World Health Organization

Closed Setting Transmission Investigation template protocol for respiratory pathogens with pandemic potential

Unity Studies
Respiratory Investigations & Studies

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Abbreviations

CONSISE	Consortium for the Standardization of Influenza Seroepidemiology
COVID-19	Coronavirus disease 2019
FFX	First Few X
GIP	Global Influenza Programme
GOARN	Global Outbreak Alert and Response Network
HHTI	Household Transmission Investigation
IHR	International Health Regulations
IPSS	Influenza Pandemic Special Investigations and Studies
IQR	Interquartile Range
PCR	Polymerase Chain Reaction
PPE	Personal Protective Equipment
R_0	Basic reproductive number
R_{eff}	Effective reproductive number
RNA	Ribonucleic acid
SAR	Secondary Attack Rate
SARI	Severe Acute Respiratory Infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCAR	Secondary Clinical Attack Rate
WHE	Health Emergencies Programme
WHO	World Health Organization

Summary

This document sets out the methods to guide data collection in [Country Y] for the **comprehensive assessment of a new or re-emerging respiratory pathogen with pandemic potential in closed settings. For the purposes of this protocol, the conceptual pan-respiratory pathogen will be referred to as pathogen X, which causes Disease X.**

The detection and spread of a novel or re-emerging pathogen with pandemic potential is accompanied by uncertainty over the key epidemiological, clinical and virological (if applicable) characteristics of the novel pathogen and particularly its ability to spread in the human population and its virulence (case-severity). Closed settings have a well-defined population that do not mix readily with the larger surrounding community, and therefore such settings provide a strategic way to track infection and characterise transmission patterns. As such they can provide key epidemiological data to complement and reinforce findings of the First Few X (FFX) cases and contacts investigation protocol of pathogen X in [Country Y], as part of the the Respiratory Investigations and Studies, Unity Studies initiative. CLICK TO VIEW

The World Health Organization (WHO), in collaboration with technical partners, has developed a series of enhanced surveillance protocols that are harmonized to help provide detailed insight into the epidemiological characteristics of respiratory pathogens with pandemic potential or disease X. They build on previous protocols developed by the global Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) *(1)*, WHO's Influenza Pandemic Special Investigations and Studies (IPSS), as well as those developed by WHO as part of the Unity Studies for COVID-19 *(2)* and for Middle East respiratory syndrome coronavirus (MERS-CoV) *(3)*.

All WHO Respiratory Investigations and Studies protocols are available on the WHO website. CLICK TO VIEW

Comments for the user's consideration are provided in purple text throughout the document, as there may be a need to modify methods slightly because of the local context in which this investigation will be carried out.

Full title of study	Closed setting transmission investigation template protocol for respiratory pathogens with pandemic potential or disease X [Country Y]
Population	Closed setting close contacts of confirmed cases of pathogen X
Potential output and analysis	Transmissibility in closed settings such as schools, hospitals and military barracks. Provide key epidemiological data to complement and reinforce findings of the First Few X cases and contacts (FFX) investigation protocol for **pathogen X** in the areas of primarily: • the overall infection and clinical attack rate, and by key factors such as age and sex; • the secondary infection rate (SIR) and secondary clinical attack rate of pathogen X infection among close contact, overall, and by key factors such as setting, age and sex; • the clinical presentation and course of associated disease; • the symptomatic and asymptomatic proportions of cases and; • preliminary case- (i.e. disease) hospitalization and fatality ratios, and infection-hospitalization and fatality ratios. and secondarily: • the serial interval; • possible routes of transmission; • risk and/or protective factors for transmission or severe disease. Advance related objectives: • the basic reproduction number (R_0); • the effective reproductive number (R_{eff}); • the incubation period, and; • the generation interval.
Study design	Prospective case-ascertained closed setting transmission study
Timing of the investigation	Prospective study, at best before widespread community transmission occurs.
Duration	Recruitment and follow-up of an index case and all contacts within the closed setting for 28 days from recruitment.
Minimum data and specimens to be obtained from participants	Epidemiological, clinical, virological (if applicable i.e. if pathogen X is a virus) and serological data will be collected from each participant at multiple times during the investigation – including surveys at baseline and day 28, symptom diaries from days 2-28, and specimen collection.

1. Background and objectives

1.1 Background to Pandemic Investigations and Studies

Following a review of the global response to the last influenza pandemic (2009 influenza pandemic H1N1) *(4)*, the global Consortium for the Standardization of Influenza Seroepidemiology (CONSISE) *(1)*, and World Health Organization's (WHO) Influenza Pandemic Special Investigations and Studies initiative were established to develop a suite of standardized early investigation protocols, supported by the Global Influenza Programme *(5)* and the Pandemic Influenza Preparedness (PIP) Framework *(6)*. Standardized protocols were also implemented following the emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 *(3)*, and Zika virus in 2016 *(7)*.

In January 2020, the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19) was declared a public health emergency of international concern by the WHO. This required rapid implementation of early investigations to inform appropriate national and global public health actions. Adaptation of existing protocols was initiated from the first weeks of the detection of the novel coronavirus and further developed under the WHO initiative, Unity Studies *(2)*. The Unity Studies protocols standardized methods and facilitated rapid generation of local data for public health action and comparison of key epidemiological parameters across regions and globally *(2, 8–10)*.

Based on the learning of the COVID-19 response, a series of standardized template protocols have been developed for both disease specific investigations such as influenza and for any novel respiratory pathogen of pandemic potential for the implementation of standardized and quality investigations and studies to ensure readiness in advance of a future pandemic (link to new webpage once available). These have been developed as part of the WHO Investigations and Studies, Unity Studies initiative. CLICK TO VIEW The initiative aims to provide an 'at the ready' international framework for preparedness and response to future pandemics, providing a suite of enhanced surveillance and investigational activities that are harmonized to help provide detailed insight into the epidemiological characteristics of emerging or re-emerging respiratory pathogens of pandemic potential. They are included in both the Global Influenza Strategy *(11)* (pillar 6: "Number of sites (or geographical coverage) primed to conduct at least one of the WHO Pandemic Influenza Special Investigations in case of a pandemic with target for 2023: "At least 2 operationally ready sites in each WHO region (so 12 sites)") and the third version of the High-Level Implementation Plan (HLIP III) for pandemic preparedness (PIP) *(12)* for the 2024-2030 period under Output Indicator 2.11 "Number of sites participating in the WHO Investigations and studies network (Unity Studies)".

Investigations and Studies are also included in the Mosaic Respiratory Surveillance Framework *(13)*. The Mosaic framework presents respiratory virus surveillance systems into a collaborative context where they are each focused on the objectives to which they are best suited. As it is impossible to address the many complex needs of respiratory virus surveillance with a single system, multiple fit-for-purpose surveillance approaches and complementary investigations must fit together as tiles in a "mosaic". Only together will

these approaches provide a complete picture of respiratory viruses and the impact of associated illnesses and interventions at the country level *(13)*. Discrete studies and early investigations such as the Unity Studies can address certain public health objectives that are not efficiently met by existing systems such as rapidly assess transmissibility, estimate population susceptibility/immunity and infection severity, aid identification of population groups in need to target interventions, and estimate burden of disease and vaccine effectiveness *(13)*.

The detection and spread of respiratory pathogens with pandemic potential, or disease X, are accompanied by scientific uncertainty relating to their epidemiological and serologic characteristics, transmissibility (i.e., ability to spread in a population), and virulence (i.e., severity) *(14)*. Looking ahead, leveraging smart surveillance approaches through protocol implementation and standardization will be key to prepare for future potential pan-respiratory pathogen threats *(15)*. These types of enhanced surveillance investigations can be used to inform public health responses to respiratory pathogens of pandemic potential. Pathogen X might be a novel pathogen (e.g., SARS-CoV-2 in late 2019) or a re-emerging existing pathogen (e.g., novel strains of influenza).

1.2 Introduction to Closed Setting Transmission Investigations and their approach

As with many novel respiratory pathogens, key epidemiological, clinical and virological (if applicable i.e. if pathogen X is a virus) parameters of the pathogen and the transmission dynamics are unknown at the beginning. This is the situation for pathogen X, first detected in [Country Y] in [mm/yyyy].

Comment: Findings from any relevant Respiratory Investigations and Studies or any other preliminary studies on pathogen X could be considered here, and relevant updates can be made to the section below accordingly.

This **closed setting transmission protocol** will provide additional early information to **reinforce and supplement the findings from FFX and other investigations of pathogen X.** Additionally, this study will **produce setting-specific estimates of key transmissibility and severity parameters**; and the risk of secondary infection, as well as estimating the asymptomatic fraction.

Closed settings represent a strategic setting to track infections and transmission among close contacts, as the denominator can be well-defined and follow-up of close contacts is generally more feasible than in an undefined setting *(16)*.

Follow-up and testing of respiratory specimens and serum of close contacts can provide useful information about newly identified cases, as well as the spectrum of illness and frequency (by for example age) of asymptomatic and symptomatic pathogen X infection. Infections identified in close contacts may potentially be generalizable to naturally-acquired pathogen X infections (in contrast to for example only cases presenting for emergency care among which there would be fewer mild cases).

Closed settings are also useful to observe chains of transmission during a pandemic as the pool of susceptible, exposed individuals is larger. Therefore, in the case of multiple waves of infection through the closed setting, unique insight into transmission dynamics can be derived in the early stages of a pandemic.

Closed setting studies also provide the opportunity to follow up confirmed cases to ascertain antibody kinetics, and can be extended if there is a desire to understand longer term serological markers.

The following protocol has been designed to investigate transmission of pathogen X in closed settings. The study is not intended as a case-counting system, but rather as an **enhanced surveillance investigation protocol** for prospectively collecting information on important epidemiologic parameters in a sample of cases and their close contacts in closed settings.

This case-ascertained prospective transmission study of pathogen X in closed settings will be conducted across several countries or sites with geographic and demographic diversity. These sites will be part of a network of pre-determined and capacity built sites (WHO Unity Studies sites). However, any country can use and implement the closed setting investigation protocol.

By using a standardized protocol such as the one described here, epidemiological exposure data and biological samples can be systematically collected and shared rapidly in a format that can be easily aggregated, tabulated and analyzed across many different settings globally. This will facilitate timely estimates of the infection-severity and transmissibility of pathogen X infection, as well as informing public health responses and policy decisions. This is particularly important in the context of a novel respiratory pathogen, such as pathogen X.

Each country may need to tailor some aspects of this protocol to align with local public health, laboratory and clinical systems, according to their country capacity and availability of resources, as well as the cultural appropriateness of the protocol. The protocol should also align with country plans for case and contact clinical and public health management, including infection prevention and control measures for both health workers and the cases and contacts.

Toolkit item

The timely and standardized implementation of this protocol should be supported by a toolkit developed by WHO and implementing partners. The toolkit will comprise components to support different elements of the protocol. These will be highlighted throughout the protocol and discussed in Section 5. Toolkit components will be available on the WHO website. CLICK TO VIEW

Toolkit items to support this section may include:

- Checklist for Unity Studies alignment
- Terms of Reference for Unity Studies network sites

See additional 'Toolkit item' boxes throughout this document.

Other Respiratory Investigations and Studies can be undertaken to collect further information relating to pathogen X depending on availability of resources and capacity. These will include household transmission investigation studies, and the First Few X studies.

This protocol may be undertaken **subsequently** to the First Few X (FFX) study for example (but also from the household transmission study; or **simultaneously** to these studies, depending on the epidemiological situation and country capacity.

The table in Appendix A summarizes the different features and complementarity of the three protocols. All protocols are available on the WHO website. CLICK TO VIEW

1.3 Objectives

The overall aim of this protocol is to gain an understanding of the transmission dynamics of pathogen X among close contacts of cases of pathogen X in closed settings, as well as rapid and early information on key clinical, epidemiological and virological (if applicable) characteristics of pathogen X infection.

The ability of a closed setting investigation to answer each objective below will ultimately depend on the type and frequency of data and/or specimen collection. The rationale for specimen sampling is provided in Section 2.4. CLICK TO VIEW

1 Primary objectives

The **primary objectives** of the closed setting investigation among cases and close contacts are to provide **closed setting-specific estimates** of transmissibility and severity:

Transmissibility

1. Overall infection rate of pathogen X infection, and by key factors such as age and sex;
2. Overall clinical attack rate of pathogen X infection, and by key factors such as age and sex;
3. Secondary infection rate (SIR)[1] of pathogen X infection, and by key factors such age and sex;
4. Secondary clinical attack rate (SCAR) as a proxy measure of pathogen X infection among close contacts, overall, and by key factors such as age and sex;

Severity

1. Clinical presentation of pathogen X infection and course of associated disease;
2. Symptomatic and asymptomatic proportions of pathogen X cases, and;
3. Preliminary case- (i.e., disease) and infection-hospitalization and fatality ratios.

2 Secondary objectives

The **secondary objectives** are to provide data to support the estimation of further characteristics of the transmissibility and severity of pathogen X:

Transmissibility

1. Serial interval of pathogen X;
2. Possible routes of transmission;

Severity

1. Risk and/or protective factors for transmission or severe disease.

+ Advanced related objectives

The **advanced related objectives**, to be addressed with the inclusion of modelling or genomic analysis, enable further characterisation of the transmissibility of pathogen X:

Transmissibility

1. Basic reproduction number (R_0) of pathogen X;
2. Effective reproduction number (R_{eff}) of pathogen X;
3. Incubation period of pathogen X, and;
4. Generation interval of pathogen X.

1 Alternative terminology for this parameter is the "secondary infection risk". It represents an overall risk of infection among close contacts for a defined time period. "Secondary infection rate" is used here as this term is widely used and recognised throughout the literature.

The following glossary provides definitions for key epidemiological terms used in this protocol.

- The **overall infection rate** is a measure of the **total number of infections** of pathogen X among contacts of confirmed cases in a defined period of time, as determined by a positive pathogen X laboratory result. *In other words, it is the rate of contacts being infected, assessed through polymerase chain reaction (PCR) or serological assays on paired samples.*

- The **overall clinical attack rate** is a measure of the **total number of new symptomatic persons** among contacts in a defined period of time. *In other words, it is a proxy measure of the SIR, representing the rate of clinical manifestation of the infection in contacts – it is dependent on the clinical criteria being used in case definitions.*

- The **secondary infection rate (SIR)**[1] is a measure of the frequency of new **infections** of pathogen X among contacts of confirmed cases in a defined period of time, as determined by a positive pathogen X laboratory result. *In other words, it is the rate of contacts being infected, assessed through polymerase chain reaction (PCR) or serological assays on paired samples.*

- The **secondary clinical attack rate (SCAR)** is a measure of the frequency of new symptomatic persons among contacts in a defined period of time[2]. *In other words, it is a proxy measure of the SIR, representing the rate of clinical manifestation of the infection in contacts – it is dependent on the clinical criteria being used in case definitions.*

- The **asymptomatic proportion of cases** is a measure of the frequency of asymptomatic infections of pathogen X among all confirmed cases in a defined period of time. *In other words, it represents the proportion of laboratory confirmed cases who do not display symptoms of disease – an individual's symptom status is dependent on the clinical criteria being used in case-definitions.*

- The **infection-hospitalization ratio**[3] is defined as the proportion of persons with a laboratory confirmed pathogen X infection who are admitted to hospital for clinical management or treatment.

- The **infection-fatality ratio**[3] is defined as the proportion of persons with a laboratory confirmed pathogen X infection who die as a direct or indirect consequence of their infection.

- The **serial interval** is defined as the period of time from the onset of symptoms in the primary case to the onset of symptoms in a secondary case.

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2 This can be determined by a positive pathogen X result along with presence of symptoms, or by only the presence of symptoms, however relying on symptoms alone could result in incorrect classification of contacts as the cause of symptoms may be from other respiratory pathogens and not pathogen X.

3 If laboratory confirmation is not available for all contacts, there may be undetected infections. In this instance, only **case-hospitalization and case-fatality** ratios can be calculated.

- The **basic reproduction number R_0** is defined as the number of infections produced, on average, by an infected individual in the early stages of the epidemic, when virtually all contacts are susceptible. Note that this assumes that there is very little to no population-level immunity to pathogen X.

- Once interventions are put in place or the number of susceptible individuals declines, the transmission potential of the disease at a given time (t) is measured in terms of the **effective reproduction number R_{eff}**.

- The **incubation period** is defined as the period of time between an exposure resulting in pathogen X infection and the onset of the first clinical symptoms of the disease.

- The **duration of infectiousness** is the time for which virus is shed and able to be transmitted, regardless of clinical symptoms.

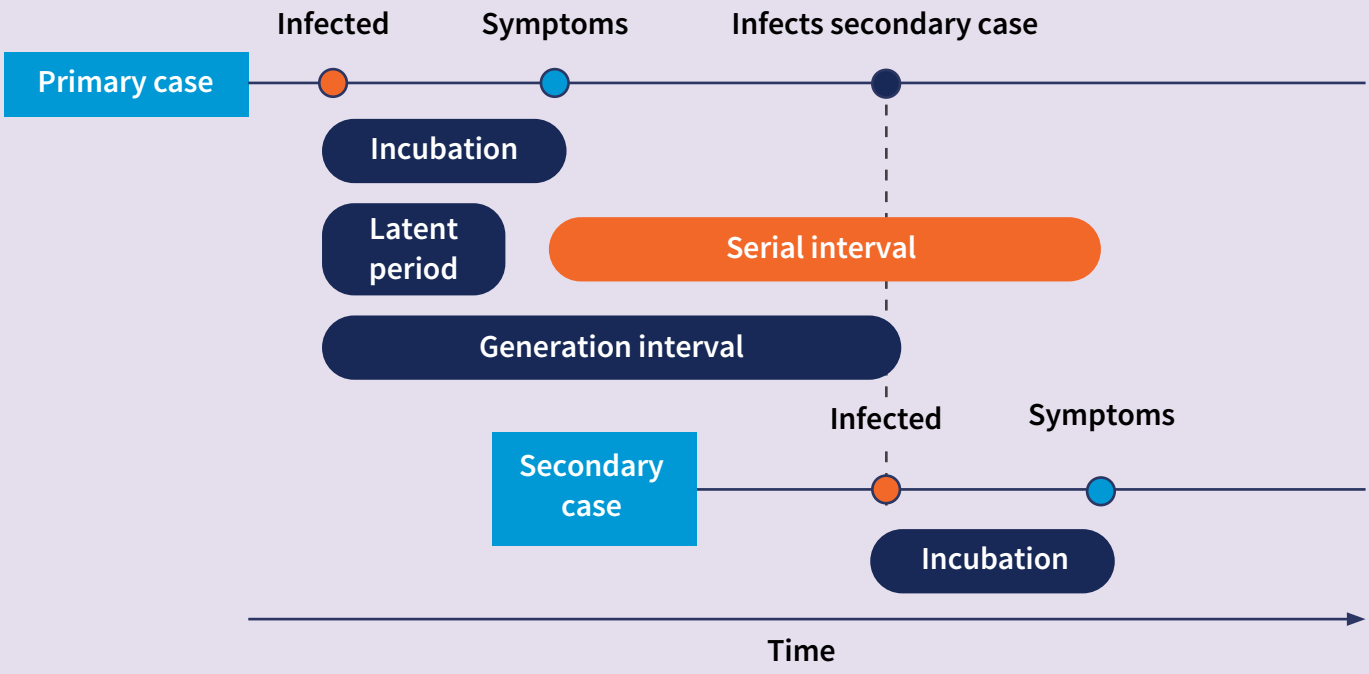
- The **generation interval** is defined as the period of time from infection in a primary case to infection of a secondary case.

- The **latent period** is defined as the period of time between when an individual is infected by pathogen X and when they become infectious.

- The **duration of viral shedding** is the time for which pathogen X is shed, regardless of clinical symptoms.

The relationship of time periods related to a primary case and a secondary case and the main epidemiological parameters can be summarized as below (Figure 1).

Figure 1: Relationship of time periods related to a primary and a secondary case and the main epidemiological parameters



1.4 Overview of methodology

Section 2 of this protocol will describe in detail the methodology for this investigation including the study design, start and duration of the investigation, case and closed setting definitions, data collection, data management, specimen collection and transport, laboratory testing and ethical considerations.

Coordination of investigations and sharing of information in real-time will be needed at both country and global levels. Epidemiologists, modelers, virologists, statisticians, clinicians and public health experts will all assist in developing early estimates of key clinical, epidemiological and virological parameters of pathogen X. Table 1 shows the roles and responsibilities involved for [Country Y].

Table 1: Coordination matrix of roles and responsibilities in [Country Y]

What?	Who?
Overall coordination of the investigation	[Cite institution/body/person(s)]
Case detection and investigation	[Cite institution/body/person(s)]
Contact identification and follow-up	[Cite institution/body/person(s)]
Analysis of data	[Cite institution/body/person(s)]
Data management	[Cite institution/body/person(s)]
IT management	[Cite institution/body/person(s)]
[add more roles, as per country context]	[Cite institution/body/person(s)]

The data will be maintained centrally by [cite institution/body/person(s)]. Centralized coordination will require development of a "command and control" plan, to allow for triage and prioritization of investigations.

It is noted that undertaking this kind of enhanced investigation, will require resources and implementation plans need to be developed in advance.

Toolkit item

Toolkit items to support this section may include:

- Funding guidance
- How to access support
- Project management/budgeting guidance

Toolkit components will be available on the WHO website. CLICK TO VIEW

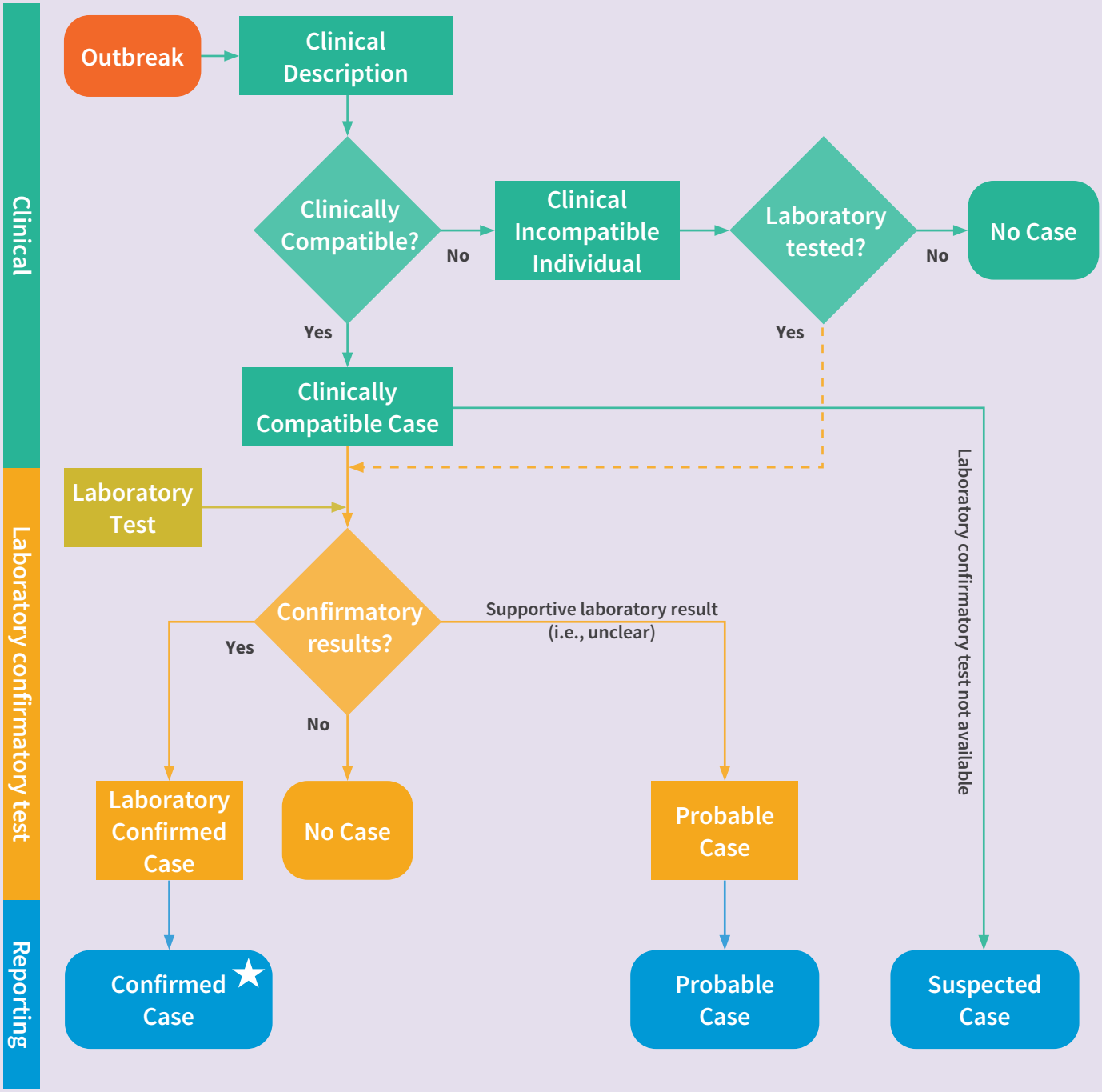
2. Methods

2.1 Definitions used in the closed settings protocol

2.1.1 Case definitions

Case definitions are necessary to standardise the identification of cases. A case definition should include when, where, and who is affected, **and outline all criteria determining how an individual is identified as a case.**

Figure 2: Clinical and laboratory steps for the identification of a confirmed case in a closed setting investigation.



For pathogen X, cases must be reported as *Confirmed, Probable or Suspected* cases based on a series of epidemiological, clinical and laboratory criteria (Figure 2 CLICK TO VIEW) to ensure data specificity and comparability.

A summary of relevant definitions that will be used to form the case definitions *(17)* for pathogen X include:

1) Clinical Description: A description of the illness – signs, symptoms (e.g., cough, sore throat, fever), severity, and individual characteristics where relevant (e.g., international travel history) – associated with the outbreak;
2) Clinically compatible case: An individual experiencing a clinical syndrome compatible with the clinical description in *(1)*;
3) Laboratory confirmed case: a case that is confirmed by one or more of the laboratory methods listed in the case definition under laboratory criteria for diagnosis, irrespective of clinical criteria in *(2)*;
4) Supportive or presumptive laboratory result: meets the clinical criteria in *(2)*, yet does not fully meet the criteria for laboratory confirmation due to unclear results from laboratory testing

Comment: In the early stages of an outbreak of pathogen X, the appropriate identification and enrolment of index cases contributes to the internal validity of the FFX study *(18)*.

The case definitions for pathogen X reporting will be published on the WHO website when available.

For the purpose of this protocol and with these definitions in mind, **the generic interim case definitions for pathogen X are proposed in Box 1.** These definitions will be subject to change as more information and additional diagnostics become available. For instance, the case definition may be adapted to incorporate point of care or rapid antigen tests with proven sufficient sensitivity and specificity as they become available.

Comment: An index case is the first case of pathogen X reported or identified within a cluster/closed setting. It is the identification of the index case that leads to recruitment into the study. The definition of an index case is explored further in Section 2.1.3.

Box 1. Case definitions in the Closed Setting protocol

Confirmed case:
A person with laboratory confirmation of pathogen X infection, irrespective of meeting the clinical description (i.e., irrespective of clinical signs and symptoms). Laboratory confirmation includes receiving a positive result from polymerase chain reaction (PCR), virus isolation or from other validated laboratory methods.

Probable case:
A person meeting the clinical description and has a supportive or presumptive laboratory result

Suspected case:
A person meeting the clinical description, with no laboratory confirmation or testing results.

Comment: The enrolment of confirmed index cases into closed setting investigations must be prioritised where possible. In a scenario where a laboratory confirmatory test is not yet available, it may be feasible to recruit suspected index cases (as defined above and according to the WHO guidance for Pathogen X) as the starting point for a closed setting investigation, however they would need to be recorded as non-laboratory confirmed. The limitations of using non-laboratory confirmed cases must be noted and accounted for in the analysis. Where feasible, consider if samples from suspected cases could be collected and stored for future testing when a confirmatory test becomes available. For these cases, the outcome of laboratory diagnosis should be recorded and reflected in data analysis as soon as it becomes available.

2.1.2 Closed setting and close contact definitions

Contacts are defined as all individuals who are associated with some sphere of activity of the case within the closed setting. **Close contacts** are a subset of contacts who meet a level of interaction with the case that may increase their exposure to the index case (see Box 2).

As with the case definitions, generic contact definitions for pathogen X will be available on the WHO website. These definitions will be subject to change as more information becomes available about pathogen X.

Close contacts can also be defined considering:

- Plausible modes of transmission (e.g., droplets, aerosols, fomites);
- Duration and/or intensity of contact;
- Setting of contact within the closed setting (i.e., indoor or outdoor);
- Infectiousness of pathogen X relative to symptom onset;
- The period of time from symptom onset in an index case (see Section 2.1.3) to testing, notification and recruitment into the closed setting investigation

For the purpose of this protocol, interim and generic definitions of closed settings, close contacts and other contacts are proposed in Box 2.

Comment: Implementing countries may wish to consider more detailed definitions of closed settings and closed setting contacts if appropriate.

Box 2: Closed setting and close contact in a closed setting definitions

Closed setting:

For the purpose of this generic protocol, a closed environment is defined as: **any setting where the local population is relatively secluded from the general community and there is mixing within the local population.**

In practice, the technical definition may vary due to social, political and cultural practices *(16)*.

Examples of closed environments may include (and are not limited to):

- **Substantially closed environments** (e.g. prisons where inmates have little direct contact with the general community, except through prison workers; nursing homes; or secluded military facilities), or;
- **Or semi-closed environments**, where there is interaction with the general community (e.g. regular schools, boarding schools/hostels, camps, healthcare facilities with frequent visitors, etc.).

Close contact: any person in the closed setting who had contact (within 2 meters and for more than 5 minutes)

- With a symptomatic case during their **symptomatic** period, 2 days before symptom onset, and in the 10 days after the onset of symptoms, or;
- With a confirmed **asymptomatic** case, including 2 days before and the 10 days after the date on which the sample was taken which led to confirmation;

Comment: The contact does not have to be direct physical contact

Other contact: any other individual present in the closed setting during the exposure period (2 days before symptom onset, and in the 10 days after the onset of symptoms in the case) who has not met the criteria to be defined as a close contact

Comment: It is important that the definitions are consistently applied throughout the investigation and well detailed in any reporting of the investigation for the purposes of comparability between investigations

2.1.3 Classification of closed setting participants

During the course of the closed setting study, transmission events associated with an index case will be observed (or inferred) through laboratory testing and symptom monitoring of close contacts. These observations will help identify the chains of transmission within clusters and allow for final classification of all participants, as described below.

Box 3: Classification of participants in the closed setting study

A. Index case: the first case of pathogen X identified within the cluster/closed setting according to the case definition (see Box 1). It is the identification of the index case that leads to recruitment into the study*.

B. Primary case: an individual who has the first evidence of infection/disease within the recruited cluster/closed setting (see Box 1) i.e., the case with the earliest symptom onset date and/or positive laboratory test within a cluster.

C. Co-primary case(s): of the first cases identified within a cluster/closed setting, two or more cases identified within the same 24 hour period are considered to be **"co-primary" cases**.

Comment: Cases in A), B) and C) must also be classified further as confirmed, probable or suspected cases according to Box 1. The relevant clinical and laboratory criteria for pathogen X must be added into the definitions above when available.

* In some instances, the index case is also the primary case but this is not always the case. Following investigation, index cases may be classified as a primary, co-primary or secondary case *(19)*.

D. Imported case: an index, primary or co-primary case with a history of travel from an affected area [define "affected area"] in the 14 days before disease onset.

E. Subsequent cases are contacts meeting the:

1. Case definition throughout the duration of the closed setting investigation,
   OR those demonstrating evidence of;
2. Seroconversion, of which a generalized definition is a 4-fold increase in pathogen X specific antibody titre between paired serum samples, collected at baseline (day 1) and follow-up.

F. Secondary cases: are contacts meeting the:

1. Case definition between 24 hours to 10 days after the confirmation or symptom onset of the primary and/or co-primary case(s)

It is important to consider the timing of exposure and virological characteristics (if applicable) of pathogen X when classifying subsequent cases as secondary cases. Testing protocols, symptom information and genomic sequencing data may help to distinguish between secondary cases and subsequent cases.

Comment: When laboratory diagnostics are not available for case classification, the limitations of classifying cases according to the suspected or probable case definition must be noted and accounted for in the analysis.

G. Unrelated case: includes other cases for the purposes of the closed setting investigation, including cases infected from external sources

Genomic sequencing data may help to distinguish between subsequent and unrelated cases.

Comment: Cases in E), F), G) may also be classified as confirmed, probable or suspected secondary cases according to Box 1. The relevant clinical and laboratory criteria for pathogen X must be added into the definitions above.

2.2 Study design, duration and population of interest

2.2.1 Study design

This closed setting investigation is a case-ascertained prospective study of index cases of pathogen X and closed setting contacts, including infants and children. Study participants and settings are identified from those with pathogen X infection. This is distinct from a cohort study in which a group of disease-free individuals are recruited and then followed over time. Case-ascertained transmission studies are more efficient than cohort studies when interest is in early estimation of the clinical, epidemiological and virological (if applicable) characteristics of an emerging pathogen. This is because the risk of primary or secondary infection in a cohort would be expected to be low during the early stage of the pandemic before widespread community transmission was established.

Closed setting transmission studies have also their limitations, as described in the literature *(16, 20)*.

2.2.2 Timing of the study

This closed setting investigation should be established as soon as possible after the identification of the first cases of pathogen X infection in [Country Y]. It is intended to be conducted before widespread community transmission occurs, that is, within the early phases of the pathogen X epidemic in the country. However, a study can continue for as long as is determined feasible by the country implementing the investigation, particularly if objectives shift to address alternative questions.

2.2.3 Population of interest & study representativeness

The study population is cases of pathogen X and their contacts within a closed setting in [Country Y]. Index cases will be identified through national line listings/ initial case register or other relevant surveillance systems.

Comment: Public health officials should consider the appropriateness of generalising findings from one closed setting investigation to 'similar' closed settings, i.e., the demographics of individuals within each closed setting may vary, impacting parameter estimates.

Closed settings will be enrolled in the study once a pathogen X case is identified in at least one member of the closed setting. Closed settings are subsequently followed up to observe subsequent (and secondary) infections in all contacts.

These studies will be resource intensive as there is likely to be a large number of closed setting contacts per index case.

2.3 Eligibility criteria of cases for the study

Inclusion criteria:

- **Cases of pandemic pathogen X in [Country Y]** should be enrolled according to the case definitions provided in Box 1.
- Participating individuals give appropriate informed consent (See Section 2.9 CLICK TO VIEW for further details)

2.4 Variations to the closed setting study

Adapting the closed setting study into a longitudinal study may be appropriate to assess questions relating to the development and protectiveness of immunity in a rapidly changing epidemic.

For closed setting investigations that are extended over longer periods of time, or conducted in later stages of the pandemic, it is advised that they be conducted in geographical locations that are representative of the study country where possible, so that results may be generalizable to the general population.

2.5 Data collection

This closed setting protocol calls for the recruitment and follow-up of index cases and their contacts for a maximum period of 28 days from identification of the index case. **The first day of participation in the closed setting investigation will be defined as Day 1.** The duration of follow-up may vary and need to be adapted, depending on the characteristics and transmission dynamics of the pathogen, antibody kinetics and specific public health priorities – see the sampling rationale for more information.

Every effort should be made to include all closed setting contacts, including infants and children, of the index case, to generate the specimen and data sampling time frame for follow-up.

Epidemiological, clinical, virological (if applicable) and serological data will be collected from each participant at multiple times during the study – including surveys at baseline and day 28, symptom diaries from days 2-28 and specimen collection (as per Section 2.5 CLICK TO VIEW and 2.6 CLICK TO VIEW). This information can be obtained through a combination of methods including: face-to-face or telephone interviews/consults with participants (or family members if the case is too ill to be interviewed), self-reporting, interview of health workers and/or review of medical records, self-swabbing and professional/medical specimen collection services.

Comment: Additional study visits can be included to collect further clinical information and specimens as required. For example, at day 7, 14 and 21.

Toolkit item

Toolkit items to support this section may include:

- Data dictionaries
- Data quality checklist
- Study team training template

Toolkit components will be available on the WHO website. CLICK TO VIEW

2.5.1 Clinical and epidemiological data collection

Once an index case has been identified and recruited into the investigation, an initial study visit or phone interview will need to be conducted to identify all close contacts for recruitment into the study.

A summary of the data and specimen collection forms can be found in Table 2 and Figure 3.

Ideally, data collection should be conducted for all contacts in the closed setting. In situations **with limited resources, data collection from close contacts can be prioritised.**

For index cases, data will be collected using **Form A1** CLICK TO VIEW for the baseline visit (day 1), followed by **Form A2** CLICK TO VIEW for the follow up visit (day 28) to collect relevant sociodemographic and clinical information.

For contacts in the closed setting, data will be collected using **Form B1** CLICK TO VIEW for the baseline visit (day 1), followed by **Form B2** CLICK TO VIEW for the follow up visit (day 28) to collect relevant sociodemographic and clinical information.

Form C CLICK TO VIEW will be used for **all** specimen collection visits (throughout day 1 to day 28) for cases and contacts in the closed setting.

Form D – symptom diaries CLICK TO VIEW (template available in Appendix B of this protocol) will be provided for all cases and contacts in the closed setting to complete (throughout day 2 to day 28), to record the presence or absence of various signs or symptoms. A proxy may fill out the symptom diaries on behalf of those unable to complete the form themselves. Note that symptoms are recorded on day 1 as part of the baseline form (**Form A1** CLICK TO VIEW or **Form B1** CLICK TO VIEW)

Some aspects to keep in mind are:

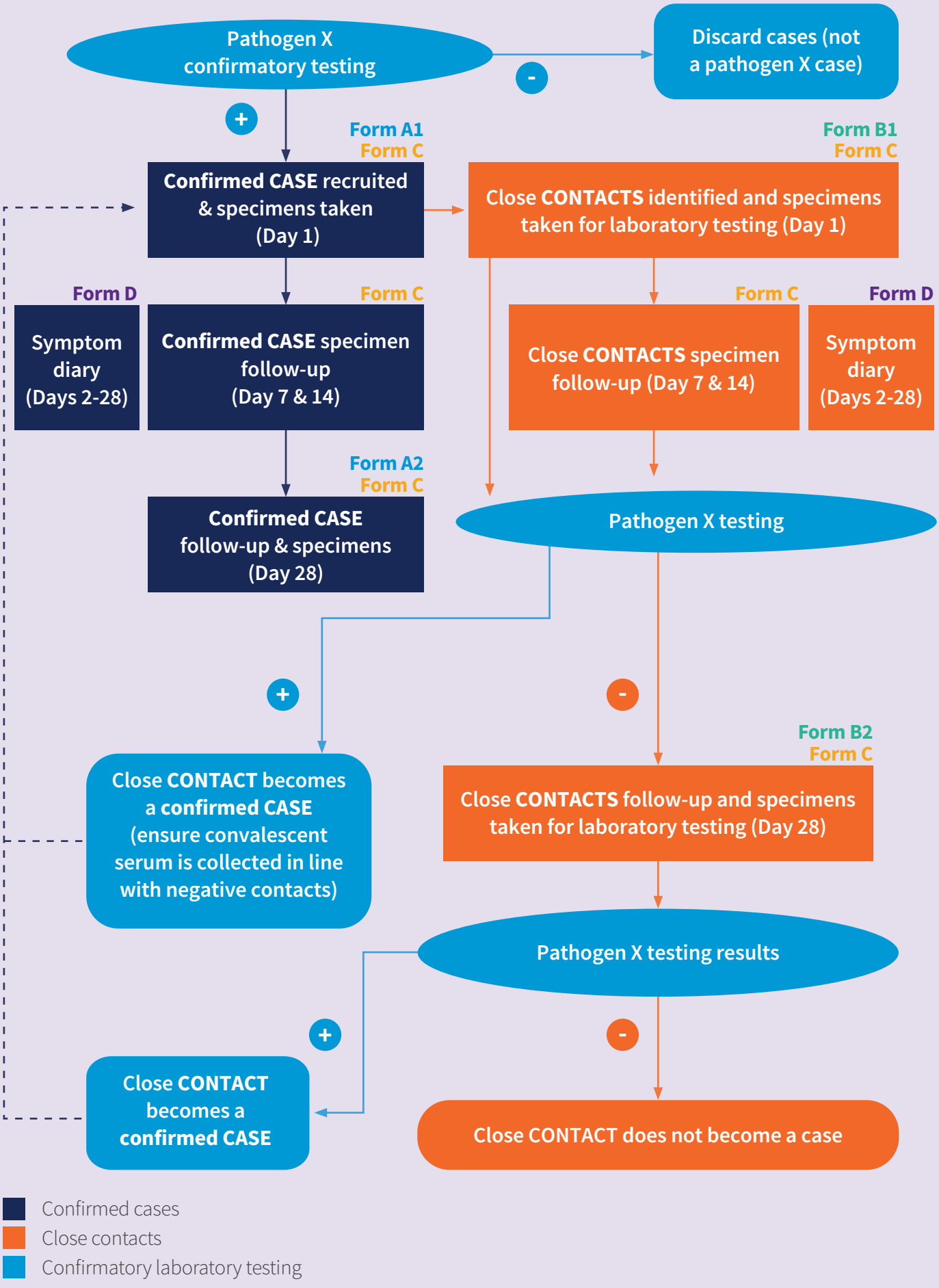
- Contacts in the closed setting found to be infected with pathogen X would be reclassified as **confirmed cases** (dotted line in Figure 3) and follow-up would occur as described in the case investigation algorithm. The data collection process may or may not be re-triggered in this instance, but would depend on the country resources and type of contact (for example, if the contact is a health worker, then a further investigation might be warranted to inform public health action).

All **investigation questionnaires can be found in Appendix B** CLICK TO VIEW of this document. Note that the questionnaires may need to be adapted based on the local setting of implementation and the specific characteristics of the pathogen. For example, the required duration of symptom diaries may be shortened to 14 days where pathogen X does not cause prolonged symptoms in cases (i.e., where disease is acute and short in duration, is not known to cause post-viral sequelae after recovery or testing negative) and where chains of infection amongst contacts in the closed setting are not prolonged across the study period.

Table 2: Summary of data collection tools

Form number	Purpose of form	Collecting from whom?	When should it be collected?
CASES			
Form A1	Case **initial** report form	For pathogen X index cases	Day of recruitment into the closed setting investigation (as soon as possible after identification of a case) **(Day 1)**
Form A2	Case **follow-up** form	For pathogen X index cases: final outcome	28 days after completion of Form A1 **(Day 28)** Updates should be obtained regularly, if all the required information is not available at the time of completing this form
CONTACTS			
Form B1	Contact **initial** reporting form	For contacts of pathogen X index cases	Day of recruitment into the closed setting investigation (ideally within 24 hours after identification of the index case) **(Day 1)**
Form B2	Contact **follow-up** form	For contacts of pathogen X index cases: final outcome	28 days after completion of Form B1 **(Day 28)**
CASES & CONTACTS			
Form C	Track and summarize **all laboratory results (and methods used)**	For pathogen X index cases and contacts	This table will need to be filled/updated at **each specimen collection time point**
Form D: Symptom diary	Record the presence or absence of various signs or symptoms	For pathogen X index cases and contacts	Between **days 2 and 28** after administration of the initial questionnaire

Figure 3: Case investigation algorithm and summary of data-collection tools



2.6 Specimen collection and transport

The following is intended to guide specimen collection from index cases and their close contacts in a closed setting. Careful planning should be done to ensure arrangements are in place for who will collect the samples, how to access required Personal Protective Equipment (PPE) and how to arrange safe sample collection and transport of specimens. Sample collection and transport should follow national guidelines.

Comment: Guidance on laboratory testing is subject to change, depending on the context of the specific evolution of the epidemic/pandemic, along with the possible development of point of care or rapid antigen tests with proven accuracy as they become available.

Toolkit item

Toolkit items to support this section may include:

- Standard operating procedure for sample collection
- Advice for specimen types to be collected

Toolkit components will be available on the WHO website. CLICK TO VIEW

2.6.1 Sampling rationale

This section outlines the rationale for the collection of respiratory and serological specimens from cases and contacts (Box 4).

Box 4. Rationale for specimen collection

In general, the collection of specimens helps to characterise pathogen transmission patterns through:

- Confirming infection in close contacts and classifying participants (Box 3);
- Studying transmission dynamics (infection attack rates, incubation period, infectiousness relative to symptom onset, generation time);
- Determining the extent and fraction of mild or asymptomatic infection;
- Identify symptomatic infections with atypical clinical presentation, and;
- Detecting prolonged viral shedding in cases.

Serological specimens will help to:

- Identify seroconversion – increase in pathogen specific antibody titres between baseline and convalescent paired samples, in cases and contacts;
- Identify any cases in close contacts not identified by PCR with or without symptoms, and;
- Study transmission dynamics (infection attack rates).

Genomic analyses of specimens may help to:

- Conduct alternative analyses of transmission dynamics;
- Strengthen inference on relatedness of infections and geographic spread;
- Quantify genetic diversity, and;
- Identify genetic differences by variants/subtypes/lineages and strengthen inference on phenotypic differences, if any.

The collection of respiratory specimens from (cases and) close contacts should consider:

- The **timing and frequency of sample collection** in relation to the generation interval (see Figure 1 CLICK TO VIEW) and the setting of contact to accurately define infection events.

Comment: Specimen collection should be sufficiently late to allow identification of secondary cases, but early enough to avoid capturing tertiary (those with evidence of being infected by a secondary case) (or later) cases for estimation of the secondary attack rate.

Comment: Characterising pathogens with a short generation time and/or high transmissibility requires respiratory samples to be collected at a higher frequency to identify and observe chains of infection.

- The **types of respiratory specimen** collected (i.e., nasal swabs, nasopharyngeal swab, throat swabs, saliva, sputum, and combinations of these) and the demonstrated sensitivity and specificity of each for detecting pathogen X using RT-PCR or the laboratory method being recommended for pathogen detection (Appendix C CLICK TO VIEW);

Comment: In some cases, several specimen types may be indicated.

- **How the specimens will be collected** (professionally or self-collected). It may be possible for participants to self-collect respiratory specimens. This may reduce staffing burden/costs on study nurses or professional collection services and enable frequent sampling when required per the sampling strategy. For example, self-swabbing has been demonstrated to be a reliable method for influenza and SARS-CoV-2 testing *(21)*, although this is dependent on pre-planning, logistics of transport and the quality of training provided to participants *(21, 22)*.

Comment: Investigators may wish to consider self-swabbing to supplement study visits from a research/study nurse or professional specimen collection service. However the first and last study visits should be carried out by study personnel.

The collection of serological specimens from (cases and) close contacts should consider:

- The **number of serological specimens**. At a minimum, paired samples should be taken at baseline and at day 28 (i.e., at the end of follow-up) to allow time for the maturation and development of the immune response.

Comment: Additional serological samples collected during the study period may help to better characterise immune responses in relation to exposure, infection, disease onset, and maturation/development of immunity over time. This may be especially important if pathogen X is novel.

Comment: If reliable serology for pathogen X is not available, consider how these specimens will be stored for future testing. Testing can also be performed at a reference laboratory.

2.6.2 Sampling strategy

The sampling strategy for the investigation is presented in this section in Figure 4.
CLICK TO VIEW

The strategy involves the mandatory collection of respiratory and serology specimens from **the index case and all contacts – irrespective of symptoms** – at determined timepoints.

Comment: Adherence to the harmonised schedules is critical, especially in closed settings where chains of transmission may be rapid.

The initial respiratory specimen aims to identify co-primary cases as well as subsequent cases as quickly as possible after they are infected, to minimise the risk of misclassification of participants.

A final respiratory and serological specimen is mandatory at the end of follow-up to study the immune response and inform estimates of overall attack rates and any prolonged viral shedding.

Comment: If testing is not frequent enough or case ascertainment is based on clinical signs and symptoms only, subsequent or unrelated cases may be misclassified as secondary cases.

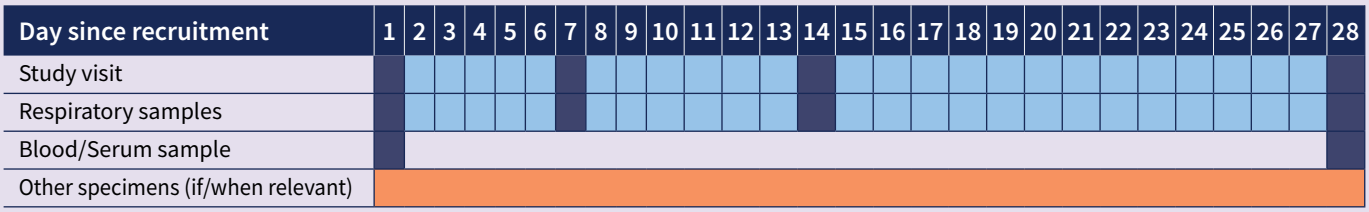
In addition to this generic protocol, the chosen sampling strategy in the closed setting investigation in [Country Y] should be informed by current knowledge of the biological and epidemiological characteristics of pathogen X (e.g., the incubation period, latent period) and the expected time delays associated with testing, notification, and recruitment of a case). The strategy should be readily adapted/flexible to new information as more becomes known about pathogen X over time.

Where appropriate, **other specimens** (e.g., oral fluid, urine, faeces) may be collected, according to clinical presentation and observed patterns of viral shedding upon infection.

Comment: The onset of acute respiratory illness in contacts may prompt further testing, however this must be **in addition** to the mandatory components of the proposed sampling schedule and not a replacement for standardised testing.

Comment: Countries undertaking closed setting investigations may wish to modify their sampling requirements depending on their specific or additional study objectives and availability of resources. We strongly advise that coordinators consult the sampling rationale and statistical analysis plan prior to adapting or modifying this strategy.

Figure 4: Sampling strategy



BLUE BOXES indicate activities that are **mandatory** for the investigation of pathogen X.

LIGHT BLUE BOXES indicate activities that may be undertaken in high resourced settings where there is substantial uncertainty in the biological and epidemiological characteristics of pathogen X.

ORANGE BOXES indicate where additional specimen types could be collected to increase the information available.

2.6.3 Specimen collection and transport

Appropriate PPE should be worn when specimens are being collected from index cases and all contacts from professional/health-care specimen collection services *(23)*. All those involved in collecting and transporting specimens should be trained in the safe handling of infectious substances and infectious spill decontamination procedures. For details regarding the collection and transport of samples, please refer to the case management algorithm and laboratory guidance in the country, and to WHO laboratory guidance *(23)*.

For each biological sample collected, the time of collection, the conditions for transportation and the time of arrival at the laboratory should be recorded. Specimens should ideally be collected within 3 days of the onset of clinical symptoms and reach the laboratory as soon as possible after collection. If the specimen is not likely to reach the laboratory and to be processed within 48 hours, it should be frozen, preferably at –80 °C, and shipped on dry ice as per applicable WHO guidance *(24)*. It is, however, important to aliquot each sample to avoid the deleterious effects of such handling on the infectivity of virus and the yield of genetic material. The storage of respiratory and serum specimens in domestic frost-free freezers should be avoided, owing to their wide temperature fluctuations. Serum should be separated from whole blood and can be stored at 4 °C for one week and shipped at 4 °C or frozen to –20 °C or lower and shipped on dry ice.

Transport of specimens within national borders should comply with applicable national regulations. International transport of specimens should follow applicable international regulations as described in the WHO Guidance on regulations for the transport of infectious substances 2021–2022 *(25)*.

2.7 Laboratory evaluations

2.7.1 Laboratory analysis

Comment: Guidance on laboratory testing is preliminary and may change, depending on the characteristics of pathogen X, the availability of laboratory tests for pathogen X and the context of the specific evolution of the epidemic/pandemic.

Laboratory testing guidance of [Country Y] for pathogen X can be found in Appendix xx (country to insert)

Toolkit item

Toolkit items to support this section may include:

- Protocols/standard operating procedures

Toolkit components will be available on the WHO website. CLICK TO VIEW

2.8 Data management generalities

The closed setting data system will be maintained centrally by [cite institution/body/person(s) in the country].

Toolkit item

Toolkit items to support this section may include:

- Data collection/entry guidance
- Data transfer
- Data quality checklist
- Data dictionaries
- Data cleaning
- Data security

Toolkit components will be available on the WHO website. CLICK TO VIEW

2.9 Ethical considerations

National and local ethical requirements must be followed. Ethical approval should be sought as per individual country requirements as ethical requirements will vary by country. In some countries, this investigation may fall under public health surveillance (emergency response) acts and may not require ethical approval from an institutional review board. It will be upon national authorities to advise on the specific requirements for the investigation in [Country Y].

It is important that, wherever possible, ethics pre-approval is sought in advance of a pandemic to reduce time to activation of Respiratory Investigations and Studies in accordance with local, regional and national authorities. This will ensure that investigations are implemented when necessary and with minimal delay.

For further information on the ethical considerations of importance to public health surveillance can be found in key WHO guidance:

- Guidance for managing ethical issues in infectious disease outbreaks (who.int) *(26)* CLICK TO VIEW
- WHO guidelines on ethical issues in public health surveillance *(27)* CLICK TO VIEW

Toolkit item

Toolkit items to support this section may include:

- Ethical exemption/clearance letter templates
- Links to key WHO guidance on ethical considerations of importance to public health surveillance
- Template consent and assent forms

Toolkit components will be available on the WHO website. CLICK TO VIEW

2.9.1 Informed consent and assent

The purpose of the investigation will be explained to all individuals willing to participate, before the start of the investigation. For all investigation activities not included in routine public health management, informed consent and assent may be required. This will depend on the country's national ethical requirements. Informed consent will seek relevant approvals for the collection of all data and specimens for the purposes of this investigation as determined by [Country Y].

- **Consent** for:
  Adults; and
  Children under the legal age of consent (usually 18 years, but will vary from country to country) from a parent or legal guardian.

- **Assent** from:
  Children and adolescents under the legal age of consent, but who can understand the implications of informed consent and go through the necessary procedures. This is usually children over the age of 12 to 13 years, but this will vary by country. A consent form from a parent or legal guardian will be collected in addition.

Comment: The age of consent may vary by country. Check the requirements of local, regional or national authorities.

Comment: If older adults are being included, assessment of cognitive function (affecting ability to consent) could be included, and consent of legal guardians might be required for adults with cognitive decline if these individuals are to be considered for inclusion.

Template informed consent and assent forms will be included in the supporting closed setting investigation toolkit.

All eligible individuals, regardless of whether or not they are well or unwell should be able to participate in the investigation. For individuals who lack the decisional capacity to consent at the time of the investigation, consent/assent by proxy (parent/ legal guardian/ spouse/ family member) may be considered so as to not unduly exclude individuals from participating in the investigation.

The processes related to withdrawal of a participant need to be described both in the protocol and in the information given to the participant at the time of enrolment. In this description it must be made clear that a participant can withdraw from the investigation, without justification, at any time by informing one of the members of the investigation team. The contact details of one of the members of the investigation need to be provided in the information for the participant. If any participant decides to withdraw from the investigation, the samples collected and data should be discarded, except if the participant indicates that these can be kept for the purpose of conducting the investigation, or for future studies of other infectious pathogens (See Section 2.9.5 CLICK TO VIEW).

Informed consent will seek approval to collect blood, respiratory samples, any other relevant samples and epidemiological data for the intended purpose of this investigation. It may also seek approval that samples may be shipped outside of the country for additional testing; and that samples may be stored and used for future public health needs, in accordance with national laws and regulations. Additional detail in the consent/ assent forms may be needed, according to national laws and regulations, if the investigation calls for storage and future use of samples. See further details in Section 2.9.5. CLICK TO VIEW

Comment: Participants or their parent/legal guardian/spouse will be informed about the test results, with an explanation of the interpretation and implications of the test results.

2.9.2 Risks and benefits for subjects

This investigation poses minimal risk to participants, involving the collection of a small amount of blood and respiratory specimens. The direct benefit to the participant is the possibility for early detection of pandemic pathogen X infection, which would allow for appropriate monitoring and treatment for themselves and their close contacts. The primary benefit of the investigation is indirect, in that data collected will help improve and guide efforts to understand transmission of pandemic pathogen X and inform appropriate public health responses.

In terms of treatment of cases, case management will be facilitated by early detection of the disease and will follow national guidance, but the investigators may or may not be directly involved in clinical management of patients. Processes on how cases will be referred for medical care, as well as details on provisions of care as part of the investigation will need to be detailed.

There will be no incentives while participating in this investigation, but participants will be provided relevant and updated health advice to reduce the risk of transmission and severe outcomes where possible.

2.9.3 Reporting of serious adverse events, including death of a participant

Any serious adverse event[4], including death, of a participant during the investigation period, needs to be immediately (within 24h) reported to the Principal Investigator and the institution responsible for the investigation. The contact details for reporting serious adverse events needs to be provided to each member of the investigation team.

In accordance with national regulations, any serious adverse event, may also have to be reported to the local ethical review committee, if the adapted protocol was not deemed exempt from local ethical review committee.

2.9.4 Confidentiality

Participant confidentiality will be maintained throughout the investigation. All subjects who participate in the investigation will be assigned a unique identification number by the investigation team, for the labelling of questionnaires and clinical specimens. The link of this identification number to individuals will be maintained by the investigation team and will not be disclosed elsewhere.

4 An adverse event can be defined as: An injury related to medical management, in contrast to complications of disease *(30)*.

Data and specimens must be securely stored. If the data are shared by the implementing organization with WHO or any agency or institution providing support for data analysis, the shared data will include only the investigation identification number and not any personally identifiable information. Data sharing outside [Country Y] must be managed according to national laws and regulations, as appropriate.

Comment: The investigators will need to describe how data and specimens will be securely stored, the duration of storage and the destruction of data and specimens at the end of the duration of storage, in accordance with national laws and regulations.

Article 45 of the International Health Regulations (2005) (IHR) describes the "treatment of personal data" *(28)*. Personally identifiable data collected under the IHR should be kept confidential and processed anonymously, as required by national law. However, such data may be disclosed for assessments and management of public health risks, provided the data are processed fairly and lawfully.

2.9.5 Future use of samples

The investigators may decide on potential future use of specimens and the time-frame for their destruction and seek appropriate approvals for this. If this is the case, the investigators will need to provide more specific information on potential future use of specimens and the time-frame for their destruction, including in the information for the participant and the informed consent/assent form. Additional consent forms may need to be developed by the country, to comply with national laws and regulations.

2.9.6 Prevention of pathogen X infection among investigation personnel

All personnel involved in the investigation visits must be trained in procedures for infection prevention and control (as determined by national or local guidelines) *(29)* when collecting data or specimens in proximity to cases and close contacts. These procedures should include proper hand hygiene and the correct use of surgical or respiratory face masks, to minimize their risk of infection.

WHO technical guidance on infection prevention and control specific to pathogen X will be published on the WHO website.

3. Statistical analyses

3.1 Sample size

Every effort should be made to include all contacts of the index case within the closed setting, to improve the precision and reduce bias in parameter estimates.

For further details please refer to the Toolkit item, Statistical Analysis Plan, available on the WHO website. CLICK TO VIEW

Sample sizes can be calculated using **statistical formulas or tools** available online (e.g., http://www.openepi.com/Menu/OE_Menu.htm CLICK TO VIEW) or in standard statistical packages.

3.2 Plan of analysis

Closed setting investigations will not be able to answer every question we have about pathogen X infection, but they will contribute key data in the early stages of an epidemic, which can inform an appropriate public health response. Other protocols for investigations adapted for pathogen X can assist in providing supplementary data to help with the calculation of key epidemiological parameters.

Prior to commencing the investigation, an analysis plan should be developed incorporating the study objectives, definitions and planned analysis to address each objective. Pre-specifying the analysis plan will help to ensure that all relevant data are being collected. Please refer to the WHO Statistical Analysis Plan as part of the supporting Toolkit.

A descriptive analysis (time, place, person) of the FFX should provide preliminary insight into the demographics of individuals infected with pathogen X, as well as, severity, the clinical spectrum and course of disease – for example, the initial population groups most affected, by age and underlying risk factors. See Figure 5 and Section 4 CLICK TO VIEW for more details.

A statistical analysis (epidemiological parameters estimation) of the FFX data will provide estimates of the transmissibility and severity of pathogen X – for example, the overall infection or attack rate or hospitalization/fatality rate by age and other risk factors. See Figure 5 and Section 4 CLICK TO VIEW for more details.

Additional complex analyses can be conducted using the FFX forms/questionnaires and specimens generated as described in Figure 5. These require more computationally intensive analysis methods, i.e., mathematical modelling approaches.

Genomic analysis of the specimens generated through this investigation can help provide a detailed insight into the origin of the pandemic; monitor the potential spread of antiviral

resistance; and identify transmission chains using the confirmed case as a potential origin (by comparing the relatedness of two virus isolates), which in turn will help with estimation of the basic reproduction number. Genomic analyses can be useful for determination of the extent of community transmission that is occurring in the early stages of the pandemic and whether the strain was locally acquired or imported from another region.

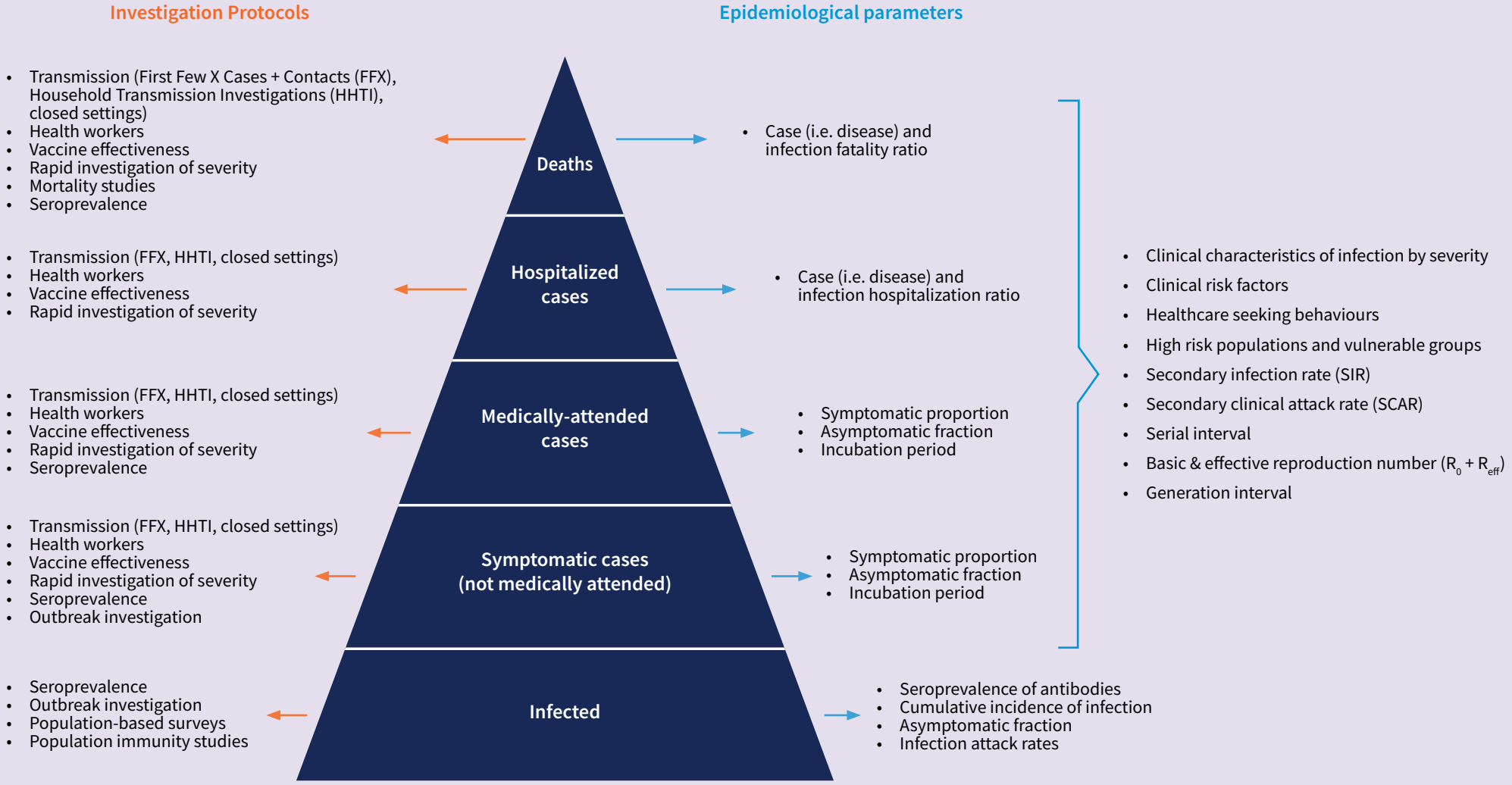
Toolkit item

Toolkit items to support this section may include:

- Template statistical analysis plans
- Data analysis scripts
- SOP for interpretation
- Reporting guidelines for outcomes

Toolkit components will be available on the WHO website. CLICK TO VIEW

Figure 5: **Disease pyramid with associated epidemiological parameters to be estimated through implementation of Unity Studies protocols**



4. Data sharing and reporting of findings

4.1 Data sharing

Data from these WHO Respiratory Investigations and Studies may be **pooled and aggregated across multiple sites** by WHO if the data are collected in a consistent manner, to increase analytic power and improve precision in estimates of severity and transmissibility. The pooling of this data will depend on how transmission dynamics vary between countries. If the data are shared by the implementing organization or country, with WHO or with any agency or institution providing support for data analysis, data shared will include only the investigation identification number and not any personally identifiable information.

Any data sharing must also be covered by any ethical approvals, where relevant, or national regulations.

Toolkit item

Toolkit items to support this section may include:

- Data sharing agreement templates
- Platforms for data sharing
- Standardized formats/templates for data sharing

Toolkit components will be available on the WHO website. CLICK TO VIEW

4.2 Reporting of findings

Any investigation of this nature should include reporting on the following information, stratified by age, sex and relevant time and place characteristics if sample size permits:

- the number of cases initially identified in the setting (symptomatic and asymptomatic)
- the number of contacts (close and other), and
- the number of cases among contacts;
- the number of symptomatic contacts;
- the number of contacts with serologic evidence of infection, and;
- parameter estimates with uncertainty.

If sample size permits, these numbers should be stratified by age, sex or other relevant characteristics.

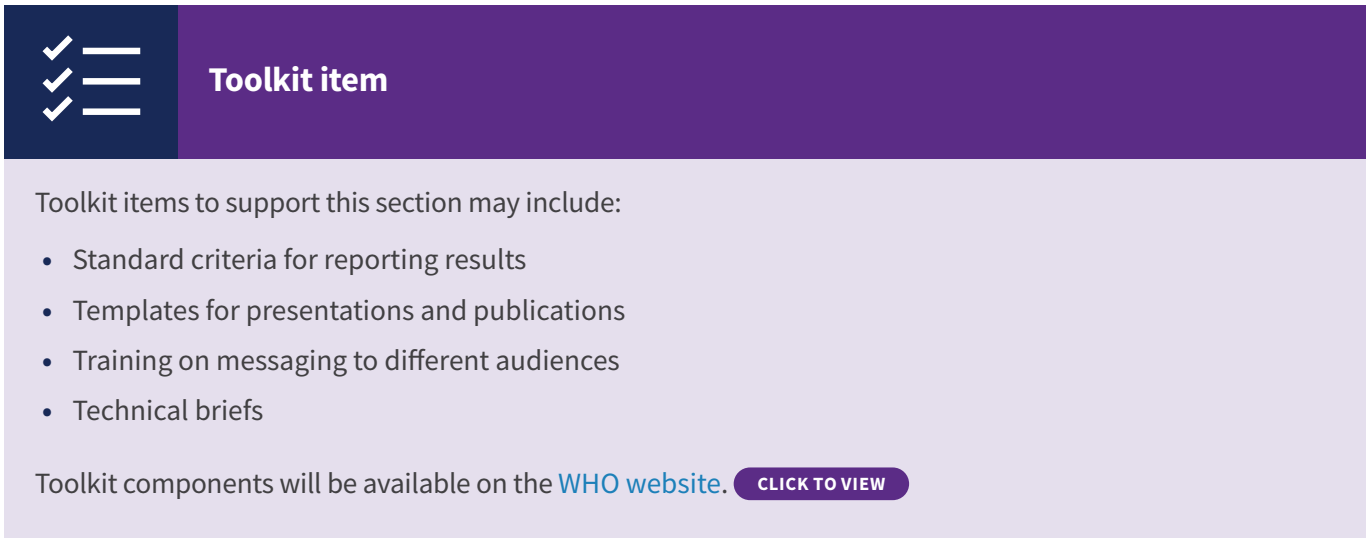
In addition, further details regarding the study should be reported, including:

- the timing of the study;
- inclusion / exclusion criteria of cases and contacts and any loss to follow up;
- case, contact and closed setting definitions used
- context of the study e.g. community incidence/transmission, geographical spread, any pharmaceutical/non-pharmaceutical interventions where applicable, and;
- statistical methods used to calculate estimates.

Timely dissemination of the results of this investigation is critical to update guidance and inform local, national and international public health responses and policies for infection prevention and control. WHO needs to be able to adapt WHO global recommendations in a timely manner. Countries are encouraged to share with WHO in line with IHR requirements and in a confidential manner, any early findings, especially if they will impact WHO global guidance.

It is also important to fully **document the investigation design**, including but not limited to the definition of close contacts; the approach to ascertainment of primary cases and subsequent cases (including any inclusion and exclusion criteria); the duration of follow-up; and the laboratory methods used to ensure that data can be pooled to increase the precision of epidemiological parameter estimates.

Information should be collected in a **standardized format** according to the questionnaires and tools in this generic protocol, to assist with data harmonization and comparison of results (see forms in Appendix B CLICK TO VIEW).



4.3 Science translation for decision makers

Translation science should be implemented to assure timely and understandable information from the investigations is available to decision makers and key stakeholders in order to inform timely policy-relevant decisions.

Toolkit item

Toolkit items to support this section may include:

- Training on messaging to different audiences
- Policy makers questions that will be answered by study objectives

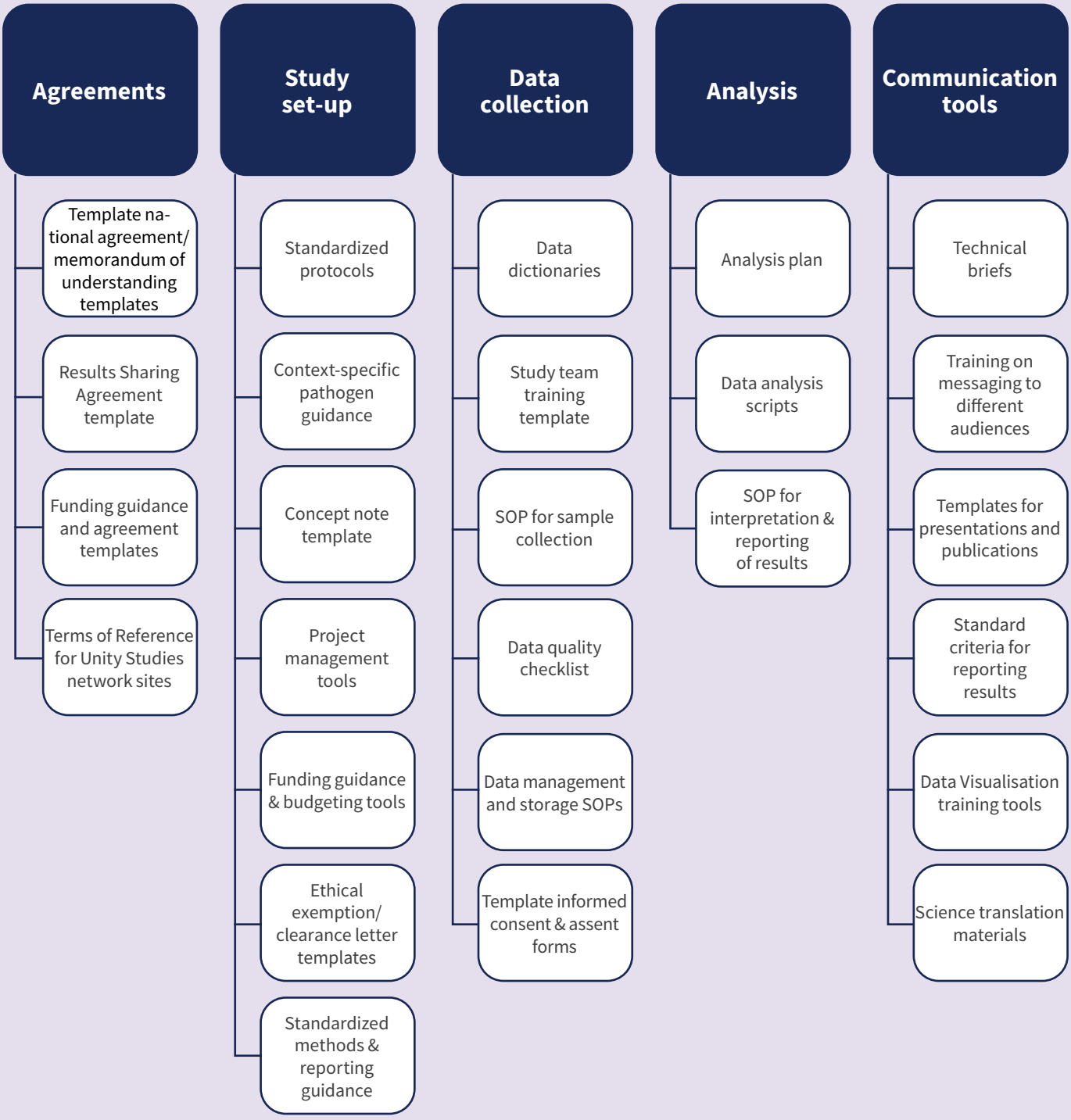
Toolkit components will be available on the WHO website. CLICK TO VIEW

5. Protocol Toolkit

5.1 Protocol Toolkit

The timely and quality implementation of this protocol should be supported by the use of toolkits developed by WHO and implementing partners. These will include components such as pre-planned agreements, study set-up resources, data collection, analysis and communication tools as shown in Figure 6 and highlighted throughout the protocol.

Figure 6: Proposed toolkit components to support quality implementation of Respiratory Investigations and Studies protocols



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8. Appendix

Appendix A: Comparison between the features and complementarity of the main respiratory pathogens of pandemic potential investigation protocols

	The First Few X cases and contacts (FFX) investigation protocol for respiratory pathogens of pandemic potential	Household transmission investigation protocol for respiratory pathogens of pandemic potential	Closed setting transmission investigation protocol for respiratory pathogens of pandemic potential
Population	The First Few X cases of pathogen X and their close contacts in the general population	Household close contacts of index cases of pathogen X (smaller epidemiological unit than FFX)	Contacts of index cases in the closed setting (larger epidemiological unit)
Aim	Transmission dynamics, severity and clinical spectrum, in a proxy of the general population	Transmission dynamics, severity and clinical spectrum, in household settings	Transmissibility- chains of infection in closed settings such as schools, hospitals and army barracks
Potential output and analysis	Transmission dynamics, severity and clinical spectrum, through estimates of, primarily: • the secondary infection rate (SIR) and secondary clinical attack rate of pathogen X, and by key factors such as setting age and sex • the clinical presentation of pathogen X infection and course of associated disease • the symptomatic & asymptomatic proportions of pathogen X cases • preliminary case and infection hospitalization and fatality ratios. and secondarily: • the serial interval of pathogen X • duration of viral shedding (if samples are taken at higher frequency and adequate resources are available) • identification of possible routes of transmission including possible animal/human transmission • risk and/or protective factors for transmission or severe disease Advance related objectives: • the basic reproduction number (R_0) of pathogen X • the effective reproductive number (R_{eff}) of pathogen X • the incubation period of pathogen X • the generation interval of pathogen X	Key data **to complement and reinforce the findings of FFX, through estimates of, primarily:** • the secondary infection rate (SIR) and secondary clinical attack rate of pathogen X in households, and by key factors such as age and sex • the clinical presentation of pathogen X infection and course of associated disease • the symptomatic & asymptomatic proportions of pathogen X cases • preliminary case and infection hospitalization and fatality ratios. and secondarily: • the serial interval of pathogen X • duration of viral shedding (if samples are taken at higher frequency and adequate resources are available) • risk and/or protective factors for transmission or severe disease Advance related objectives: • the incubation period of pathogen X	Key data **to complement and reinforce the findings of FFX, through estimates of, primarily:** • the overall infection and clinical attack rate of pathogen X, and by key factors such as age and sex • the secondary infection rate (SIR) and secondary clinical attack rate of pathogen X infection overall, and by key factors such as setting age and sex • the clinical presentation of pathogen X infection and course of associated disease • the symptomatic & asymptomatic proportions of pathogen X cases • preliminary case and infection hospitalization and fatality ratios. and secondarily: • the serial interval of pathogen X • risk and/or protective factors for transmission or severe disease Advance related objectives: • the basic reproduction number (R_0) of pathogen X • the effective reproductive number (R_{eff}) of pathogen X • the incubation period of pathogen X • the generation interval of pathogen X

	The First Few X cases and contacts (FFX) investigation protocol for respiratory pathogens of pandemic potential	Household transmission investigation protocol for respiratory pathogens of pandemic potential	Closed setting transmission investigation protocol for respiratory pathogens of pandemic potential
Duration	Recruitment and follow-up of index cases and their close contacts for a maximum period of 28 days from laboratory confirmation of the index case.	Recruitment and follow-up of index cases and their household contacts for a maximum period of 28 days from laboratory confirmation of the index case.	Recruitment and follow-up of index cases and their close contact in a closed setting for a maximum period of 28 days from laboratory confirmation of the index case.
Start of the investigation	To be initiated in the first days after the confirmation of a case of pathogen X in [Country Y].	Prospective study, ideally before widespread community transmission occurs, within 2-3 months after identification of initial cases.	Prospective study, ideally before widespread community transmission occurs, within 2-3 months after identification of initial cases.
Recruitment	The first few cases of pathogen X in [Country Y], and their close contacts, will be first few participants to be recruited.	Household contacts of index cases of pathogen X.	Contacts within closed settings will be enrolled
Minimum data and specimens to be obtained from participants	Epidemiological, clinical, virological (if applicable) and serological data will be collection from each participant at multiple times during the study – including surveys at baseline and Day 28, symptom diaries from Day 2-28 and specimen collection.		

Appendix B: Questionnaires and guidance

Closed setting investigation protocol for respiratory pathogens of pandemic potential

FOR CASES

- **Form A1**: Case initial report form – for pathogen X index cases (Day 1)
- **Form A2**: Case follow-up form – for pathogen X index cases (Day 28)

FOR CONTACTS

- **Form B1**: Contact initial reporting form – for close contacts of pathogen X cases (Day 1)
- **Form B2**: Contact follow-up reporting form – for close contacts of pathogen X cases (Day 28)

FOR CASES AND CONTACTS

- **Form C**: Specimen collection and laboratory results
- **Form D**: Symptom diary for all participants – pathogen X index cases and close contacts

1. For cases

Form A1: Case initial reporting form – for pathogen X index cases (Day 1)

Unique Case ID/Closed setting number (if applicable):

1. Current status

☐ Alive ☐ Dead ☐ Unknown/lost to follow-up

2. Data collector information

Name of data collector	
Data collector institution	
Data collector telephone number	
Data collector email	
Form completion date (dd/mm/yyyy)	____/____/____

3. Interview respondent information (if the person providing the information is not the index case)

First name	
Family name	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Relationship to case (select all that are relevant)	☐ Household member ☐ Immediate family member ☐ Extended family member ☐ Healthcare worker looking after case ☐ Friend ☐ Co-worker ☐ Teacher ☐ Carer ☐ Acquaintance ☐ Unknown
Respondent address	
Telephone (mobile) number	

Form A1: Case initial reporting form – for pathogen X index cases (Day 1) (continued)

4. Patient identifier information	
First name*	
Family name*	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)*	____/____/____ ☐ Unknown
Telephone (mobile) number	
Age (years, months)	____ years ____ months ☐ Unknown
Email	
Address*	
National social number/identifier (if applicable)*	
Country of residence	
Nationality	
Case occupation (specify location/facility)	☐ Health care worker ☐ Working with animals ☐ Health laboratory worker ☐ Other, specify: For each occupation, please specify location or facility: _____
Ethnicity (optional)	☐ Arab ☐ Black ☐ East Asian ☐ South Asian ☐ West Asian ☐ Latin American ☐ White ☐ Aboriginal/First Nations ☐ Other: _____ ☐ Unknown
Is this case part of an institutional outbreak (e.g., aged care facility, hospital, group home?	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Name of institution involved in outbreak	

* These identifiers are commonly accepted as personally identifiable information and must be kept confidential, however these may vary by country and should be updated by Country Y according to national guidelines.

5. Closed setting information	
Location of closed setting / Address of case	
Type of closed setting	☐ Substantially closed setting ☐ Prison or correctional facility ☐ Nursing homes ☐ Other, specify _____ ☐ Semi-closed setting ☐ School ☐ Boarding school ☐ Hostel ☐ Camp ☐ Health-care facility ☐ Other, specify _____

COMMENT: Additional questions can be added to the below to capture more information relevant to the closed setting	
Size of closed setting (number of people attended the closed setting during the relevant exposure period) Note: This may be challenging to quantify in very large and dynamic semi-closed settings	
Do individuals within the closed setting share bedroom/sleeping spaces?	☐ Yes ☐ No ☐ Unknown If yes, number of bedrooms/sleeping spaces _____
Do individuals within the closed setting share bathrooms spaces?	☐ Yes ☐ No ☐ Unknown If yes, number of bathrooms _____
Do individuals within the closed setting share kitchen spaces?	☐ Yes ☐ No ☐ Unknown If yes, number of shared kitchen spaces _____

6a. Case symptoms (from onset of symptoms)	
Date of first symptom onset (dd/mm/yyyy)	____/____/____ ☐ No symptoms ☐ Unknown
Fever (≥38 °C) or history of fever since disease onset	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
6b. Respiratory symptoms	
Sore throat	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Runny nose	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Cough	☐ Yes ☐ No ☐ Unknown If Yes to cough, productive, ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry, ☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
Shortness of breath	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy): ____/____/____
6c. General symptoms	
Chills	☐ Yes ☐ No ☐ Unknown
Anosmia (loss of smell)	☐ Yes ☐ No ☐ Unknown
Ageusia (loss of taste)	☐ Yes ☐ No ☐ Unknown
Vomiting	☐ Yes ☐ No ☐ Unknown
Nausea	☐ Yes ☐ No ☐ Unknown
Diarrhoea	☐ Yes ☐ No ☐ Unknown
Headache	☐ Yes ☐ No ☐ Unknown
Rash	☐ Yes ☐ No ☐ Unknown
Conjunctivitis	☐ Yes ☐ No ☐ Unknown
Muscle aches	☐ Yes ☐ No ☐ Unknown
Joint ache	☐ Yes ☐ No ☐ Unknown
Loss of appetite	☐ Yes ☐ No ☐ Unknown

Nose bleed	☐ Yes ☐ No ☐ Unknown
Fatigue	☐ Yes ☐ No ☐ Unknown
Chest pain	☐ Yes ☐ No ☐ Unknown
6d. Neurological symptoms	
Seizures	☐ Yes ☐ No ☐ Unknown
Altered level of consciousness	☐ Yes ☐ No ☐ Unknown
Other neurological signs	☐ Yes ☐ No ☐ Unknown If Yes, specify:
6e. Other symptoms	
Other symptoms	☐ Yes ☐ No ☐ Unknown If Yes, specify:

7. Isolation and hygiene practices within the household	
Has the case practiced any heightened isolation and/or hygiene measures since developing symptoms or becoming a case of pathogen X?	☐ Yes ☐ No If yes, dates that these measures were used (dd/mm/yyyy): ____/____/____ If yes, select all protective equipment measures that are relevant ☐ Worn a surgical/medical mask ☐ Worn a NIOSH-certified N95 or an EU standard FFP2 mask ☐ Worn an FFP3 mask If yes, select all isolation measures that are relevant ☐ Isolated in a separate bedroom from other household members ☐ Used a separate bathroom from other household members ☐ Isolated in a different location/house If yes, select all hygiene measures that are relevant ☐ Avoided shared spaces ☐ Shared spaces cleaned after use Other measures ☐ Yes ☐ No If yes, specify:

8. Primary health-care center/treating physician's details	
Date of first primary health facility visit (including traditional care) (dd/mm/yyyy)	____/____/____ ☐ Not applicable (NA) ☐ Unknown
Total health facilities visited to date	☐ NA ☐ Unknown Specify:
Visit to primary healthcare (PHC; GP, etc) (repeat for as many visits as required)	☐ Yes ☐ No ☐ Unknown
If yes, date of first PHC contact (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
If yes, Name of health-care center	
If yes, Name of treating physician	
If yes, Telephone number	
If yes, Fax	
If yes, Address	

9. Other health-care interactions	
Contact with emergency number/ hotline	☐ Yes ☐ No ☐ Unknown
Date of emergency contact (dd/mm/yyyy)	____/____/____ ☐ Unknown
Visited emergency department (A&E) (repeat for as many contacts as required)	☐ Yes ☐ No ☐ Unknown
Date of first A&E contact (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
Hospitalization (repeat for as many admissions as required)	☐ Yes ☐ No ☐ Unknown
Date of admission to hospital (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
Name of hospital	
Location of hospital	
Date of discharge from hospital (dd/mm/yyyy)	____/____/____ or ☐ Ongoing
Reason for hospitalization	☐ Isolation/quarantine ☐ Clinical management ☐ Other If Other, specify: _____
ICU (intensive care unit) admission	☐ Yes ☐ No ☐ Unknown
Date of ICU admission (dd/mm/yyyy)	____/____/____ ☐ Unknown
Date of discharge from ICU (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Mechanical ventilation	☐ Yes ☐ No ☐ Unknown
Dates of mechanical ventilation (dd/mm/yyyy)	Start: ____/____/____ Stop: ____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Length of ventilation (days)	

10. Case symptoms: complications	
Acute respiratory distress syndrome (ARDS)	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Acute renal failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Cardiac failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Consumptive coagulopathy	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Pneumonia by chest X-ray	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Other complications	☐ Yes ☐ No ☐ Unknown If Yes, secondary bacterial infection* ☐ Yes ☐ No ☐ Unknown Specify infection: _____ If other complication, specify: _____ * Fill out relevant laboratory information in specimen collection form
Hypotension requiring vasopressors	☐ Yes ☐ No ☐ Unknown
Extracorporeal membrane oxygenation (ECMO) required	☐ Yes ☐ No ☐ Unknown
Outcome (current)	☐ Alive ☐ Dead, if Yes, specify date of death (dd/mm/yyyy): ____/____/____ ☐ Unknown/lost to follow-up

11. Treatment with antivirals	
Did the case receive an antiviral treatment in the last 14 days?	☐ Yes ☐ No ☐ Unknown (If no or unknown skip to next question) If Yes Specify which antiviral was received? _____ Date started® (dd/mm/yyyy): ____/____/____ Date stopped® (dd/mm/yyyy): ____/____/____ Dosage (specify): What were antivirals prescribed for? ☐ Treatment ☐ Prophylaxis

Form A1: Case initial reporting form – for pathogen X index cases (Day 1) (continued)

12. Patient pre-existing condition(s)	
Pregnancy	☐ Yes ☐ No ☐ Unknown If Yes, specify trimester: ☐ First ☐ Second ☐ Third ☐ Unknown
Obesity	☐ Yes ☐ No ☐ Unknown
Cancer	☐ Yes ☐ No ☐ Unknown
Diabetes	☐ Yes ☐ No ☐ Unknown
HIV/other immune deficiency	☐ Yes ☐ No ☐ Unknown
Heart disease	☐ Yes ☐ No ☐ Unknown
Asthma (requiring medication)	☐ Yes ☐ No ☐ Unknown
Chronic lung disease (non-asthma)	☐ Yes ☐ No ☐ Unknown
Chronic liver disease	☐ Yes ☐ No ☐ Unknown
Chronic haematological disorder	☐ Yes ☐ No ☐ Unknown
Chronic kidney disease	☐ Yes ☐ No ☐ Unknown
Chronic neurological impairment/disease	☐ Yes ☐ No ☐ Unknown
Organ or bone marrow recipient	☐ Yes ☐ No ☐ Unknown
Other pre-existing condition(s)	☐ Yes ☐ No ☐ Unknown If Yes, specify:

13. Vaccination	
Case has been vaccinated for pathogen X/disease X in the 12 months prior to onset of symptoms Comment: this field will need to be adapted to include a vaccine for pathogen/disease X (if one is available), or to include others that may be associated with pathogen/disease X	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____
Case was vaccinated for seasonal influenza in the 12 months prior to onset of symptoms	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____
Case was vaccinated for SARS-CoV-2 in the 12 months prior to onset of symptoms	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____ Date of last infection (dd/mm/yyyy): ____/____/____ or ☐ Unknown
Case was vaccinated with pneumococcal vaccine	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy) ____/____/____

14. Human exposures in the days before symptom onset (in the past 14 days)	
Have you travelled within the last 14 days domestically?	☐ Yes ☐ No ☐ Unknown If Yes, dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Regions visited: Cities visited:
Have you travelled within the last 14 days internationally?	☐ Yes ☐ No ☐ Unknown If Yes, dates of travel (dd/mm/yyyy): ____/____/____ to ____/____/____ Regions visited: Cities visited:
Has the case had contact with a anyone with suspected or confirmed pathogen X infection in the past 14 days?	☐ Yes ☐ No ☐ Unknown If Yes, dates of last contact (dd/mm/yyyy): ____/____/____
If yes, location of exposure	☐ Home ☐ Hospital ☐ Workplace ☐ Tour group ☐ School ☐ Unknown ☐ Other, specify:
Has the case attended a festival or mass gathering in the past 14 days?	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Has the case visited or been admitted to an inpatient health facility in the past 14 days?	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Has the case visited an outpatient treatment facility in the past 14 days?	☐ Yes ☐ No ☐ Unknown If Yes, specify:
Has the case visited a traditional healer in the past 14 days?	☐ Yes ☐ No ☐ Unknown If Yes, specify type:

15. Status of form completion	
Form completed	☐ Yes ☐ No or partially If No or partially, reason: ☐ Missed ☐ Not attempted ☐ Not performed ☐ Refusal ☐ Other, specify:

Form A2: Case follow-up reporting form – for pathogen X index cases (Day 28)

Unique Case ID/Cluster number (if applicable):

1. Data collector information

Name of data collector	
Data collector institution	
Data collector telephone number	
Data collector email	
Form completion date (dd/mm/yyyy)	____/____/____

2. Interview respondent information (if the person providing the information is not the index case)

First name	
Family name	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Relationship to case (select all that are relevant)	☐ Household member ☐ Immediate family member ☐ Extended family member ☐ Health-care worker looking after case ☐ Friend ☐ Co-worker ☐ Teacher ☐ Carer ☐ Acquaintance ☐ Unknown
Respondent address	
Telephone (mobile) number	

3. Outcome/status

Status	☐ Alive ☐ Dead, if Yes, specify date of death (dd/mm/yyyy): ____/____/____ ☐ Unknown/lost to follow-up
Hospitalization ever required?	☐ Yes ☐ No ☐ Unknown

(NB: If the information below is not currently available, please leave blank and send through an update as soon as results are available)	
If dead, contribution of Pathogen X to death:	☐ Underlying/primary ☐ Contributing/secondary ☐ No contribution to death ☐ Unknown
If dead, was a post mortem performed?	☐ Yes ☐ No ☐ Unknown
If dead, results of postmortem's report where available:	
If dead, cause of death on Death certificate (specify)	

4. Hospital health-care interactions since baseline

Hospitalization since baseline	☐ Yes ☐ No ☐ Unknown
Date of admission to hospital (dd/mm/yyyy)	____/____/____ ☐ Unknown
Name of hospital	
Location of hospital	
Date of discharge from hospital (dd/mm/yyyy)	____/____/____ or ☐ Ongoing
Reason for hospitalization	☐ Isolation/quarantine ☐ Clinical management ☐ Other If Other, specify: _____
ICU (intensive care unit) admission	☐ Yes ☐ No ☐ Unknown
Date of ICU admission (dd/mm/yyyy)	____/____/____ ☐ Unknown
Date of discharge from ICU (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Mechanical ventilation since baseline	☐ Yes ☐ No ☐ Unknown
Dates of mechanical ventilation (dd/mm/yyyy)	Start: ____/____/____ Stop: ____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Length of ventilation (days)	

5. Case symptoms: complications

Acute respiratory distress syndrome (ARDS)	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Acute renal failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Cardiac failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Consumptive coagulopathy	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____
Pneumonia by chest X-ray	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy): ____/____/____

Other complications	☐ Yes ☐ No ☐ Unknown If Yes, secondary bacterial infection* ☐ Yes ☐ No ☐ Unknown Specify infection: _____ If other complication, specify: _____ * Fill out relevant laboratory information in specimen collection form
Hypotension requiring vasopressors	☐ Yes ☐ No ☐ Unknown
Extracorporeal membrane oxygenation (ECMO) required	☐ Yes ☐ No ☐ Unknown

6. Patient pre-existing condition(s)

Pregnancy	☐ Yes ☐ No ☐ Unknown If Yes, specify trimester: ☐ First ☐ Second ☐ Third ☐ Unknown

7. Treatment with antivirals

Did the case receive an antiviral treatment in the last 14 days (or since baseline)?	☐ Yes ☐ No ☐ Unknown (If No or Unknown, skip to next question) If Yes, which antiviral was received? _____ Date started ® (dd/mm/yyyy) ____/____/____ Date stopped ® (dd/mm/yyyy) ____/____/____ Dosage (specify): What were antivirals prescribed for? ☐ Treatment ☐ Prophylaxis

8. Final case classification

Final case classification (select one from each category that apply)	☐ Confirmed ☐ Probable ☐ Suspected & ☐ Primary ☐ Co-primary ☐ Secondary ☐ Other, specify: (e.g., tertiary case) & (optional) ☐ Imported & (optional) ☐ Unrelated

Form A2: Case follow-up reporting form – for pathogen X index cases (Day 28) (continued)

9. Status of form completion	
Form completed	☐ Yes ☐ No or partially If No or partially, reason: ☐ Missed ☐ Not attempted ☐ Not performed ☐ Refusal ☐ Other, specify:

2. For contacts

Form B1: Contact initial reporting form – for close contacts of pathogen X index cases (Day 1)

Unique Index Case ID/Closed setting number (if applicable):

Contact ID Number (C…):
Note: Contact ID numbers should be issued at the time of completion of Form A1/Contact Line List.

1. Current status

☐ Alive ☐ Dead ☐ Unknown/lost to follow-up

2. Data collector information

Name of data collector	
Data collector institution	
Data collector telephone number	
Data collector email	
Form completion date (dd/mm/yyyy)	____/____/____

3. Interview respondent information (if the person providing the information is not the contact)

First name	
Family name	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Relationship to contact (select all that are relevant)	☐ Household member ☐ Immediate family member ☐ Extended family member ☐ Health-care worker looking after contact ☐ Friend ☐ Co-worker ☐ Teacher ☐ Carer ☐ Acquaintance ☐ Unknown
Respondent address	
Telephone (mobile) number	

Form B1: Contact initial reporting form – for close contacts of pathogen X index cases (Day 1) (continued)

4. Contact details (details of the contact)	
First name*	
Family name*	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)*	____/____/____ ☐ Unknown
Relationship to case (select all that are relevant) Comment: this field will need to be adapted to be relevant to the specific closed setting	☐ Household member ☐ Immediate family member ☐ Extended family member ☐ Health-care worker looking after contact ☐ Friend ☐ Co-worker ☐ Teacher ☐ Carer ☐ Acquaintance ☐ Unknown
Address (village/town, district, province/region)*	
Telephone (mobile) number	
Email	
Preferred mode of contact	☐ Mobile ☐ Work ☐ Home ☐ Email
Nationality	
Country of residence	
National social number/identifier (optional)*	
Ethnicity (optional)	☐ Arab ☐ Black ☐ East Asian ☐ South Asian ☐ West Asian ☐ Latin American ☐ White ☐ Aboriginal/First Nations ☐ Other: _____ ☐ Unknown

* These identifiers are commonly accepted as personally identifiable information and must be kept confidential, however these may vary by country and should be updated by Country Y according to national guidelines.

5. Exposure information

Specify characteristics of contact with the case (from 2 days before symptom onset, to the current date – day 1) Please repeat this as required for each date with known contact COMMENT: this field will need to be adapted to be relevant to the specific closed setting	Date, dd/mm/yyyy) ____/____/____ Type of contact (select all that are relevant) ☐ Ate from the same plate ☐ Drank from the same glass/mug ☐ Hugged ☐ Kissed on the lips ☐ Shared a bathroom (e.g. shared shower, bath or toilet) ☐ Shared a bedroom ☐ Shared a meal ☐ Shared utensils ☐ Shook hands ☐ Socialising (e.g., watching tv, playing board games, talking in close proximity) ☐ Provided care to case ☐ Received care from case ☐ Other, specify: Total duration of contact: ____ (minutes) On this date, did you practice any heightened isolation and/or hygiene measure? Select all that are relevant ☐ Worn a surgical/medical mask ☐ Worn a NIOSH-certified N95 or an EU standard FFP2 mask ☐ Worn an FFP3 mask ☐ Avoided being in the same room as the case ☐ Avoided being close to the case ☐ Other, specify:

6a. Symptoms in contact

Has the contact experienced any respiratory symptoms (sore throat, runny nose, cough, shortness of breath) in the period from 10 days **before** symptom onset in the index case until the present?	☐ Yes ☐ No
Has the contact experienced any respiratory symptoms (sore throat, runny nose, cough, shortness of breath) in the period up to 10 days **after** the last contact or until the present date, whichever is the earlier?	☐ Yes ☐ No
Date (dd/mm/yyyy) and time of first symptom onset	____/____/____ _____ ☐ am ☐ pm
Fever (>38 °C) or history of fever since disease onset	☐ Yes ☐ No ☐ Unknown If Yes, date ____/____/____

6b. Respiratory symptoms	
Sore throat	☐ Yes ☐ No ☐ Unknown If Yes, date ____/____/____
Runny nose	☐ Yes ☐ No ☐ Unknown If Yes, date ____/____/____
Cough	☐ Yes ☐ No ☐ Unknown If Yes to cough, productive, ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry, ☐ Yes ☐ No ☐ Unknown If Yes, date ____/____/____
Shortness of breath	☐ Yes ☐ No ☐ Unknown If Yes, date ____/____/____
6c. General symptoms	
Chills	☐ Yes ☐ No ☐ Unknown
Anosmia (loss of smell)	☐ Yes ☐ No ☐ Unknown
Ageusia (loss of taste)	☐ Yes ☐ No ☐ Unknown
Vomiting	☐ Yes ☐ No ☐ Unknown
Nausea	☐ Yes ☐ No ☐ Unknown
Diarrhoea	☐ Yes ☐ No ☐ Unknown
Headache	☐ Yes ☐ No ☐ Unknown
Rash	☐ Yes ☐ No ☐ Unknown
Conjunctivitis	☐ Yes ☐ No ☐ Unknown
Muscle aches	☐ Yes ☐ No ☐ Unknown
Joint ache	☐ Yes ☐ No ☐ Unknown
Loss of appetite	☐ Yes ☐ No ☐ Unknown
Nose bleed	☐ Yes ☐ No ☐ Unknown
Fatigue	☐ Yes ☐ No ☐ Unknown
Chest pain	☐ Yes ☐ No ☐ Unknown
6d. Neurological symptoms	
Seizures	☐ Yes ☐ No ☐ Unknown
Altered level of consciousness	☐ Yes ☐ No ☐ Unknown
Other neurological signs	☐ Yes ☐ No ☐ Unknown If Yes, specify:

6e. Other symptoms	
Other symptoms	☐ Yes ☐ No ☐ Unknown If Yes, specify:

7. If ill, health-care center/treating physician's details	
Date of first health facility visit (including traditional care) (dd/mm/yyyy)	____/____/____ ☐ NA ☐ Unknown
Total health facilities visited to date	☐ NA ☐ Unknown Specify:
Visit to primary healthcare (PHC; GP, etc) (repeat for as many visits as required)	☐ Yes ☐ No ☐ Unknown
If yes, date of first PHC contact (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
If yes, Name of health-care center	
If yes, Name of treating physician	
If yes, Telephone number	
If yes, Fax	
If yes, Address	

8. If ill, other health-care interactions	
Contact with emergency number/ hotline	☐ Yes ☐ No ☐ Unknown
Date of emergency contact (dd/mm/yyyy)	____/____/____ ☐ Unknown
Visited emergency department (A&E) (repeat for as many contacts as required)	☐ Yes ☐ No ☐ Unknown
Date of first A&E contact (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
Hospitalization (repeat for as many admissions as required)	☐ Yes ☐ No ☐ Unknown
Date of admission to hospital (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
Name and place of hospital	
Date of discharge from hospital (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Reason for hospitalization	☐ Isolation/quarantine ☐ Clinical management ☐ Other If Other, specify: _____
ICU (intensive care unit) admission	☐ Yes ☐ No ☐ Unknown
Date of ICU admission (dd/mm/yyyy)	____/____/____ ☐ Unknown
Date of discharge from ICU (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA

Mechanical ventilation	☐ Yes ☐ No ☐ Unknown
Dates of mechanical ventilation (dd/mm/yyyy)	Start: ____/____/____ Stop: ____/____/____ or ☐ Ongoing ☐ Unknown
Length of ventilation (days)	

9. If ill, contact symptoms: complications

Acute respiratory distress syndrome (ARDS)	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Acute renal failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Cardiac failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Consumptive coagulopathy	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Pneumonia by chest X-ray	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Other complications	☐ Yes ☐ No ☐ Unknown If Yes, secondary bacterial infection* ☐ Yes ☐ No ☐ Unknown Specify infection: If other complication, specify: *Fill out relevant laboratory information in specimen collection form
Hypotension requiring vasopressors	☐ Yes ☐ No ☐ Unknown
Extracorporeal membrane oxygenation (ECMO) required	☐ Yes ☐ No ☐ Unknown
Outcome	☐ Alive ☐ Dead, if Yes, specify date of death (dd/mm/yyyy): ____/____/____ ☐ Unknown/lost to follow-up
Outcome current as of date (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA

10. Contact pre-existing condition(s)

Pregnancy	☐ Yes ☐ No ☐ Unknown If Yes, specify trimester: ☐ First ☐ Second ☐ Third ☐ Unknown
Obesity	☐ Yes ☐ No ☐ Unknown
Cancer	☐ Yes ☐ No ☐ Unknown
Diabetes	☐ Yes ☐ No ☐ Unknown
HIV/other immune deficiency	☐ Yes ☐ No ☐ Unknown
Heart disease	☐ Yes ☐ No ☐ Unknown
Asthma (requiring medication)	☐ Yes ☐ No ☐ Unknown
Chronic lung disease (non-asthma)	☐ Yes ☐ No ☐ Unknown

Chronic liver disease	☐ Yes ☐ No ☐ Unknown
Chronic haematological disorder	☐ Yes ☐ No ☐ Unknown
Chronic kidney disease	☐ Yes ☐ No ☐ Unknown
Chronic neurological impairment/disease	☐ Yes ☐ No ☐ Unknown
Organ or bone marrow recipient	☐ Yes ☐ No ☐ Unknown
Other pre-existing condition(s)	☐ Yes ☐ No ☐ Unknown If Yes, specify:

11. Vaccination

Contact has been vaccinated for pathogen X/disease X in the 12 months prior to onset of symptoms Comment: this field will need to be adapted to include a vaccine for pathogen/disease X (if one is available), or to include others that may be associated with pathogen/disease X	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____
Contact was vaccinated for seasonal influenza in the 12 months prior to onset of symptoms	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____
Contact was vaccinated for SARS-CoV-2 in the 12 months prior to onset of symptoms	☐ Yes ☐ No ☐ Unknown If Yes, date of vaccination, country of vaccination (dd/mm/yyyy): ____/____/____ Country: _____ Date of last infection (dd/mm/yyyy): ____/____/____ or ☐ Unknown
Contact was vaccinated with pneumococcal vaccine	☐ Yes ☐ No ☐ Unknown If Yes, date (dd/mm/yyyy) ____/____/____

12. Status of form completion

Form completed	☐ Yes ☐ No or partially If No or partially, reason: ☐ Missed ☐ Not attempted ☐ Not performed ☐ Refusal ☐ Other, specify:

Form B2: Contact follow-up reporting form – for close contacts of pathogen X index cases (Day 28)

Unique Index Case ID/Cluster number (if applicable):	
Contact ID Number (C…): Note: Contact ID numbers should be issued at the time of completion of Form A1/Contact Line List.	

1. Data collector information

Name of data collector	
Data collector institution	
Data collector telephone number	
Data collector email	
Form completion date (dd/mm/yyyy)	____/____/____

2. Interview respondent information (if the person providing the information is not the contact)

First name	
Family name	
Sex	☐ Male ☐ Female ☐ Non-binary ☐ Not known
Date of birth (dd/mm/yyyy)	____/____/____ ☐ Unknown
Relationship to contact (select all that are relevant)	☐ Household member ☐ Immediate family member ☐ Extended family member ☐ Health-care worker looking after contact ☐ Friend ☐ Co-worker ☐ Teacher ☐ Carer ☐ Acquaintance ☐ Unknown
Respondent address	
Telephone (mobile) number	

3. Exposure information

Specify characteristics of contact with the case from first contact, while the primary case was **symptomatic**, until the last unprotected** contact **If still in contact use today's date (Add as many dates as required)	Date (dd/mm/yyyy)	____/____/____
	Duration	____(minutes)
	Setting	☐ Home/household ☐ Hospital/health care ☐ Workplace ☐ Tour group ☐ Other, specify:

4. Outcome/status

Status	☐ Alive ☐ Dead, if Yes, specify date of death (dd/mm/yyyy): ____/____/____ ☐ Unknown/lost to follow-up
Hospitalization ever required?	☐ Yes ☐ No ☐ Unknown
(NB. If the information below is not currently available, please leave blank and send through an update as soon as results are available)	
If dead, contribution of Pathogen X to death:	☐ Underlying/primary ☐ Contributing/secondary ☐ No contribution to death ☐ Unknown
If dead, was a post mortem performed?	☐ Yes ☐ No ☐ Unknown
If dead, results of postmortem's report where available:	
If dead, cause of death on Death certificate (specify)	

5. Hospital health-care interactions since baseline

Hospitalization since baseline	☐ Yes ☐ No ☐ Unknown
Date of first hospitalization (dd/mm/yyyy)	____/____/____ ☐ Unknown ☐ NA
Name and place of hospital	
Date of discharge from hospital (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Reason for hospitalization	☐ Isolation/quarantine ☐ Clinical management ☐ Other If Other, specify: _____
ICU (intensive care unit) admission since baseline	☐ Yes ☐ No ☐ Unknown
Date of ICU admission (dd/mm/yyyy)	____/____/____ ☐ Unknown
Date of discharge from ICU (dd/mm/yyyy)	____/____/____ or ☐ Ongoing ☐ Unknown ☐ NA
Mechanical ventilation since baseline	☐ Yes ☐ No ☐ Unknown
Dates of mechanical ventilation (dd/mm/yyyy)	Start: ____/____/____ Stop: ____/____/____ or ☐ Ongoing ☐ Unknown
Length of ventilation (days)	

6. Contact symptoms: complications	
Acute respiratory distress syndrome (ARDS)	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Acute renal failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Cardiac failure	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Consumptive coagulopathy	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Pneumonia by chest X-ray	☐ Yes ☐ No ☐ Unknown If Yes, date started (dd/mm/yyyy) ____/____/____
Other complications	☐ Yes ☐ No ☐ Unknown If Yes, secondary bacterial infection* ☐ Yes ☐ No ☐ Unknown Specify infection: If other complication, specify: *Fill out relevant laboratory information in specimen collection form
Hypotension requiring vasopressors	☐ Yes ☐ No ☐ Unknown
Extracorporeal membrane oxygenation (ECMO) required	☐ Yes ☐ No ☐ Unknown

7. Contact pre-existing condition(s)	
Pregnancy	☐ Yes ☐ No ☐ Unknown If Yes, specify trimester: ☐ First ☐ Second ☐ Third ☐ Unknown

8. Treatment with antivirals	
Did the contact receive an antiviral treatment in the last 14 days (or since baseline)?	☐ Yes ☐ No ☐ Unknown (If No or Unknown, skip to next question) If Yes, which antiviral was received? _____ Date started (dd/mm/yyyy) ____/____/____ Date stopped (dd/mm/yyyy) ____/____/____ Dosage (specify): What were antivirals prescribed for? ☐ Treatment ☐ Prophylaxis

9. Final contact classification

Contact was identified as a case during the investigation	☐ Yes ☐ No If no, the contact is a non-case
If contact was identified as a case during the investigation, final case classification (select one from each category that apply)	☐ Confirmed ☐ Probable ☐ Suspected & ☐ Primary ☐ Co-primary ☐ Secondary ☐ Other, specify: (e.g., tertiary case) & (optional) ☐ Imported & (optional) ☐ Unrelated

10. Status of form completion

Form completed	☐ Yes ☐ No or partially If No or partially, reason: ☐ Missed ☐ Not attempted ☐ Not performed ☐ Refusal ☐ Other, specify:

3. For cases and contacts

Form C: Specimen collection forms and laboratory results

Comment: Please note that this table will need to be filled/ updated for each respiratory and serological specimen collected per the mandatory sampling strategy

1. Case and contact details	
Unique ID for participant (use unique case or contact ID)	
Classification at recruitment	☐ Index case ☐ Co-index case ☐ Close contact

2. Respiratory specimen collection	
Date of sample collection	____/____/____
Day of specimen collection per sampling strategy	(insert day number)
Type of sample collection	☐ Nasal swab ☐ Throat swab ☐ Nasopharyngeal swab ☐ Other, specify _____
Who collected the respiratory specimen?	☐ Study staff/ research nurse ☐ Self-collected ☐ Other professional specimen collection service
Which laboratory was the specimen sent to?	
Date sample received by laboratory (dd/mm/yyyy)	____/____/____
Laboratory identification number	
Diagnostic method	☐ PCR ☐ Viral culture or virus isolation ☐ Other, specify
Date of result	____/____/____
Pathogen X Result	☐ Positive ☐ Negative ☐ Inconclusive/probable If positive (and applicable), subtype* ☐ Subtype A ☐ Subtype B ☐ Subtype C ☐ Not able to be typed *Adapt based on known information on pathogen X

Form C: Specimen collection forms and laboratory results (continued)

Other laboratory results	☐ Other pathogens, specify[#]: ☐ Negative ☐ NA / not tested [#] Include any secondary (bacterial) infections in this section
Sample sent to WHO CC (if applicable) (dd/mm/yyyy)	☐ Yes ☐ No If yes, Date: ____/____/____ Name of collaborating centre:

3. Serology testing methods and results:	
Date of sample collection	____/____/____
Day of specimen collection per sampling strategy	(insert day number)
Type of sample collection	☐ Whole blood ☐ Serum ☐ Dried blood spot ☐ Other, specify:
Who collected the respiratory specimen?	☐ Study staff/ research nurse ☐ Other professional specimen collection service
Which laboratory was the specimen sent to?	
Date sample received by laboratory (dd/mm/yyyy)	____/____/____
Laboratory identification number	
Diagnostic method/assay used	☐ Total antibody ☐ Microneutralisation ☐ Other, specify:
Antigen used (if applicable)	
Date of result	____/____/____
Pathogen X Result (according to assay thresholds/cut-offs – please report these)	☐ Positive ☐ Negative ☐ Indeterminate/probable Titre (irrespective of result):
Sample sent to WHO CC (if applicable) (dd/mm/yyyy)	☐ Yes ☐ No If yes, Date: ____/____/____ Name of collaborating centre:

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28)

Symptom diaries will be provided to all participants, for recording the presence or absence of various signs or symptoms for 28 days after the administration of the initial case and contact questionnaires (Form A1 and B1).

The symptom diary template provided below is generic.

Comment: In the context of a novel pathogen with uncertain clinical presentation and spectrum, symptom diaries may be broadened to include vomiting, diarrhoea, abdominal pain, etc., as relevant.

Comment: You may wish to expand the symptom diaries to include more specific options relating to personal protective equipment and isolation measures taken by cases and contacts in the closed setting.

Symptom diaries

Case or contact ID number :

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
2	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
3	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

* Please select None for No symptoms. If no symptoms are experienced, then consider the entry complete

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28) (continued)

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
4	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
5	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
6	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
7	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
8	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28) (continued)

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
9	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
10	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
11	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
12	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
13	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28) (continued)

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
14	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
15	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
16	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
17	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
18	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28) (continued)

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
19	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
20	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
21	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
22	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
23	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

Form D: Symptom diary for index cases of pathogen X and close contacts (Day 2–28) (continued)

Day	Symptoms*						
	No symptoms (check if none experienced)	**Fever ≥38 °C**	**Runny nose**	**Cough**	**Sore throat**	**Shortness of breath**	**Other symptoms: specify**
24	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
25	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
26	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
27	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	
28	☐ None	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No If Yes to cough, productive? ☐ Yes ☐ No ☐ Unknown If Yes to cough, dry? ☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ No	☐ Yes ☐ No	

Appendix C: Considerations for specimen collection

Laboratory expertise should be sought for guidance on the most appropriate specimens prior to the conduct of the closed setting study. Furthermore, collection and testing of appropriate specimens from cases and contacts should be conducted according to the appropriate sampling strategy.

Table 1 (Appendix C) provides a list of possible specimens that may be collected for identification of respiratory pathogens. The type of specimen recommended depends on the pathogen, and in some cases several specimen types may be indicated. For example, lower respiratory tract specimens are preferred for detection of MERS-CoV *(31)*, whereas upper and lower respiratory tract specimens as well as serum are preferred for influenza virus detection *(32, 33)*. When the event aetiology is unknown, it is useful to collect various specimens when feasible, to maximise opportunities for detection and characterisation *(34)*.

Comment: Investigators need to be familiar with the correct collection techniques (including the appropriate use of PPE for different types of specimens collected and established infection control guidelines), and the safety standards for specimen storage, packaging and transport.

Appendix C Table 1: Specimen type, transportation and storage guidelines for testing for presence of respiratory pathogens. (Adapted from Table 1, WHO protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases *(34)*)

Specimen type	Transport medium	Transport to laboratory	Storage until testing	Comment
Nasopharyngeal wash*	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	
Mid-turbinate 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	
Saliva	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	
Sputum	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	It may be difficult to ensure the material is from the lower respiratory tract
Nasal swab	VTM	4°C	≤5 days: 4 °C >5 days: -70 °C	Nasal and throat swabs may be combined to increase likelihood of detection
Throat swab	VTM	4°C	≤5 days: 4 °C >5 days: -70 °C	As above
Nasal wash*	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	
Nasopharyngeal aspirate*	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	

Specimen type	Transport medium	Transport to laboratory	Storage until testing	Comment
Bronchoalveolar lavage*	N/A	4°C	≤48 hours: 4 °C >48 hours: –70 °C	
Serum	N/A	4°C	≤5 days: 4 °C >5 days: –70 °C	Paired samples are required: acute at baseline and convalescent, 2 to 4 weeks later
Whole blood	EDTA tube	4°C	≤5 days: 4 °C >5 days: –70 °C	For antigen detection particularly during the first week of illness
Urine	N/A	4°C	≤5 days: 4 °C >5 days: –70 °C	

* More invasive specimen types which may cause patient discomfort and are not performed routinely.

N/A, Not applicable