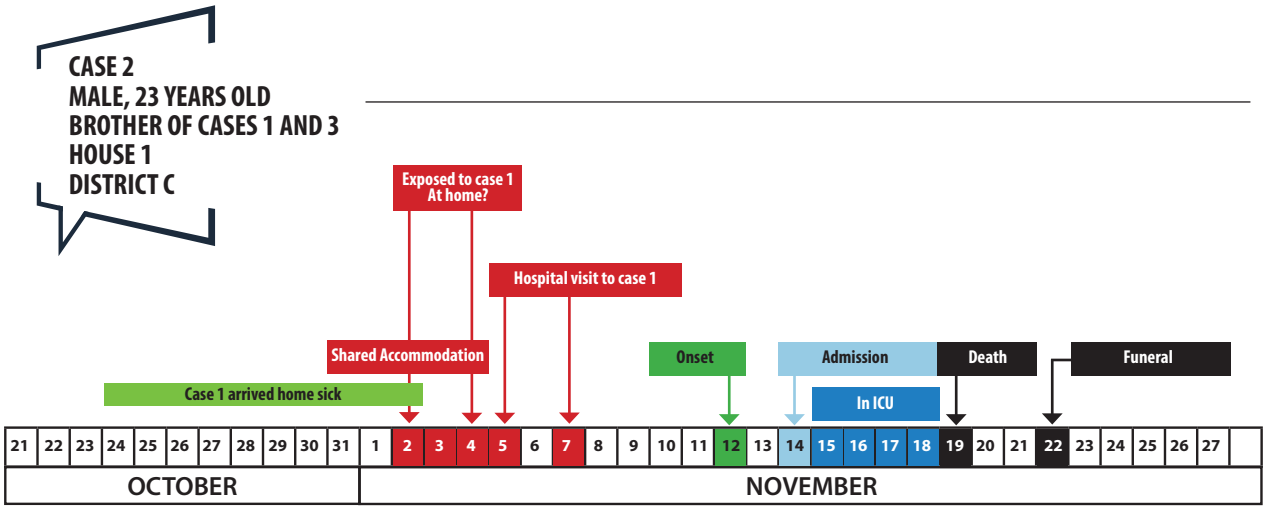


Fig. 4. – Example of timeline showing exposure, onset and disease outcome for a secondary case in a disease event

Individual case timelines can be used to construct a transmission map to visually communicate the dynamics and pattern of spread. An example of a MERS-CoV transmission map can be seen in Fig. 5. This map highlights the nosocomial spread resulting from an index patient who infected 26 secondary cases at one hospital, which then resulted in further chains of transmission at that hospital as well as other health facilities where some patients had been relocated.

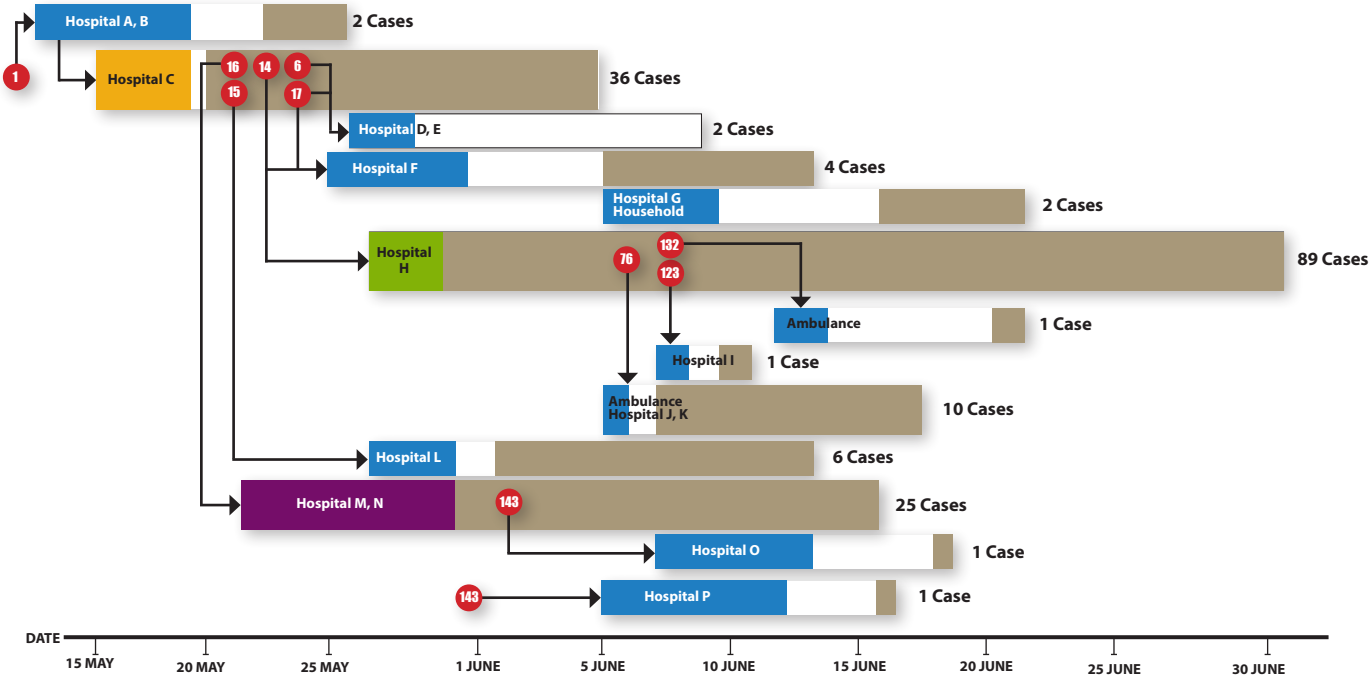


Fig. 5. – Example of transmission map of 182 confirmed cases of MERS-CoV infection in the Republic of Korea by July 2015 (*33*, *34*)

For emerging pathogens causing severe acute respiratory disease such as avian influenza A(H5N1) virus, SARS or MERS-CoV, determine whether the pathogen has acquired improved ability to cause human disease or improved its transmissibility between humans. Molecular characterization of the pathogen and transmission experiments in laboratory animals can indicate changes in transmissibility or adaptability.

Epidemiological assessment of the pattern of spread can also indicate changes in transmissibility. Fig. 6 shows an example of an outbreak of avian influenza A(H5N1) in which one zoonotic case led to propagated human-to-human transmission of the virus. Data from outlier cases or superspreaders should be fully analysed to identify possible factors for the increased infectiousness or transmission pattern.

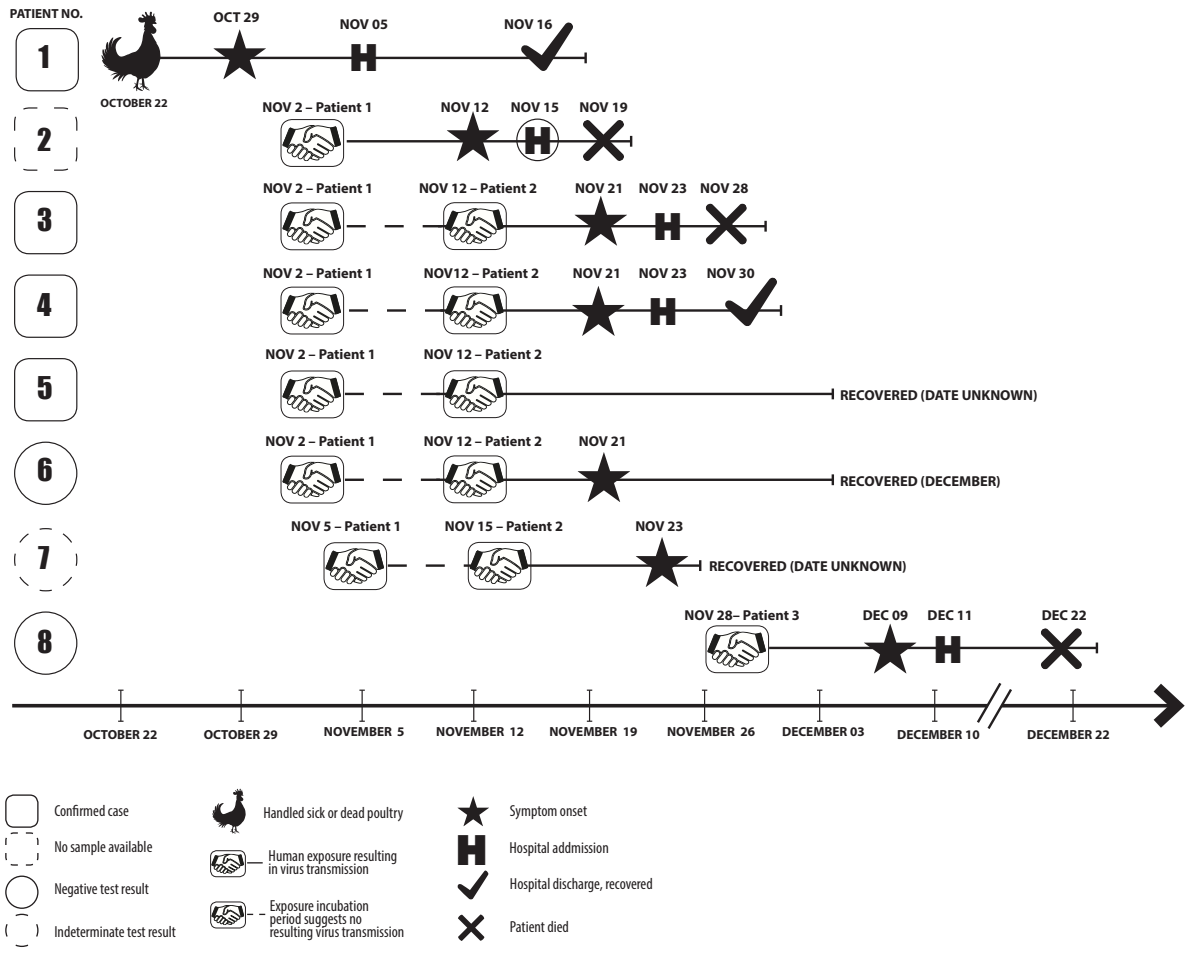


Fig. 6. – Example of path of infection in a cluster of avian influenza A(H5N1) cases in Pakistan, 2007 (*35*)

For non-seasonal influenza events where there is evidence of human-to-human transmission, consider conducting a pandemic risk assessment by asking:

- *What is the risk of sustained human-to-human transmission of the virus?*

Consider contacting WHO to undertake a global risk assessment for this virus using the Tool for influenza pandemic risk assessment (TIPRA, *36*)

Key epidemiological questions to consider for zoonotic diseases with potential for increased human-to-human transmissibility include:

- Is there a sharp increase in the number of cases or suspect cases despite adequate control measures in the animal population?
- Is there increased cluster frequency, size, duration or spread within a specific area?
- Is there a clustering of cases with evidence of two or more generations or chains of transmission based on person exposure and illness onset timelines?
- Are there cases in non-family member contacts?
- Are cases mildly or moderately ill?
- Is there absence of animal exposures?
- Are there changes in epidemiological features such as the age distribution or severity of disease?

Any of the above factors should raise concern that the pathogen could be acquiring the necessary transmission properties that might suggest greater spread of virus among humans, and that could allow it to cause a pandemic. The findings may affect the national and international event-notification requirements, and may trigger broader preparedness measures for disease control.

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

FURTHER COMPLEMENTARY STUDIES

Many of the questions regarding the clinical manifestations and epidemiological characteristics of the disease will only be answered by detailed investigations of cases. Table 3 summarizes some public health questions that may require complementary studies during an event of non-seasonal influenza or other emerging acute respiratory diseases. The findings should be used to inform decisions on response measures or revision of long-term practices. Specific investigation protocols for influenza and MERS-CoV are available and can be rapidly adopted for the event context *(8, 11)*.

Consider reassessing the public health risk of the event when new information or analyses become available.

Findings can then be used to guide further decisions on control measures and additional data needs.

Table 3.– Potential studies that can address public health questions during an investigation

QUESTION	INVESTIGATION	PUBLIC HEALTH DECISION
How easily does human-to-human transmission occur?	• Survey of exposed health-care workers with serological and microbiological testing • Contact tracing of exposed family and social contacts supported by serological testing • Laboratory studies to assess markers of mammalian adaptation or human infectivity	• Isolation and quarantine needed to prevent and control transmission
What exposures result in infection?	• Interview of case patients or proxies • Case–control study with contacts from communities affected by the event or those with occupational exposure	• Measures to prevent or mitigate exposures
What is the clinical appearance and course of illness?	• Collection of clinical and laboratory data on case patients	• Development of case definitions • Improvement of clinical management practices
What is the source of the pathogen?	• Microbiological and serological testing of animals, foods and environmental sampling • Seroepidemiological surveys of specific human risk groups • Testing of stored animal specimens	• Implementation of biosafety measures at the interface between animal and human; modification of animal husbandry and trading practices • Control of animal populations
Is the pathogen new? When did it first appear?	• Review of recent surveillance data, admission records and vital statistics data for the relevant clinical syndrome • Retrospective testing of stored clinical specimens from studies, surveillance or health facility archives • Genomic characterization and phylogenetic analysis	• Feasibility of containment, region or regions to focus investigations on, and urgency of response

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

IMPLEMENT RESPONSE AND CONTROL MEASURES

6.1 Manage the sick

The clinical evaluation, triage and management processes for cases detected in the event should be standardized. As an example, Fig. 7 shows an algorithm for managing potential cases in an event of non-seasonal influenza (*37*). The algorithm facilitates early recognition of patients, implementation of IPC measures, collection of specimens for laboratory diagnosis, early supportive therapy and monitoring, and management of severe illness. Generally, the approach can be applied to both children and adults, and can be adapted for use with other respiratory diseases. However, this approach is not meant to replace detailed clinical management protocols, and it does not address the needs of patients with special considerations such as pregnant women or immunocompromised individuals. In consultation with specialists, the algorithm should be adapted to the event and the local circumstances.

The algorithm should be provided to health-care workers involved in patient evaluation, triage and management, as should updated information about the event, patient clinical presentation and the event's case definition. Other guidance can be distributed to refresh health-care worker knowledge in respiratory disease management and one example is the video on emergency guidelines for the management of patients with respiratory distress and shock (*38*). Practical training will be required to ensure that health-care workers can provide appropriate care to the patients.

If the event is caused by an emerging pathogen for which clinical information is limited, investigators should consider participation and use of the clinical characterization data tools developed by the International Severe Acute Respiratory and Emerging Infection Consortium (*38*). These data tools facilitate the collection of detailed data for emerging SARIs, and apply clear definitions and standardized end-points.

Consider a risk assessment to address the question:

- *What is the public health risk of health-care workers involved in patient care becoming infected?*

This may guide decisions on the need for additional training, IPC measures, and adjusting patient flow and triage.

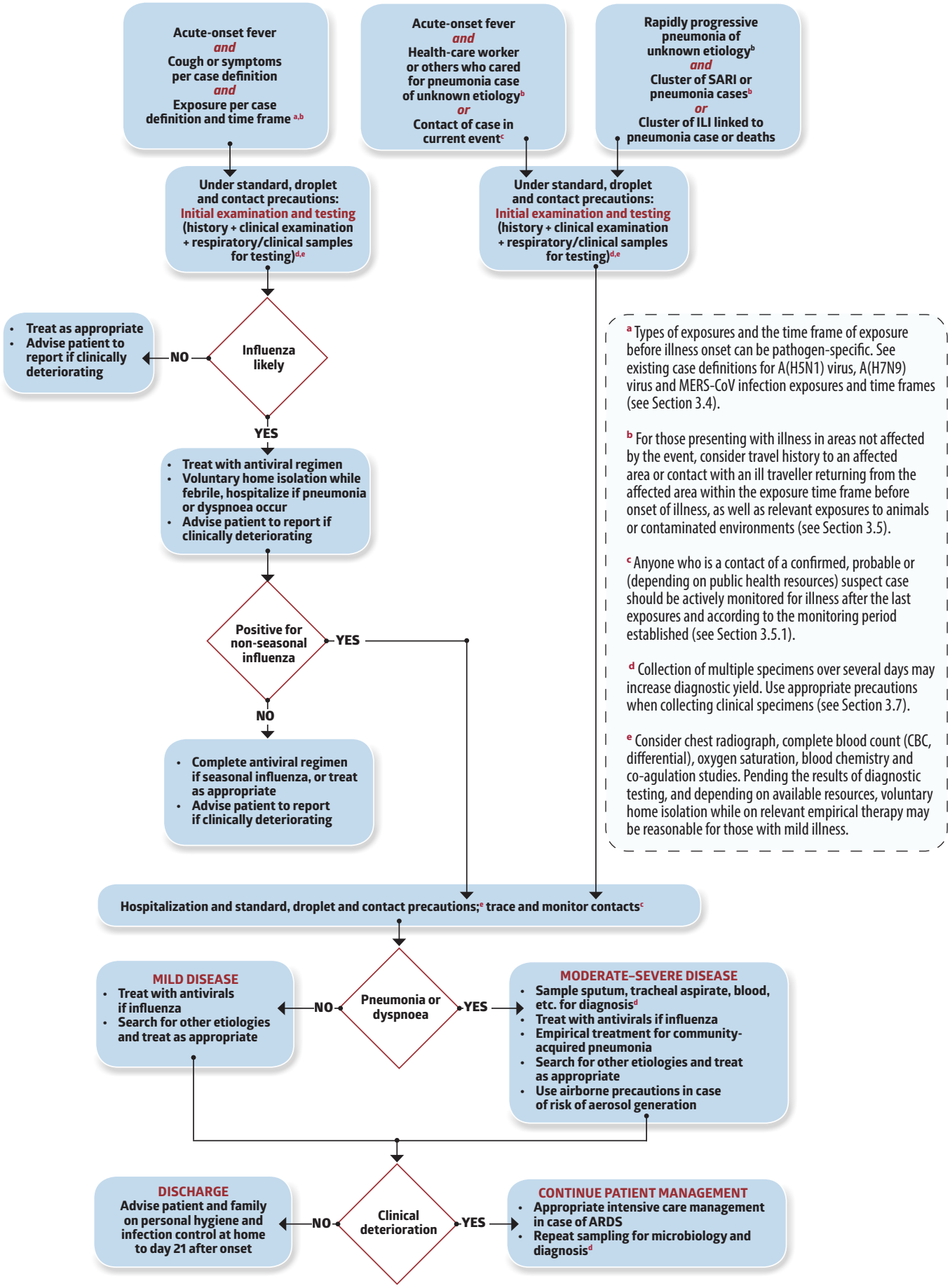


Fig. 7. – Clinical management algorithm for potential cases in an event of non-seasonal influenza
ARDS, acute respiratory distress; ILI, influenza-like illness; SARI, severe acute respiratory infection

6.2 Prevent further transmission

Public health interventions should be selected to prevent further disease transmission depending on the suspected etiology, source and most probable mode or modes of transmission. As can be seen from Table 4 below, various interventions can be considered, and they can be directed at the source or individuals at risk of infection. Not all of these interventions have to be applied, and decisions should be based on the latest evidence and risk assessment outputs.

Table 4. – Public health interventions to prevent disease transmission and spread (*39*)

INTERVENTIONS DIRECTED AT THE SOURCE:	INTERVENTIONS DIRECTED AT SUSCEPTIBLE INDIVIDUALS:
• promote respiratory hygiene; • treat cases with specific therapeutics or supportive therapy as relevant; • place patients with the same etiological diagnosis in designated areas or wards (cohorting), and those with the same suspected diagnosis in a separate area or ward; • quarantine exposed individuals, or contaminated sites and sources; • involve animal health authorities for relevant control measures if the animal source has been identified; • prevent mass gatherings and limit people movement; • involve food safety authorities for relevant control measures if the food source has been identified; • clean and disinfect contaminated surfaces or environments; and • modify behaviour (e.g. wear surgical masks) or avoid physical contact such as hand-shaking.	• administer prophylaxis, as relevant; • vaccinate, if vaccine is available; • use barrier nursing techniques; • prevent mass gatherings and limit people movement; • modify behaviour such as hand hygiene at key moments (such as before handling food, after using the toilet and after touching secretions); • use shelter-in-place (i.e. reverse quarantine); • trace and monitor contacts; and • communicate prevention strategies through media or health alerts and notices.

When the source and modes of transmission are unknown for a respiratory disease event, a precautionary approach should be used in attempting to stop transmission. Social distancing measures may be required; for example, school closures, avoidance of suspected food sources or culling of animals. These measures require coordination with relevant intersectoral authorities, are difficult to implement and monitor, may not be effective and can be costly to those affected. Therefore, it is important to carefully assess their likely impact before committing to these measures. Interventions should be regularly reviewed and modified based on increasing evidence about the event.

6.3 Infection prevention and control

As observed during SARS and MERS-CoV virus outbreaks, health facilities can become foci for disease transmission, both within a single facility and between facilities. Health-care workers may be especially at risk, and PPE should be available and used rigorously. Patient movement and transfers should be carefully regulated to prevent disease spread, and health-care workers who work in different wards or facilities should be closely monitored. Updates about the event should be shared frequently with facility managers in the affected areas, and clear systems established for triage and referrals. Facility managers should have a clear event manager focal point for regular reporting and information exchange.

A summary of levels of IPC needed during routine patient care (excluding aerosol-generating procedures) is given in Annex 6. Further detailed IPC guidance for respiratory infections is available (*16)*. To prevent nosocomial infections, standard measures include strict infection control during:

- delivery of care and isolation of cases;
- collection, transportation and testing of laboratory specimens in patients suspected of having the disease; and
- administration of treatment to cases, initiation of active case finding, active monitoring of contacts and enhanced surveillance.

6.4 Communicate the risk

The public should be informed about the event, and community outreach about prevention and coping methods to prevent disease spread should be initiated. The aim of public risk communication is to enable the target population to make informed decisions about recommended personal and community-based prevention and mitigation measures.

During the investigation, efficient and timely communication with the public and the media is critical. Risk communication is successful when there is communication based on trust between those who know (experts), those in charge (authorities) and those affected. The credibility of those giving information and advice, their expressions of caring and empathy, and their ability to identify with the public are factors that make risk communication effective.

Investigators should gather insight into stakeholder perceptions, concerns and beliefs, as well as their knowledge and practices. It is important to manage rumours, misinformation and other communication challenges. The information gathered can be used to develop culturally sensitive and appropriate communication messages about specific risk factors and behaviours, and how such risks can be reduced. Depending on the event context, it may be helpful to use a variety of communications techniques, ranging from written media and social media communications to mass communications, and stakeholder and community engagement. Early self-reporting of illness and consultation with public health officials should be encouraged, so that prompt and appropriate testing and clinical care and treatment can be provided.

6.5 Monitor the event and the response

Until the event is contained, it is important to maintain active surveillance, routine data analysis, regular risk assessment and frequent communication and feedback to clinicians, public health teams, the community and other identified stakeholders. It is also important to provide these stakeholders with updated case and clinical data, event magnitude, laboratory findings and effective prevention measures, especially for emerging diseases for which the evidence-base is yet to be established. An event is deemed to be contained if active surveillance in the at-risk population has not yielded new cases during twice the presumed incubation period for that disease.

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

REPORT AND NOTIFY

7.1 Report results of the investigation

During the investigation, daily situation reports should be provided to relevant authorities and stakeholders. Stakeholders may be at local, national and international level, and may include the public or the media. Even before analyses are complete, certain information should be regularly reported (e.g. interventions and the time of their introduction), to inform risk assessment and decision-making.

Once the investigation has concluded, a risk assessment should be conducted to assess the public health risk of the event reoccurring (*7*). Based on the assessment and the field investigation findings, a report can then be prepared that details the characteristics of the event and any conclusions as to the etiology, source, probable mode or modes of transmission and populations affected. This report should immediately be disseminated to the entity that engaged the team, relevant health facilities and laboratories, other relevant agencies and stakeholders. A sample report outline is given in Annex 7.

The event report serves as a document for action, outlining what control and prevention measures have taken place and are recommended. The report can also provide details on novel findings about the disease; for example, newly discovered transmission mechanisms, reservoirs or interventions that were successful. Hence, publication of findings or sharing the report widely would benefit other administrative regions or countries in their own preparedness measures.

Results of ongoing surveillance activities and special studies should be communicated to WHO. National authorities are encouraged to share with WHO additional information such as onset dates, age and sex, outcome, clinical spectrum of illness, underlying conditions, exposure information, travel history and treatment. Such information will be used to inform global risk assessment and the development or revision of technical guidance to improve future responses.

7.2 Notification

Detection of a possible human case of non-seasonal influenza, MERS-CoV or other emerging pathogen causing severe acute respiratory disease should immediately be notified to local, subnational and national public health authorities. This will allow these authorities to make immediate decisions about launching the investigation and the extent of response measures. Detection of such a case should be used to trigger notification of traditional and nontraditional health providers, hospitals and outpatient

facilities, and community leaders in the area where the case patients lived or travelled, as part of active case-finding efforts.

In line with the International Health Regulations (IHR) (2005) (*12*), the national health authority must notify WHO within 24 hours of all events that may constitute a public health emergency of international concern according to defined criteria. The notification should occur through the regional contact point for IHR at the appropriate WHO regional office. The IHR decision instrument should be used to determine whether an event is to be reported to WHO. For MERS-CoV, a specific IHR reporting form is available (*40*). Further guidance on the use of the IHR decision instrument, including examples of its application, is available *(12)*.

The national animal health authority must notify OIE of certain animal diseases detected on its territory. OIE focal points should be contacted for further details (*41*).

PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

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PROTOCOL TO INVESTIGATE NON-SEASONAL INFLUENZA AND OTHER EMERGING ACUTE RESPIRATORY DISEASES

ANNEXES

Annex 1: Example of investigation tool kit

Epidemiological supplies
- ❑ Case definitions
- ❑ Reporting forms
- ❑ Questionnaires
- ❑ Office stationery

Medical supplies
- ❑ Antiviral medications
- ❑ Stethoscope
- ❑ Thermometers

Laboratory supplies
- ❑ Specimen collection material
- ❑ Transport containers
- ❑ Viral transport media
- ❑ Sterile blood-drawing equipment (e.g. needles, syringes and tubes)
- ❑ Labels and permanent markers
- ❑ Specimen collection bags
- ❑ Coolers and cold packs

Infection control
- ❑ Respirators
- ❑ Gloves
- ❑ Gown, goggles and boots
- ❑ Bucket and solution for decontamination of surfaces

Electronic equipment
- ❑ Laptops, tablets, USB sticks
- ❑ Cell phones with chargers
- ❑ Epidemiology, statistical and antivirus software
- ❑ GPS devices

Educational materials for the community
- ❑ Information brochures and posters with simple, culturally appropriate messages
- ❑ Guidelines for contacts
- ❑ Communications materials

Miscellaneous
- ❑ Money
- ❑ Identification badge
- ❑ Official letter of introduction
- ❑ Proof of employment
- ❑ Access to scientific e-library
- ❑ Information on cases already gathered
- ❑ List of important contacts and resources
- ❑ Protocols (e.g. for case management and specimen collection)

Annex 2: Generic respiratory disease case investigation form

Section 1: Essential basic information

A. Data collector information

1	Name of data collector	
2	Data collector telephone number	
3	Data collector institution	
4	Form completion date (dd/mm/yyyy)	__ / __ / ____

B. Interview respondent information (if not patient)

5	Name of respondent	
6	Respondent telephone number	
7	Respondent address	
8	Relationship to patient	

C. Patient identifier information

9	Unique case ID/cluster number (if applicable)	
10	Case status (confirmed, probable, suspect, other)	
11	Family name	
12	Given name(s)	
13	Country of residence	
14	Sex	☐ Male ☐ Female ☐ Unknown
15	Date of birth (dd/mm/yyyy)	__ / __ / ____ ☐ Unknown
16	Age (years, months)	_____ ☐ Unknown
17	Address (village/town, district, province/region)	
18	Patient telephone number	

Section 2: Clinical information

D. Patient clinical course

19	Date of symptom onset (dd/mm/yyyy)	__ / __ / ____ ☐ Unknown ☐ Asymptomatic
20	Date of first health facility visit (including traditional care)	__ / __ / ____ ☐ NA ☐ Unknown
21	Total health facilities visited till outcome	_____ ☐ NA ☐ Unknown
22	Date of first hospitalization	__ / __ / ____ ☐ NA ☐ Unknown
23	Date of intensive care unit admission	Start: __ /__ /____ Stop: __ /__ /____ ☐ NA ☐ Unknown
24	Date of mechanical ventilation	Start: __ /__ /____ Stop: __ /__ /____ ☐ NA ☐ Unknown
25	Antiviral treatment	Start: __ /__ /____ Stop: __ /__ /____ ☐ NA ☐ Unknown
26	Outcome	☐ Died ☐ Alive ☐ NA ☐ Unknown
27	Outcome date	__ / __ / ____ ☐ NA ☐ Unknown

Section 2: Clinical Information [continued]

E. Patient symptoms (from disease onset) and complications

28	Fever (≥38 °C) or history of fever	☐ Yes ☐ No ☐ Unknown
29	Chills	☐ Yes ☐ No ☐ Unknown
30	Cough	☐ Yes ☐ No ☐ Unknown
31	Sore throat	☐ Yes ☐ No ☐ Unknown
32	Runny nose	☐ Yes ☐ No ☐ Unknown
33	Vomiting	☐ Yes ☐ No ☐ Unknown
34	Diarrhoea	☐ Yes ☐ No ☐ Unknown
35	Headache	☐ Yes ☐ No ☐ Unknown
36	Neurological signs	☐ Yes ☐ No ☐ Unknown Specify _____
37	Rash	☐ Yes ☐ No ☐ Unknown
38	Conjunctivitis	☐ Yes ☐ No ☐ Unknown
39	Shortness of breath	☐ Yes ☐ No ☐ Unknown
40	Muscle aches	☐ Yes ☐ No ☐ Unknown
41	Pneumonia by chest X-ray	☐ Yes ☐ No ☐ Unknown Date started __ / __ / ____
42	Acute respiratory distress syndrome	☐ Yes ☐ No ☐ Unknown Date started __ / __ / ____
43	Acute renal failure	☐ Yes ☐ No ☐ Unknown Date started __ / __ / ____
44	Cardiac failure	☐ Yes ☐ No ☐ Unknown Date started __ / __ / ____
45	Consumptive coagulopathy	☐ Yes ☐ No ☐ Unknown Date started __ / __ / ____
46	Other symptoms (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____

F. Patient pre-existing condition

47	Cancer	☐ Yes ☐ No ☐ Unknown
48	Diabetes	☐ Yes ☐ No ☐ Unknown
49	HIV/other immune deficiency	☐ Yes ☐ No ☐ Unknown
50	Heart disease	☐ Yes ☐ No ☐ Unknown
51	Asthma	☐ Yes ☐ No ☐ Unknown
52	Chronic lung disease (non-asthma)	☐ Yes ☐ No ☐ Unknown
53	Chronic liver disease	☐ Yes ☐ No ☐ Unknown
54	Chronic haematological disorder	☐ Yes ☐ No ☐ Unknown
55	Pregnancy	☐ Yes ☐ No ☐ Unknown If yes, specify trimester: __
56	Chronic kidney disease	☐ Yes ☐ No ☐ Unknown
57	Chronic neurological impairment	☐ Yes ☐ No ☐ Unknown
58	Obesity	☐ Yes ☐ No ☐ Unknown
59	Other (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____
60	Patient was vaccinated for influenza in the past 12 months	☐ Yes ☐ No ☐ Unknown

Section 3: Exposure information and travel history

G. Patient occupational exposures

61	Occupation (specify location/facility)	☐ Yes ☐ No ☐ Unknown Specify _____
62	Health-care worker (if yes, specify type/location)	☐ Yes ☐ No ☐ Unknown Specify _____
63	Laboratory worker (if yes, specify type/location)	☐ Yes ☐ No ☐ Unknown Specify _____
64	Veterinary worker (if yes, specify animal types handled in the 10 days before illness)	☐ Yes ☐ No ☐ Unknown Specify _____
65	Wildlife worker (if yes, specify animal types handled in the 10 days before illness)	☐ Yes ☐ No ☐ Unknown Specify _____
66	Live animal market worker (if yes, specify animal types handled in the 10 days before illness)	☐ Yes ☐ No ☐ Unknown Specify _____
67	Farm worker (if yes, specify animal types handled in the 10 days before illness)	☐ Yes ☐ No ☐ Unknown Specify _____

H. Patient human exposures in the 14 days before illness onset

68	Patient visited outpatient treatment facility (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____
69	Patient visited traditional healer (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____
70	Patient visited or was admitted to inpatient health facility (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____
71	Patient attended festival or mass gathering (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____
72	Patient exposed to person with similar illness	☐ Yes ☐ No ☐ Unknown (Skip to Q79)
73	Type of contact (tick as needed)	☐ Close contact (within 1 metre) ☐ Handled person's bodily fluids/excreta ☐ Shared same household ☐ Admitted to the same health facility room ☐ Admitted to same health facility (but different room) ☐ Visited the same health facility (including traditional) ☐ Other, describe: _____
74	Location of exposure	☐ Home ☐ Hospital ☐ Workplace ☐ Tour Group ☐ Other Specify_____
75	Unique case ID of sick person (if available)	_____ ☐ NA ☐ Unknown
76	Relationship to current patient (specify, e.g. family, friend, health-care worker, colleague)	_____
77	Blood linked (if yes, specify link)	☐ Yes ☐ No ☐ Unknown Specify _____
78	Sick person confirmed or deemed a probable case in current event	☐ Yes ☐ No ☐ Unknown

Section 3: Exposure information and travel history [continued]

I. Patient travel history in the 14 days before illness onset (add sheets if multiple locations visited)

79 Patient travelled out of first administrative region	☐ Yes ☐ No ☐ Unknown (Skip to Q83)
80 If yes, specify location 1 (city or region, country)	Destination: _____ Mode of travel: _____ Arrival: __ /__ /____ Departure: __ /__ /____
81 If yes, specify location 2 (city or region, country)	Destination: _____ Mode of travel: _____ Arrival: __ /__ /____ Departure: __ /__ /____
82 Patient travelled with companions (if yes, specify)	☐ Yes ☐ No ☐ Unknown Specify _____

J. Patient animal exposures in the 14 days before illness onset

83 Patient handled animals	☐ Yes ☐ No ☐ Unknown (Skip to Q88)
84 Types of animals handled (e.g. pigs, chicken, ducks or others)	_____
85 Nature of contact (e.g. feed, groom or slaughter)	_____
86 Location of animal contact	☐ Home ☐ Workplace ☐ Hospital ☐ Tour Group ☐ Other Specify_____
87 Within 2 weeks before or after contact, any animals sick or dead? (if yes, specify type and number, and proportion from flock or herd)	☐ Yes ☐ No ☐ Unknown Specify _____
88 Patient exposed to animals in environment but did not handle them (e.g. in neighbourhood, farm, zoo, at home, agricultural fair or work)	☐ Yes ☐ No ☐ Unknown (Skip to Q92)
89 Types of animals in that environment (e.g. pigs, chicken, ducks or others)	_____
90 Location of exposure	☐ Home ☐ Neighbourhood ☐ Market ☐ Agricultural fair/zoo ☐ Farm ☐ Other Specify_____
91 Within 2 weeks before or after exposure to animals in the environment, any animals sick or dead? (if yes, specify type and number, and proportion from flock or herd)	☐ Yes ☐ No ☐ Unknown Specify _____
92 Patient exposed to animal by-products (e.g. bird feathers) or animal excreta (if yes, specify product)	☐ Yes ☐ No ☐ Unknown Specify _____
93 Patient visited live animal market (if yes, specify market)	☐ Yes ☐ No ☐ Unknown Specify _____

Section 3: Exposure information and travel history [continued]

K. Patient food exposures in the 14 days before illness onset

94	Patient consumed raw or unpasteurized animal products (if yes, specify products)	☐ Yes ☐ No ☐ Unknown Specify _____
95	Patient consumed health or traditional remedies with raw or unpasteurized animal products (if yes, specify products)	☐ Yes ☐ No ☐ Unknown Specify _____

L. Patient perceived exposure

96	From the point of view of the patient or family, what is the likely source of infection and geographic location of exposure?	_____

Section 4: Laboratory information

M. Laboratory specimens and results

97	Specimens collected from patient (tick as needed)	☐ Nasal swab	Date collected: __ /__ /____
		☐ Throat swab	Date collected: __ /__ /____
		☐ Nasopharyngeal swab	Date collected: __ /__ /____
		☐ Nasal wash	Date collected: __ /__ /____
		☐ Sputum	Date collected: __ /__ /____
		☐ Nasopharyngeal aspirate	Date collected: __ /__ /____
		☐ Tracheal aspirate	Date collected: __ /__ /____
		☐ Bronchoalveolar lavage	Date collected: __ /__ /____
		☐ Tissue biopsy	Date collected: __ /__ /____
		☐ Serum (first sample)	Date collected: __ /__ /____
		☐ Serum (second sample)	Date collected: __ /__ /____
		☐ Whole blood	Date collected: __ /__ /____
		☐ Urine	Date collected: __ /__ /____
		☐ Other: _____	Date collected: __ /__ /____
98	Pathogen testing done (tick as needed)	☐ Influenza A/B	Test used: _____
		☐ Influenza subtyping	Test used: _____
		☐ MERS-CoV	Test used: _____
		☐ SARS	Test used: _____
		☐ RSV	Test used: _____
		☐ Human metapneumovirus	Test used: _____
		☐ Parainfluenza (1,2,3)	Test used: _____
		☐ Adenovirus	Test used: _____
		☐ Rhinovirus	Test used: _____
		☐ Enterovirus	Test used: _____
		☐ Coronavirus	Test used: _____
		☐ Chlamydia pneumonia	Test used: _____

Section 4: Laboratory information [continued]

M. Laboratory specimens and results

98 Pathogen testing done (tick as needed) [continued]	☐ Mycoplasma pneumonia Test used: _____ ☐ Legionella Test used: _____ ☐ Streptococcus pneumonia Test used: _____ ☐ Other: _____ Test used: _____
99 Specimens shipped to international reference laboratories	☐ Yes ☐ No If yes, specify recipient laboratory and shipment date: _____
100 Specify specimen(s) positive	
101 Specify pathogen(s) positive	
102 Specify targets positive (e.g. for MERS-CoV)	
103 Specify subtype positive (e.g. for influenza)	
104 Specify titres (e.g. paired serum for influenza)	

ID, identification; MERS-CoV, Middle East respiratory syndrome coronavirus; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; NA, not-applicable.

Annex 3: Example report of surveillance systems and respiratory disease activity

Information about existing surveillance systems and respiratory disease trends helps to contextualize the event. Summarize existing surveillance systems by documenting the respiratory syndromes or pathogens under surveillance, the facilities participating, the case definitions used and the catchment population. Information about existing surveillance systems will help investigators to determine the coverage and representativeness of surveillance, and the potential of the systems to detect additional cases associated with the event. An example summary is given below (Table A3.1).

Table A3.1. Acute respiratory diseases under surveillance at national level and in the area affected by the event (example summary)

ADMINISTRATIVE LEVEL AND SURVEILLANCE SYSTEM TYPE	ACUTE RESPIRATORY DISEASE UNDER SURVEILLANCE	CASE DEFINITION APPLIED IN THE SYSTEM	NUMBER AND TYPE OF FACILITIES	DATA AVAILABLE FROM (YEAR)	CATCHMENT POPULATION ESTIMATE	LABORATORY DIAGNOSTICS
National						
• Comprehensive	• Pneumonia	Radiologically confirmed	All 28 government hospitals	2008	Total population (5 million)	Nil
• Sentinel	• ILI	Measured fever of ≥38 °C; and cough; with onset within the past 10 days	10 government outpatient clinics	2010	400 000	Influenza RSV
	• SARI	History of fever or measured fever of ≥38 °C; and cough; with onset within the past 10 days; and requires hospitalization	8 government hospitals (one in each district)	2010	1.4 million	Influenza
Affected district						
• Comprehensive	• Pneumonia	Radiologically confirmed	4 government hospitals	2008	715 000	Nil
• Sentinel	• SARI	History of fever or measured fever of ≥38 °C; and cough; with onset within the past 10 days; and requires hospitalization	1 district hospital	2010	180 000	Influenza

ILI, influenza-like illness; RSV, respiratory syncytial virus; SARI, severe acute respiratory infection

Depending on resources and data availability, consider documenting on current performance for each surveillance system; in particular, for the district or region affected by the event. Include information on the following aspects:

- cases identified or enrolled per week from the affected region compared with other sites or the national average;
- timeliness of reporting from sentinel sites;
- adherence to and use of the case definition to identify or enrol cases;
- completeness and quality of the data in case forms or tabulations submitted by the site;
- number of weeks (if any) with no reporting; and
- timeliness of laboratory results from specimen collection date.

Consider presenting summary tables. Examples tables are given below (Tables A3.2 and A3.3). These tables present the severe acute respiratory infection (SARI) surveillance system's performance in 2014 and 2015, to highlight changes in performance over time. Such tables can be adjusted or replicated for the area affected by the event, other respiratory disease surveillance systems and different time periods.

Table A3.2. Performance indicators for SARI surveillance, by hospital, country level, 2014 (example table)

HOSPITAL	TOTAL ADMISSIONS (N)	SARI CASES DETECTED (%)	SARI CASES WITH SPECIMENS (%) [TARGET = 100%]	WEEKS WITHOUT REPORT [TARGET = 0]
Hospital 1	13 515	342 (2.5)	315 (92)	2
Hospital 2	24 957	442 (1.8)	380 (86)	1
Hospital 3	14 574	278 (1.9)	206 (74)	3
Hospital 4	21 542	355 (1.6)	238 (67)	0
Hospital 5	10 188	237 (2.3)	199 (84)	1
Hospital 6	14 219	321 (2.3)	308 (96)	2
Hospital 7	10 744	214 (2)	205 (96)	3
Hospital 8	12 846	264 (2.1)	222 (84)	1
Total	**122 585**	**2 453 (2)**	**2 073 (85)**	–

SARI, severe acute respiratory infection

Table A3.3. Performance indicators for SARI surveillance, by hospital, country level, 2015 (example table)

HOSPITAL	TOTAL ADMISSIONS (N)	SARI CASES DETECTED (%)	SARI CASES WITH SPECIMENS (%) [TARGET = 100%]	WEEKS WITHOUT REPORT [TARGET = 0]
Hospital 1	16 328	721 (4.4)	667 (93)	1
Hospital 2	20 025	887 (4.4)	843 (95)	0
Hospital 3	19 174	671 (3.5)	557 (83)	0
Hospital 4	20 080	854 (4.3)	658 (77)	0
Hospital 5	14 154	525 (3.7)	457 (87)	3
Hospital 6	20 387	987 (4.8)	977 (99)	0
Hospital 7	18 795	698 (3.7)	670 (96)	1
Hospital 8	12 457	755 (6.1)	634 (84)	0
Total	**141 400**	**6 098 (4.3)**	**5 462 (90)**	–

SARI, severe acute respiratory infection

Surveillance data provide a baseline understanding of the health status in the population. The data can help investigators in the event verification process and in determining whether the system can be useful in identification of additional cases. Surveillance trends can shed light on whether:

- the event is associated with a true increase in disease activity;
- the event is associated with an emerging or newly introduced pathogen or strain; and
- surveillance practices have changed, leading to a signal being triggered.

Some countries have established thresholds to assess whether current disease activity is within the expected range or is above it (and is thus suggesting of an unusual event).

Ideally, weekly or monthly trends for acute respiratory conditions such as influenza-like illness (ILI), pneumonia or SARI can be presented in figures or tables. Examples of figures and a table are presented below (Figs A3.1–A3.6, Table A3.4). These present influenza-associated SARI surveillance outputs for the national level, and can be replicated for the area affected by the event, other respiratory pathogens under surveillance and any respiratory condition that is under surveillance (e.g. ILI, pneumonia or acute lower respiratory illness).

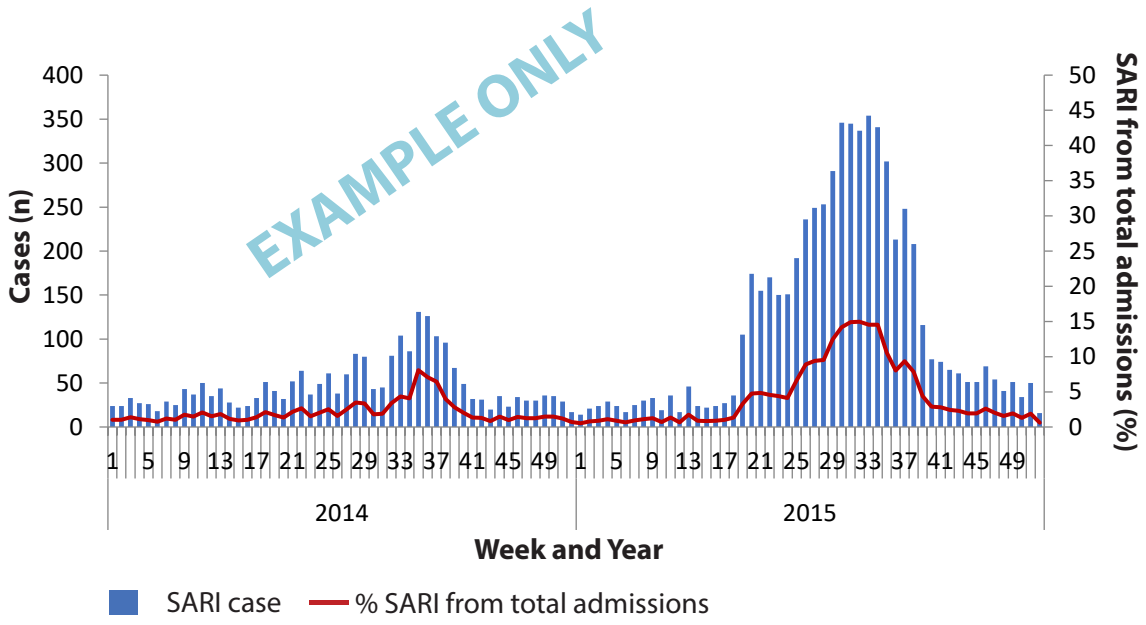

Fig. A3.1. – SARI cases from total admissions, country level, 2014–2015 (example figure)
SARI, severe acute respiratory infection

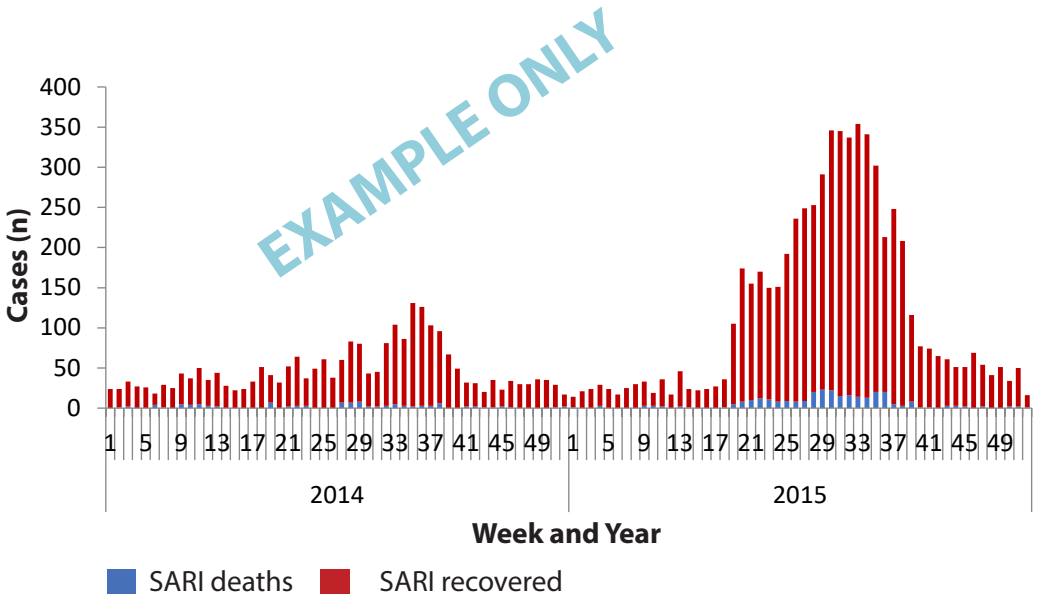

Fig. A3.2. – Deaths among SARI cases, country level, 2014–2015 (example figure)
SARI, severe acute respiratory infection

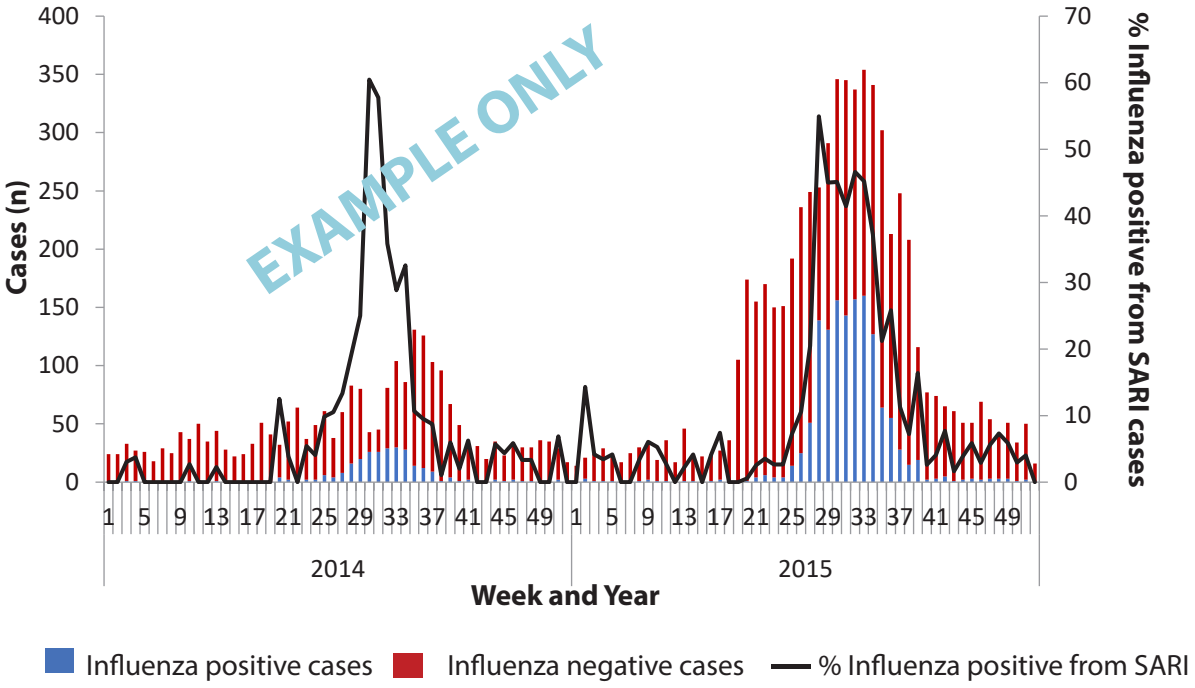

Fig. A3.3. – Proportion of influenza positive cases from SARI cases, country level, 2014–2015 (example figure)
SARI, severe acute respiratory infection

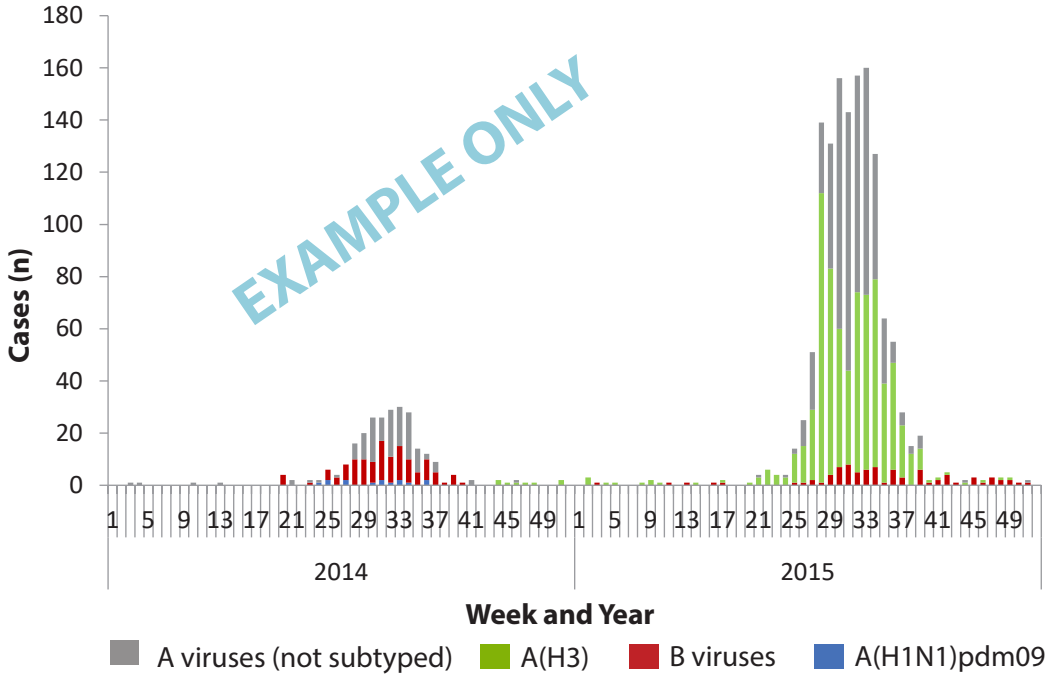

Fig. A3.4. – Viruses detected among influenza positive cases, country level, 2014–2015 (example figure)

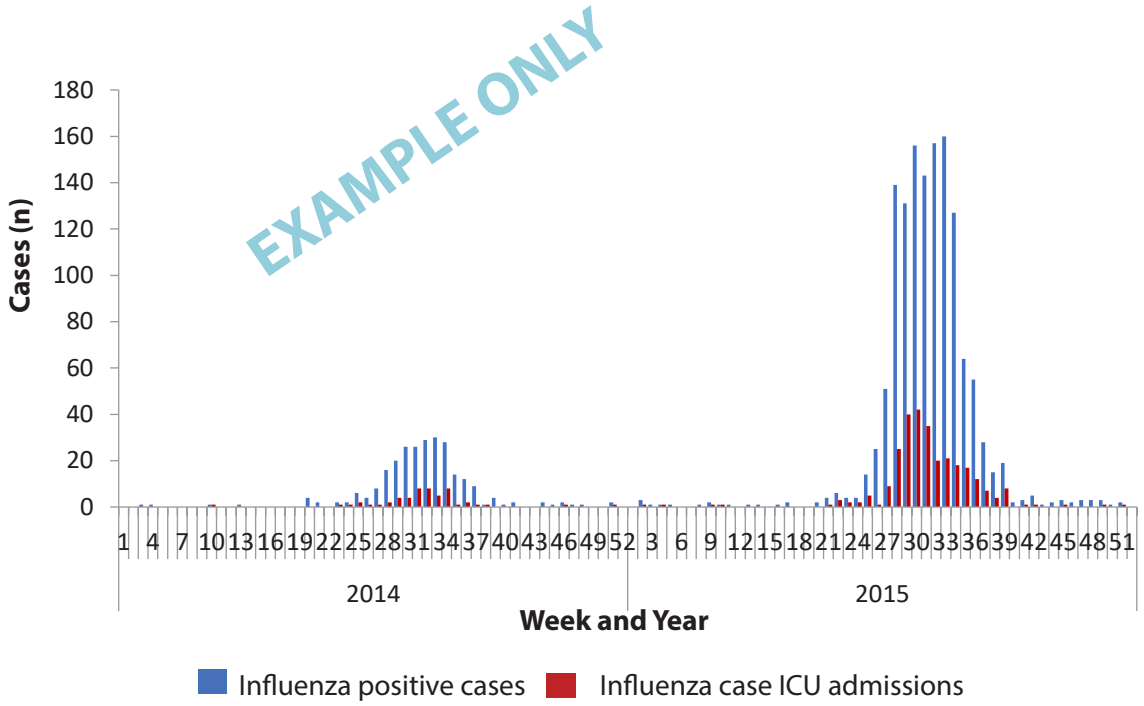

Fig. A3.5. – Influenza-associated intensive care unit (ICU) admissions, country level, 2014–2015 (example figure)

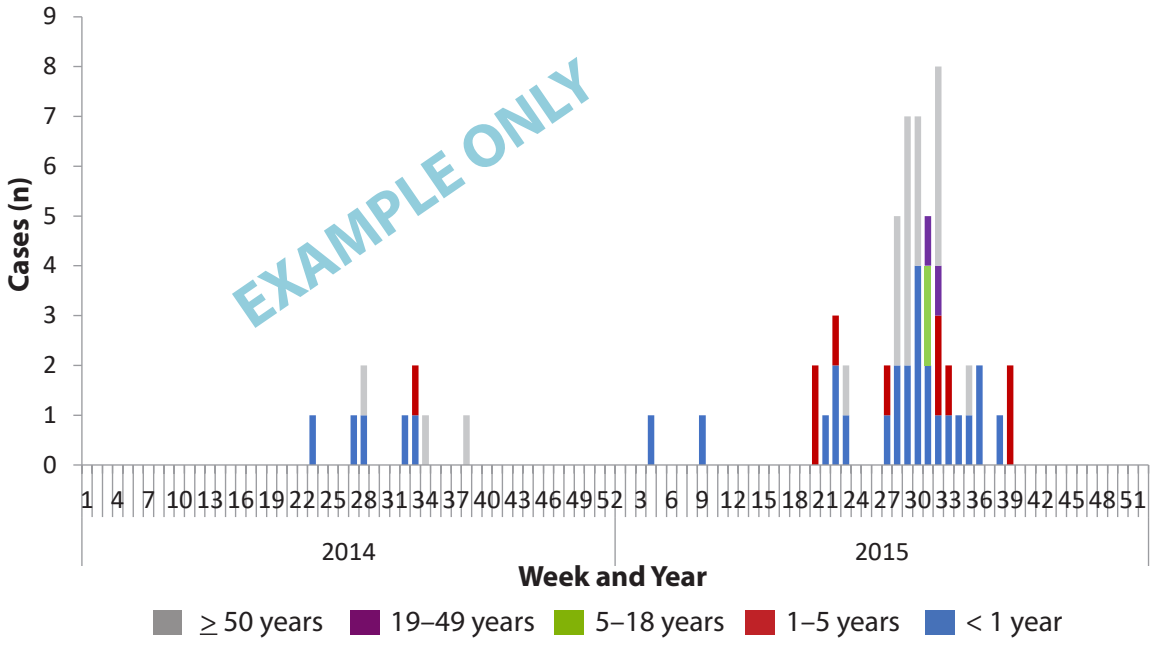

Fig. A3.6. – Influenza-associated deaths by age group, country level, 2014–2015 (example figure)

Table A3.4. Demographic characteristics, symptoms, medical histories, and outcomes for SARI and influenza positive cases, country level, 2014–2015

	SARI cases (N=8 551) n (%)	Influenza positive (N=1 609) n (%)
Gender		
Male	4 788 (56)	836 (52)
Female	3 763 (44)	773 (48)
Age		
<1 year	1 847 (22)	169 (10)
1–4 years	3 279 (39)	690 (43)
5–14 years	1 263 (15)	249 (16)
15–49 years	1 081 (13)	174 (11)
50–64 years	752 (9)	230 (14)
≥65 years	329 (4)	97 (6)
Symptoms		
History of fever	8 476 (98)	1 597 (99)
Fever ≥38 °C	5 643 (66)	1 110 (69)
Cough	8 498 (99)	1 607 (100)
Sore throat	2 821 (33)	771 (48)
Difficulty breathing	4 018 (47)	595 (37)
Vomiting	3 847 (45)	659 (41)
Pleuritic chest pain	1 710 (20)	273 (17)
Auscultation positive	2 736 (32)	482 (30)
Diarrhoea	1 881 (22)	289 (18)
Medical conditions		
Smoker	684 (8)	160 (10)
Asthma	680 (8)	182 (11)
Cardiovascular disease	86 (1)	17 (1)
Neurological disorder	87 (1)	20 (1)
Discharge conditions		
Death	397 (5)	63 (4)
X-ray conducted	2 650 (31)	434 (27)
Pneumonia on X-ray	450 (17)	78 (18)

Annex 4: Contact tracing and monitoring procedures

Establishing and maintaining contact monitoring is a resource-intensive yet critical task during an investigation. The key steps in the process are as follows:

1. ***Identify case contacts from interviews with the patient, family members, health-care workers, workplace, or others with knowledge of the patient's recent activities, health-care facility visits and travels.*** List all contacts in a contact list form. As per the example form given at Table A4.1, the contact list should record demographic information, the date of last exposure to the case, and the outcome of the contact monitoring (remained healthy or developed illness). Complete a separate contact list form for each case in the investigation.

2. ***From the contact list, determine which contacts will be monitored and assign them a contact identification number (contact ID).*** If a large number of contacts are identified or if personnel resources are limited, it may be necessary to prioritize contacts to be monitored. In prioritizing contacts for monitoring, consider the:

    - likelihood of infection in the case to which the contact was exposed, so that contacts of confirmed or probable cases are prioritized for monitoring;
    - duration, spatial proximity and intensity of the contact's exposure to the case, so that health-care workers, household contacts sharing the same sleeping or eating space, or persons providing bedside care are prioritized for monitoring; and
    - likelihood that human-to-human transmission has resulted from contact with the case.

3. ***Assign all contacts selected for monitoring to investigation team members or other public or local health-care workers tasked with the monitoring activity.*** Provide the monitoring personnel with a contact monitoring form that lists all the contacts they are required to follow up daily. As per the example form at Table A4.2, the contact monitoring form should list the contact ID and demographic identifiers, date of last contact with the case, date of last expected monitoring visit and columns to record the contact's health status during each daily visit conducted.

4. ***During the initial follow-up for each contact, ask monitoring staff to explain that getting early and good clinical care improves outcomes for most diseases, and that distancing from others while sick reduces the risk of infecting close contacts such as household members.*** Give contact options for reporting updates, such as the telephone numbers of designated monitoring staff or the event hotline number. Explain to the contact that, if they develop symptom, they should self-isolate, practise good respiratory hygiene and notify the designated monitoring staff. Ask the contact to notify the designated monitoring staff if they move or leave the area during the monitoring period.

5. ***Request all designated monitoring staff to report daily to the event investigation team on the findings from the contact follow-up.*** This can be done by phone or in person, and should incorporate information on the number of contacts:

    - followed up today (non-symptomatic);
    - followed up today (symptomatic) and actions taken;
    - discharged from follow-up today;
    - not followed up today and reasons why; and
    - total contacts currently under follow-up.

Annex 4: Contact tracing and monitoring procedures

Table A4.1. Form to list all contacts identified

CONTACT LIST FORM

Contact list form filled in by:

Case name _____ **Case ID if assigned** _____

Case neighbourhood/village _____ **Chief or Community Leader** _____

District/town _____ **Province/region** _____

CONTACT SURNAME	FIRST NAME	RELATIONSHIP TO CASE	AGE (YEARS)	SEX	VILLAGE OR NEIGHBOURHOOD	DISTRICT OR TOWN	TYPE OF CONTACT*	DATE OF LAST CONTACT	LAST DATE FOR FOLLOW-UP	ASSIGNED CONTACT ID	DATE OF FIRST VISIT	CONTACT OUTCOME

* Options include household member, health-care worker, co-worker, neighbour or other (list).

Annex 4: Contact tracing and monitoring procedures

Table A4.2. Form to monitor contacts daily

CONTACT MONITORING FORM

Name of monitoring staff:
Contact phone of monitoring staff:

CONTACT ID	SURNAME	FIRST NAME	AGE	SEX	DATE OF LAST CONTACT WITH CASE	DATE OF LAST MONITORING VISIT TO CONTACT	FINDINGS ON DAILY FOLLOW-UP*						
							1	2	3	4	5	6	7

* Days of follow-up will depend on the event and can be extended to any number of days.
Tick "0" if the contact has not developed disease symptoms
Tick "X" if the contact has developed symptoms or has died

Annex 5: Health facility register review for active case finding

During a disease event, health facilities are often asked to provide notification about any patients with signs and symptoms aligned with the disease. The purpose of a register review is to collect information on cases admitted to the health facility during a specific period, and to actively identify patients who may be cases in the current event. The process may identify individuals who need further investigation, to determine whether they are cases. The review will also help to ensure that health facilities are aware of the event, can actively apply the case definition for patient triage and have the means to notify the investigation team of any possible cases. Actions such as re-engaging or retraining health facility staff may be conducted to maximize active and systematic case finding efforts. Facilities may also need to be equipped with telecommunication capacities, to streamline notification of possible cases.

Steps in the process are as follows:

1. ***Determine the health facilities to be visited for the register review.*** Depending on the event context and location, consider prioritizing the facilities to be visited. Priorities may include:
   - inpatient facilities with more than 10 hospital beds;
   - government inpatient facilities;
   - facilities known to service the population in the affected areas;
   - large reference or teaching hospitals that receive referrals from other health facilities;
   - specialized facilities for diseases such as thoracic hospitals; and
   - facilities that provide services to populations with limited access to regular services, such as for refugee or marginalized groups.

2. ***Meet with the health facility administrators and clinical staff, provide information about the event and explain the purpose of the review.*** Emphasize that the activity is to support active case finding as part of the investigation, and is not a review of health-care worker performance.

3. ***Explain the signs and symptoms of the disease.*** Ask the facility clinical staff to identify the wards used to admit patients with such a clinical presentation. This will determine the registers that will need to be reviewed. In particular, clarify whether:

   - maternity wards, if present, would be used to admit pregnant women with the signs or symptoms of the disease, or whether such wards are reserved purely for obstetric care; and
   - the emergency unit, if present, would be used to observe patients for 1 or more days, or whether it is purely a triage facility and patients would not be kept for observation for more than a few hours; include the emergency unit in your review if patients may be kept for observation for 1 or more days.

4. ***Ask to see the register for patients admitted in the past 2–4 weeks at each ward identified in the previous step.*** The time frame for the retrospective review will depend on the event context, event start date and information on the disease's incubation period. If this information is not known, conduct the review for 4 weeks. Staff who usually fill in the register may be required to assist or to answer questions, because abbreviations or codes may be used to indicate certain conditions or patient details.

5. ***Ask how patients presenting with the disease's signs and symptoms would be documented in the register at that facility.*** Clarify whether the facility would immediately code using international classification of diseases (ICD) codes, or document patients according to disease presentation or symptoms. Documentation may include acute respiratory illness, influenza-like illness, pneumonia, respiratory distress, febrile illness or others. Decide on the codes or presentations that would be checked for in the facility's register.

6. ***Systematically look through each ward register and line-list any patients, including those who died, who meet the codes or presentations agreed upon in the previous step.*** Use the line-list template provided at Table A5.1. If a patient returned to the facility for subsequent hospitalizations relating to the same illness, only line-list that person once.

7. ***Ask the health facility staff whether any of the patients identified and line-listed were investigated or reported as possible cases in the current event.*** Check the patients' medical records to obtain more details about whether the illness, timelines and any laboratory findings suggest compatibility with the current event. The line-list generated will be used for patient follow-up for active case finding.

8. ***From the medical records staff, request the total number of patients admitted to the hospital per epidemiological week (epi-week).*** Fill in the template to enable calculation of the following proportions:

Proportion of patients with compatible illness per week	=	# patients with compatible illness per epi-week / total patients hospitalized per epi-week
Age groups of patients with compatible illness	=	# patients with compatible illness by age group / total patients with compatible illness in full time period
Sex of patients with compatible illness	=	# male (or female) patients with compatible illness / total patients with compatible illness in full time period
Proportion of patients with compatible illness reported	=	# patients line-listed who were reported by facility / total patients with compatible illness identified

9. ***Provide feedback to the health facility staff about the line-listed patients arising from the register review and the next case-identification steps.*** Provide summary data from the proportion calculations in Step 8. Use the opportunity to also:

   - review any features of case management for the illness that may help health-care workers in the facility;
   - reinforce the importance of immediate reporting and case investigation as tools for controlling this and other events; and
   - talk about how to strengthen record-keeping so that the information is collected and used for public health purposes.

10. ***Investigate the patients identified and line-listed further to determine whether they were a case in the event.***

11. ***Share findings from Step 8 and Step 10 in reports to the event management team.*** The findings can then be used to inform future risk assessments and risk management actions.

Table A5.1. Health facility register review for active case finding during an event

a) Date facility visited: _____

b) Health facility name: _____

c) Nurse/attendant name: _____

d) Nurse/attendant contact number: _____

e) Investigation team staff name and phone number: _____

f) Facility's total inpatient admissions per week (to cover up to 1 month of admissions):

Epidemiological week (e.g. Monday–Sunday)	Total patient admissions at facility
This week number: _____	
Last week number: _____	
Two weeks ago week number: _____	
Three weeks ago week number: _____	

g) For up to the past month: List all inpatients recorded in the register whose disease presentation is aligned with the case definition.

DATE ADMITTED	NAME	PATIENT AGE (YEARS)	PATIENT SEX (M/F)	ADDRESS AND PHONE	DIAGNOSIS (discharge preferred but otherwise admission)	PATIENT STATUS (died, discharged, hospitalized)	POTENTIAL CASE IN CURRENT EVENT? (Y/N)

Annex 6: Precautions during routine respiratory disease patient care

INFECTIOUS AGENT							
Level of infection prevention during routine patient care, excluding aerosol-generating procedures[a]	**No pathogen identified, no risk factor for ARI of potential concern** (e.g. influenza-like illness without risk factor for ARI of potential concern)	**Bacterial ARI,**[b] **including plague**	**Other ARI viruses** (e.g. parainfluenza RSV, adenovirus)	**Influenza virus with sustained human-to-human transmission** (e.g. seasonal influenza, pandemic influenza)	**New influenza virus with no sustained human-to-human transmission** (e.g. avian influenza)[c]	**SARS, MERS-CoV**	**Novel respiratory infection** (route of transmission unknown)[d]
Standard precautions	✓	✓	✓	✓	✓	✓	✓
Droplet precautions	✓		✓	✓	✓	✓	
Contact precautions			✓		✓	✓	✓
Airborne precautions							✓

ARI, acute respiratory infection; MERS-CoV, Middle East respiratory syndrome coronavirus; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome

Modified from Table 2.1 in World Health Organization. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. World Health Organization. 2014 (http://www.who.int/iris/handle/10665/112656#sthash.NtwwkcHw.dpuf, accessed 19 November 2015).

[a] For definitions of standard, droplet, contact and airborne precautions, refer to World Health Organization. Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection. World Health Organization. 2015 (http://www.who.int/iris/handle/10665/174652#sthash.uKt5Vjqx.dpuf, accessed 19 November 2015).

[b] Bacterial ARI refers to common bacterial respiratory infections caused by organisms such as Streptococcus pneumoniae, Haemophilus influenzae, Chlamydophila spp. and Mycoplasma pneumoniae.

[c] As of the publication of WHO's abovementioned guidelines in 2014, no sustained efficient human-to-human transmission of avian influenza A(H5N1) is known to have occurred, and the available evidence does not suggest airborne transmission from humans to humans. Therefore, a medical mask is adequate for routine care.

[d] When a novel ARI is newly identified, the mode of transmission is usually unknown. Implement the highest available level of infection prevention and control precautions until the situation and mode of transmission is clarified.

Annex 7: Sample investigation report outline[#]

Title/description (include disease/condition investigated)	
Period	**Place** **(villages, neighbourhoods, district, province)**
Executive summary	
Background	
Preliminary risk assessment findings and reasons for investigation (e.g. public health significance, threshold met)	
Methods:	
Dates of investigation	
Site(s) of investigation (health-care facilities, villages, other)	
Case finding (indicate what was done regarding case finding, e.g. register review, contact investigation, alerting other health facilities, other)	
Laboratory specimen collection	
Description of response and intervention (include dates)	
Data management	
Risk assessment (frequency, participants and specific questions for each)	
Results:	
Date and location of first known (index) case	
Date and health facility where first case was seen by the health-care system	
Results of additional case finding	
Laboratory analysis and results	
With text, describe key features of results of time, place and person analysis	
Detailed results by time (epidemic curve), place (map) and person characteristics (tables)	
Risk characterized, and confidence and key decisions from each risk assessment conducted	
Results of response and evidence of impact	
Interpretations, discussion and conclusions:	
Summary of event findings and hypotheses on source of infection, modes of transmission, exposures and magnitude	
Recommended public health actions:	
Comment on the following levels: community, health facility, district, partners, provincial and national	
Comment on methods to prevent event reoccurrence	
Date reported completed:	

[#] Modified from World Health Organization and Centers for Disease Control and Prevention. Technical guidelines for integrated disease surveillance and response (IDSR) in the African Region: 2nd edition. Geneva: WHO; 2010 (http://www.afro.who.int/publications/technical-guidelines-integrated-disease-surveillance-and-response-african-region-0, accessed 24 November 2017).

This protocol provides an approach for public health authorities and investigators at all levels to plan for and conduct investigations of nonseasonal influenza and other emerging respiratory diseases and provides tips and reminders for linking the information from the investigation with risk assessment. The disease etiology is not always known at the onset of the event; therefore, this protocol focuses on important but broadly applicable steps that should be undertaken in the investigation of an acute respiratory disease event, especially those occurring at the animal–human interface. The protocol reflects and incorporates the practical field experience gained by investigators working at international, national and subnational levels during previous investigations of non-seasonal influenza, SARS and MERSCoV outbreaks. This protocol and its tools can serve as a basis for national and local authorities to develop their own procedures, tailored to their specific needs.

WHO/WHE/IHM/GIP/2018.2

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