A MANUAL for Estimating Disease Burden Associated With Seasonal Influenza

World Health Organization

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Abbreviations and Acronyms

ALRI	Acute Lower Respiratory Infections
CFR	Case Fatality Ratio
COPD	Chronic Obstructive Pulmonary Disease
DFA	Direct Immunofluorescence Assay
EIA	Enzyme linked Immunosorbent Assay
GBD	Global Burden of Diseases, Injuries and Risk Factors
HAS	Hospital Admission Survey
HIV	Human Immunodeficiency Virus
HMIS	Health Management Information System
HUS	Healthcare Utilization Survey
ICD	International Classification of Diseases
ICU	Intensive Care Unit
IFA	Indirect Immunofluorescence Assay
ILI	Influenza-like illness
IMCI	Integrated Management of Childhood Illnesses
LCI	Lower Confidence Interval
M&E	Monitoring and Evaluation
MOH	Ministry of Health
NIC	National Influenza Center
NSO	National Surveillance Office
PCR	Polymerase Chain Reaction
POC	Point of care
RSV	Respiratory Syncytial Virus
SARI	Severe Acute Respiratory Infection
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
UCI	Upper Confidence Interval
WHO	World Health Organization
WHO CC	WHO Collaborating Centre

Introduction

Background

Globally, acute lower respiratory infections (ALRI) are the second most common cause of illness in all age groups (429.2 million cases in 2004) and the third common cause of death (4.2 million or 7% of total deaths in 2004).[1] There are wide variations in the proportional contribution of ALRI to illness and death in different age and socioeconomic groups. Viral aetiologies like respiratory syncytial virus (RSV) and influenza virus are associated with the majority of episodes of ALRI in children and the elderly.[2]

Influenza (see Appendix A1 for short description) is an underappreciated contributor to global mortality and morbidity and has significant economic consequences. Current estimates indicate that each year, seasonal influenza affects 5–10% of the world's population resulting in between 250 000 and 500 000 deaths.[3] Nair and colleagues estimate that globally, influenza is the second most commonly identified pathogen in children with ALRI.[4] It is estimated that in the United States during 2003, there were 24.7 million cases of influenza, resulting in 31.4 million outpatient visits, over 334 000 hospitalizations and approximately 41 000 deaths. The economic burden of influenza was estimated to be about $87.1 billion.[5] However, such detailed estimates are not available in most countries.

Need for reliable national disease burden estimates for influenza

There is a need for reliable disease burden estimates especially from low- and middle-income countries to provide a better understanding of the impact of influenza in vulnerable communities or subpopulations. These national estimates, if readily available, would enable governments, non-governmental agencies, and philanthropic donors to make informed evidence-based decisions when allocating scarce resources and planning intervention strategies to limit the spread of the disease and minimize associated costs.

Reliable disease burden estimates will:

1. Assist healthcare planners in informed decision-making and in the planning process by providing them with a comprehensive and comparable assessment of death, and severe disease. This is particularly relevant for augmenting vaccine manufacturing capacity in low- and middle-income countries and targeted use of antivirals for reducing influenza-related severe morbidity and mortality.
2. Assist donor agencies and national governments in prioritizing health research investments and healthcare interventions.
3. Guide healthcare planners and multilateral agencies in demand-side planning for healthcare services during outbreaks and epidemics.
4. Assist the pharmaceutical industry in planning for novel low-cost and effective interventions for the prevention and treatment of influenza.
5. Provide baseline data with which to compare data from annual influenza outbreaks and new events, such as an influenza pandemic.

Until recently, the requisite data to estimate influenza-associated disease burden were scant or absent in most of the low- and middle-income countries. However, over the last few years, many WHO Member States have set up sentinel sites for influenza epidemiological surveillance. These data can be used to estimate disease burden at the national level.

This manual outlines a standardized tool for influenza disease burden estimation in WHO Member States. It is intended to be **an adjunct to the "WHO Global Epidemiological Surveillance Standards for Influenza"**.

Target users of the manual

This manual is targeted at **epidemiologists** and **data analysts** with basic epidemiological training who are responsible for data analysis and interpretation at influenza sentinel surveillance sites and the National Surveillance Office (NSO) or Ministry of Health (MOH). Though this manual is for all WHO Member States, it has been developed with a focus on low- and middle-income countries.

Objectives and limitations of the manual

This manual is limited to estimating the disease burden associated with the respiratory manifestations of influenza (i.e. ILI and SARI or hospitalized severe ALRI). **Thus, the seasonal influenza-associated disease burden estimated using methods described in this manual will only be a proportion of the overall disease burden associated with influenza**. Methods presented in this manual may underestimate influenza-related disease that does not present primarily with respiratory complaints such as an acute myocardial event triggered by influenza infection.

This manual will equip the user with the requisite knowledge and skills to:

- Identify the various sources of data for influenza disease burden estimation
- Assess the quality and suitability of data for disease burden estimation
- Estimate influenza disease burden in the general population as well as in those with specific conditions (e.g. pregnancy, and select chronic medical conditions like asthma, and diabetes) who are vulnerable to severe disease
- Interpret the results after taking into consideration the limitations in data and the methods used in estimating the disease burden

Expected outcome of the manual

After completing the appropriate sections of the manual the end-user should be able to:

- Estimate the *morbidity burden* due to influenza-associated respiratory infections (expressed as incidence rates where data on the denominator population at risk are available) and the proportional contribution of influenza to respiratory infections.
- Estimate the proportion of influenza-associated cases of severe respiratory infections who died (case fatality ratio).
- Assess the plausibility of the results.
- Identify gaps in influenza surveillance (particularly related to data collection) and improve sentinel surveillance for influenza.

How to use this manual

This manual is structured in such a way that the user is first introduced to some basic epidemiological concepts relating to disease burden estimation irrespective of the data source being used for the burden estimates (Chapter 1 and 2). The manual is then segregated into three sections based on the

key sources of data: SARI sentinel surveillance (Chapter 3), burden estimates in specific risk groups (Chapter 4), using records from other hospitals (Chapter 5) and ILI sentinel surveillance (Chapter 6). As the methods for burden estimation using SARI, the hospital and ILI data are very similar, there are some references in chapter 5 (hospital source) and chapter 6 (ILI source) to chapter 3 (SARI source). There is then a separate section (Chapter 7) which deals with the pooling of data from a number of sentinel sites and is intended for epidemiologists working at the national level. Finally, the manual concludes with a section (Chapter 8) on interpretation and communication of key findings.

Key messages and activities are highlighted throughout the manual using the following **icons:**


Look at the example


Use your local data and make mathematical calculations with worksheets available in the Appendices (WS1 through WS16)


Apply checklist available in the Appendices (WS3)


Answer this question before reading further


Do not proceed further with this analysis. You will need to initiate certain remedial measures before using this type of data for burden estimates.


Time to reflect


Remember

Additional information useful to gain a greater understanding of the subject is also provided in the Appendices (A1 to A7).

Illustrations are provided to assist the understanding of the different methods of estimating the population denominator. These illustrations are best viewed in full colour rather than in black and white or grayscale.

Case definitions

Acute viral rhinitis, pharyngitis, laryngotracheitis, tracheobronchitis, bronchitis, bronchiolitis, and pneumonia are clinical syndromes associated with a large number of pathogens.[2] The range of symptoms observed with influenza virus infections are nonspecific and resemble the clinical syndrome of a variety of other pathogens. There is no single symptom or group of symptoms that will include all cases of influenza infections or that is only seen in influenza patients. This uncertainty poses challenges when diagnosing influenza, conducting influenza surveillance, and estimating disease burden.

Sentinel ILI surveillance monitors persons with ILI seeking care in ambulatory care facilities, while SARI surveillance identifies cases of severe respiratory illness in persons who have been admitted to hospital for medical care. Surveillance of both mild and severe disease contributes to understanding the complete spectrum of influenza illness. Monitoring both ends of the disease spectrum allows programmes to understand differences in the behaviour of different influenza viruses and factors that place individuals at increased risk for severe disease. Both can yield information that will assist programs to express the impact that the disease is having on healthcare delivery systems. Both provide valuable information about the severity of seasonal outbreaks which can serve as a baseline comparison for unusual outbreak events or global pandemics.

WHO case definitions for influenza sentinel surveillance

A variety of case definitions have been used globally for influenza and respiratory disease surveillance. These case definitions, including the currently recommended definitions for ILI and SARI, are not intended to capture all influenza cases. Nor is it intended for the diagnosis or management of influenza or SARI cases. However, using surveillance definitions that capture a stable, representative portion of the total that is comparable over time will provide useful trend information and allow an understanding of the total burden. It is useful that **one common case definition be used by all countries** to provide an understanding of disease burden in an international context. Member States are encouraged to use the standard WHO case definitions for influenza sentinel surveillance (Table 1)[1].

The non-specificity of influenza signs and symptoms requires laboratory confirmation to be certain of the role of influenza virus in either ILI or SARI. Therefore, the focus of burden estimates as discussed in this manual will be on laboratory confirmed cases and we will use the terms *influenza-associated ILI* and *influenza-associated SARI* throughout this manual to distinguish laboratory confirmed disease from the clinical syndromes.

Case definitions for influenza disease burden estimation in this manual

- **Influenza-associated ILI**: ILI case in which human influenza virus has been identified using a valid laboratory test
- **Influenza-associated SARI**: SARI case in which human influenza virus has been identified using a valid laboratory test

Table 1: **WHO case definitions for influenza sentinel surveillance****

Case	Definition criteria
Influenza like illness (ILI)	• An acute respiratory infection with Fever ≥38°C • AND cough • With onset within the last 10 days
Severe acute respiratory infections (SARI)	• An acute respiratory infection with history of fever or measured fever ≥38°C • AND cough • With onset within the last 10 days, • AND requires hospitalization

1 http://www.who.int/influenza/resources/documents/influenza_surveillance_manual/en/index.html

Mapping other case definitions to the current WHO case definition

The case definitions detailed above have been formulated after revising the previous WHO definitions. [6] However, it is possible that many sites and WHO Member States are continuing to use the previous WHO case definitions or local modifications. Additionally, data from the previous years need to be comparable with the present. Thus, it is important that the previous case definitions are mapped to the current ones (Appendix A2).

It is very likely that some of the surveillance sites might have been using a local modification of the WHO integrated management of childhood illness (IMCI) case definition for severe acute lower respiratory infections (ALRI) especially in children aged below 5 years of age. To make the data comparable, these too need to be mapped to the current WHO case definitions (Appendix A2).

What are all the case definitions for influenza disease you have used to identify case patients for mild and severe respiratory illness at your sentinel surveillance site/in your country? How do these compare with the current WHO case definitions for influenza disease?

Now using Worksheet (WS)1, map the case definitions used at your sentinel surveillance site/ country to the current WHO case definitions before proceeding further.

Natural History of Influenza Infection

Influenza infection can manifest in a variety of ways. It commonly presents as a mild illness with fever, myalgia, malaise, headache, and sometimes vomiting and diarrhoea, the gastrointestinal symptoms occurring primarily in children.[7] It can also present as or progress to severe illness, most commonly viral pneumonia, or as bronchiolitis in children. Finally, in persons with chronic medical conditions, it may be an unrecognized cause of exacerbation of the condition by triggering asthma attacks in persons with asthma[8] or a myocardial infarction in someone with cardiovascular disease. In adults, unrecognized influenza-complicating underlying medical conditions may account for a proportion of the overall disease burden.[9-11] In addition to primary viral pneumonia, influenza can be complicated by secondary bacterial infections causing a bacterial pneumonia. These are most commonly associated with *Streptococcus pneumoniae* and occasionally caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.[12-15] This secondary bacterial pneumonia generally occurs after a period of improvement in the primary illness with recrudescence of fever associated with symptoms of pneumonia.

Secondary complications of influenza infection can also occur and include cardiopulmonary complications like myocarditis,[16] neurological complications like Guillain-Barre Syndrome,[17-19] febrile seizures,[20, 21] transverse myelitis, post infectious encephalitis, and encephalopathy including Reye's Syndrome.[22-25] Influenza complications have also been rarely associated with myoglobinuria accompanying myositis, progressing on to renal failure[21, 26], particularly after an infection of influenza B.

Although influenza can infect all age groups, individuals at the extremes of the age spectrum are the most vulnerable to complications from influenza illness which can result in hospitalization and death.

01

Concepts in influenza disease burden estimation

There are various ways to express disease burden but most will fall into one of two broad categories:

1. The morbidity and mortality associated with a disease condition (medical burden)
2. The costs associated with the disease including both the direct costs associated with providing care for the diseased and the indirect costs associated with lost productivity because of illness, disability associated with sequelae of the disease, or premature death (economic burden).

For the purpose of this manual, we shall limit ourselves to estimating the burden on the health system and society in terms of morbidity and mortality, with the primary focus on morbidity.

After completing this chapter you will be able to define morbidity, incidence, mortality, and case fatality ratio.

1.1 Morbidity

Morbidity is defined as ''any departure, subjective or objective from a state of physiological and psychological well-being''.[27] In this case, an episode of illness or disease associated with influenza can be considered to define morbidity.

1.1.1 Incidence rate

Classically, morbidity is described using incidence rate.

Incidence rate is the rate at which new events occur in a population.[27] The **numerator** of the rate is the number of new events or cases that occur in a defined period of time. The **denominator** is the population at risk of experiencing the event during this period (most often expressed as person-time). Since denominator data are typically available only from cohort studies, this definition will require some modification for routine surveillance data where the person-time at risk cannot be calculated. The incidence rate most often used in public health practice is calculated from the formula in Equation 1.

Equation 1: Calculating incidence rate

$$\text{Incidence rate} = \frac{\text{Number of new events in a specified period}}{\text{Average number of persons exposed to/at risk during the same specified period}}$$

This rate is usually expressed as per 1000 population or per 100 000 population at risk. If the risk period is a year, it is called the annual incidence rate. The average size of the population is often the estimated population size at the middle of the year. Though this is usually referred to as incidence proportion or risk,[28] for simplicity we will refer to this as incidence rate.

When population denominators are not available, morbidity may need to be expressed in other ways. One is to estimate the **proportion** of cases of a specific disease syndrome, such as pneumonia, associated with a pathogen. Another is the proportion of all hospital admissions associated with the pathogen.

1.2 Mortality

While the main impact of disease burden on the health system is as a result of healthcare utilization, mortality is also of great interest to policy makers and the general public. However, mortality is extremely difficult to measure as the majority of pneumonia deaths in resource-limited low- and middle-income country settings occur outside the hospital.[29-31] Even for deaths in hospitalized cases, laboratory confirmation of influenza infection is rare[32] and death certificates are not often

accurately coded. In this manual we shall limit the mortality estimation to the case fatality ratio in hospitalized influenza associated cases.

In-hospital case fatality ratio (hCFR) is defined as the ''proportion of hospitalized cases of a specified condition that are fatal within a specified time''.[27]

Equation 2: Calculating in-hospital case fatality ratio

$$\textbf{hCFR (\%)} = \frac{\text{Number of in-hospital deaths from a disease (in a given period)}}{\text{Number of diagnosed and hospitalised cases of that disease (in the same given period)}} \times 100$$

It is worth noting that the hCFR we are computing here is a proportion of cases that have died and not the true CFR because:

- This is the CFR for only the hospitalized cases.
- We are only capturing the CFR for cases presenting with respiratory disease. The non-SARI presentations of influenza (e.g. myocarditis), which have a fatal outcome, are not counted. This again might underestimate the true burden.

02

Identifying and selecting data sources

This chapter discusses data sources for estimating the burden of influenza, describes how to review the data for quality and relevance, and assists in the selection of the appropriate data source(s).

After completing this chapter you will be able to:

1. *Identify appropriate data sources at your site*
2. *Screen them to assess their suitability to satisfy minimum criteria for inclusion*
3. *Review the data for quality and relevance towards burden estimation*
4. *Identify data that must be extracted for disease burden estimation*
5. *Employ techniques to adjust for missing data*

First, we will provide a brief overview of the key concepts. Subsequently, we will discuss in detail how to proceed further with the different kinds of data which may be available.

2.1. Identifying data sources

There are three main sources of surveillance data on influenza:

- Data from SARI sentinel sites
- Data from hospital records of ALRI patients admitted to hospitals not designated as SARI sentinel sites
- Data from ILI sentinel sites

The concepts described in this chapter are relevant to both those at a sentinel site as well as those at the national level. The additional specific issues related to those working at national level are discussed in Chapter 6. Apart from sentinel surveillance systems, data may be available from epidemiologic studies, observational studies, or vaccine trials testing for influenza.

Data from routine universal disease reporting or national notifiable disease reporting may have major limitations. There is often gross underreporting – the degree of which is unknown.

Different methods are available to potentially use this data for burden estimations and cross-validation of estimates using different methods might be helpful in some settings. Influenza disease burden using different techniques is beyond the scope of this manual.

List the data sources available for influenza disease burden estimation at your site/in your country in WS2.

2.2. Checking available data

Once the data sources have been identified and screened for quality and relevance, **age group** and **gender specific** data need to be extracted before proceeding with the analysis.

2.2.1. Age groups

The *WHO Global Epidemiological Surveillance Standards for Influenza* recommends the following age groups for reporting the surveillance data:

1. 0 to <2years
2. 2 to <5 years
3. 5 to <15 years
4. 15 to <50 years
5. 50 to <65 years
6. ≥65 years

However, disease burden estimates in children <6 months of age is also of interest when considering maternal immunization against influenza.[34] **It is recommend that where feasible and where it meets the national surveillance objectives, Member States consider additional age strata for under 2 year olds including 0 to <6 months, 6 months to <1 year, 1 to <2 years.** Conversely, some sites may be unable to identify a sufficient number of case patients during the time period of interest and within each of the recommended age groups to generate stable rate estimates. In such situations, countries may want to report rates as suggested but estimate age-stratified influenza rates for as many of the recommended age groups as will yield a stable analysis (e.g. 0 to <2, 2 to <5, 5 to <15, 15 to <50, 50 to <65 and ≥65).

2.2.2. Summary data

Table 2 is a summary of the data that will be required to be extracted for estimating medically attended influenza disease burden. All of the data listed here are unlikely to be available at one site; hence they have been categorized into two groups: essential and desirable. All data listed as **essential** must be available prior to undertaking the disease burden analysis.

Table 2: Summary data

	At SARI sentinel site, Hospital not designated as SARI sentinel site or ILI sentinel site
Essential data	Number of new SARI/ALRI/ILI cases admitted/seen*
	Number of SARI/ALRI/ILI cases that were sampled*
	Number of SARI/ALRI/ILI sampled cases that were positive for influenza*
	Number of new hospital admissions to wards with SARI/ALRI patients/Number of outpatient visits to ILI site*[§]
	Midyear population of Catchment area*[§]
Desirable data	Crude birth rate of catchment area/reference population
	Prevalence of chronic medical conditions in catchment population
	Number of death among SARI/ALRI cases admitted*
	Number of death among SARI/ALRI cases that were sampled*
	Number of death among SARI/ALRI cases that were positive for influenza(if possible by subtype)*
	Number of samples positive for influenza by subtype
	Number of samples positive for other respiratory viruses e.g. RSV

[§] Essential is either number of admission or midyear population

* Where possible data should be extracted by

- Age groups
- Gender
- Chronic medical conditions
- Pregnancy status

For influenza burden estimation, sites should collect the data by week to carry out the calculations of burden. However, if data can only be collected by month to obtain sufficient numbers to calculate burden, the influenza estimates can be completed by month.

To obtain estimates of population for the catchment area, either hospital administrative data or a health utilization survey will need to be completed to first define the catchment area of the sentinel surveillance sites.

The selected chronic medical conditions include chronic obstructive pulmonary disease, asthma, diabetes, chronic cardiac disease, chronic liver disease, chronic renal disease, immunodeficiency including HIV, and hereditary haemolytic anaemias.

If you do not have ESSENTIAL DATA you will need to review the influenza surveillance at your site and initiate steps to put in place mechanisms to capture quality essential data.

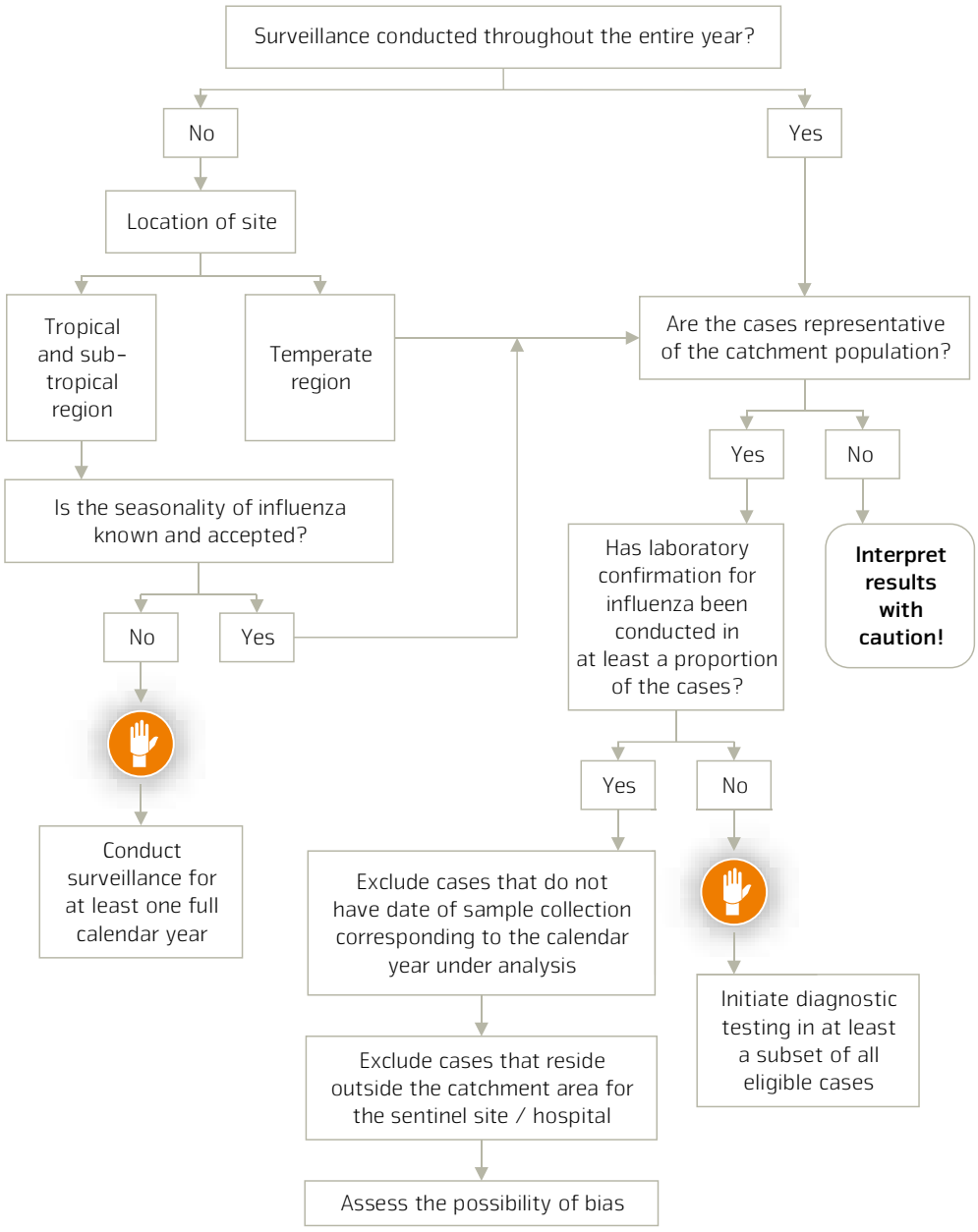
Ideally, data for at least a period of three to five years are needed to make valid inferences regarding influenza disease burden but data from at least one full calendar year can serve as a starting point. However, be cautious when interpreting your results as influenza activity varies markedly from year to year.

2.3. Reviewing the data for quality and relevance

Not all types of data listed above can be used to quantitatively estimate the influenza disease burden in a community. Some of the data can only be used to make some qualitative inferences regarding the trends of influenza transmission in the country.

Before proceeding to data analysis and interpretation, the available data will need to be reviewed carefully in the following areas (Figure 1):

Figure 1: Flowchart detailing the key decision processes while reviewing data for quality and relevance

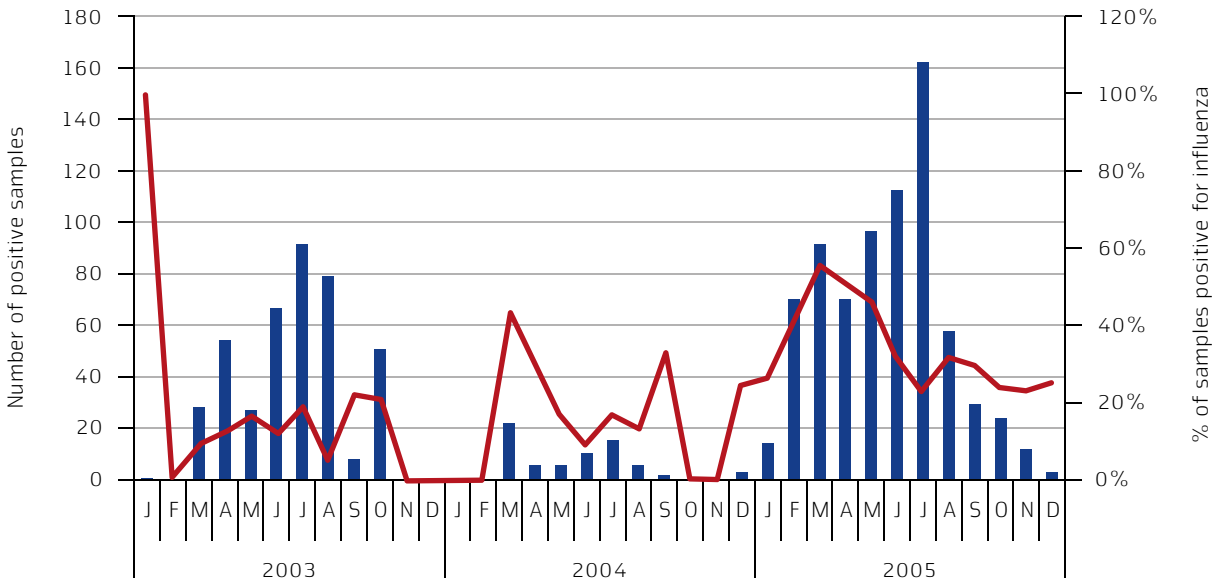


2.3.1. Completeness

Influenza transmission can occur throughout the year in tropical and sub-tropical areas (Figure 2) and the peak periods of activity of each type and sub-type of human influenza virus may vary from year to year. Therefore, you will typically need data from at least one full calendar year to estimate the burden of disease. Data from just a part of the year are not sufficient **unless the seasonality of the influenza virus at a given location has been clearly demonstrated previously and demonstrates consistency from year to year**.

In temperate climates with clear seasonality, surveillance is usually conducted beginning in early autumn and ending in the spring (Figure 3) – the time frame generally accepted as corresponding to the known influenza season. In temperate climate countries, we can assume that there is little influenza activity outside the influenza season in terms of overall burden.

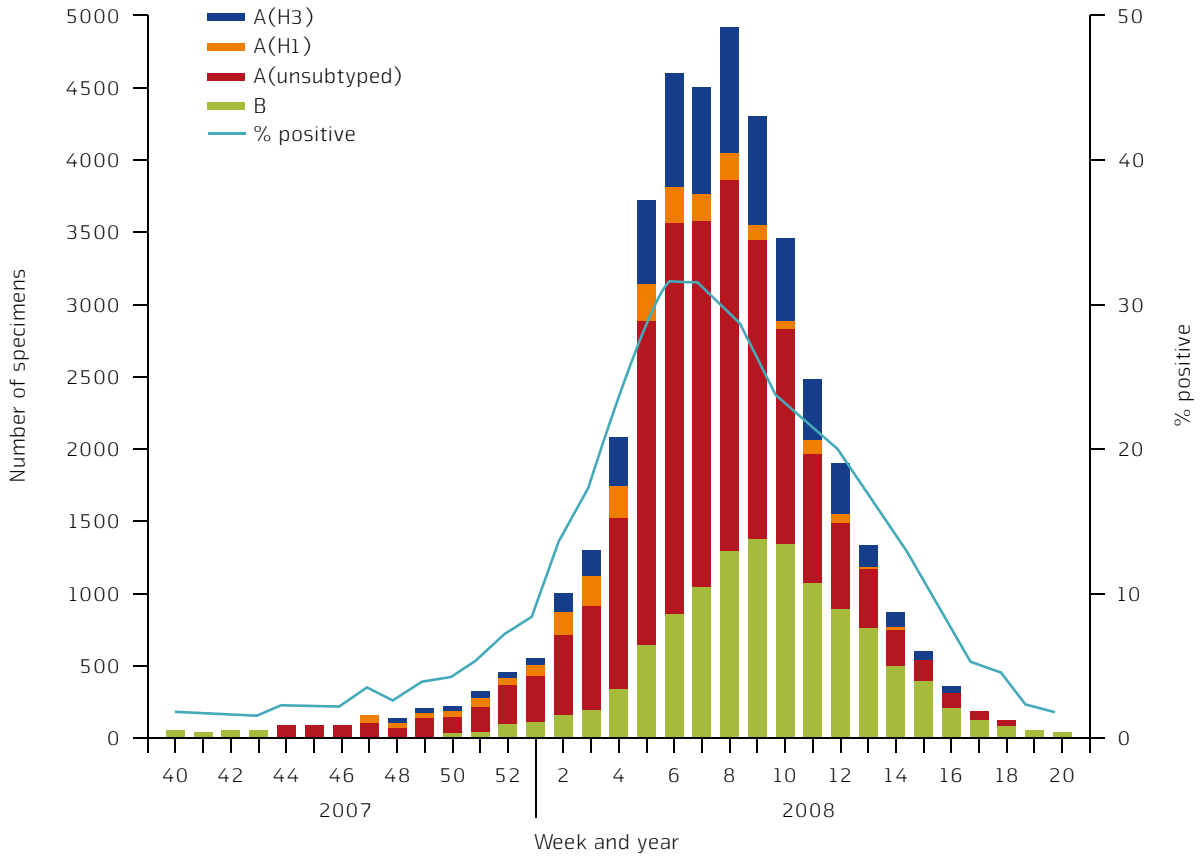
Figure 2: **Seasonal pattern of laboratory confirmed influenza activity in Nairobi, Kenya (tropical area) from 2003 to 2005.**



The number of influenza positive samples is indicated using blue bars and the proportion (%) of samples positive for influenza is indicated using a red line. Note how the period of influenza activity varies from year to year making it very difficult to delineate an influenza season.

Adapted from Nair H, et al., Lancet 2011 (web appendix).

Figure 3: Seasonal pattern of laboratory confirmed influenza activity (from week 40 in 2007 to week 20 in 2008) in the United States (temperate area with known seasonality).



Influenza surveillance in the United States is typically conducted from week 40 of a year to week 20 in the following year. There is little or no influenza activity outside the influenza season.

Reproduced from MMWR 57(25); 692-697

If your data are not for a full calendar year and if the seasonality of influenza virus has not been clearly demonstrated please STOP and identify another data set if the data are being analysed at the national level.

2.3.2. Representativeness

To make the results generalizable, the data should be representative of the population to be studied. Therefore, you will need to ascertain that the demographic and socioeconomic characteristics (age and sex distribution, ethnicity, socioeconomic status, education, access to healthcare, etc.) of the patients accessing healthcare at a sentinel site or hospital are largely similar to the general population of the area surrounding it. If these data are not available, then you will need to base the judgement on your qualitative, subjective assessment of the data's representativeness. For example, if the data source is a tertiary care hospital, patients receiving care at this hospital may not be representative of the influenza patients in the general population in the surrounding area because tertiary hospitals provide care to complicated patients referred for specialized care from a wide area. As such, the types of presenting illness and the distribution of risk factors may be very different from what is

expected in the general population surrounding the hospital. It may be possible to compensate for this by counting only patients from the primary catchment area around the facility. Similarly, a diabetes clinic, an antenatal clinic, or a hospital that restricts its clientele on basis of gender or religion is not representative of the general population.

If your data are not representative of the general population, you need not exclude the data. However, you will need to be careful when interpreting these findings.

2.3.3. Accuracy of case count

To make burden estimates, we require accurate data on the number of influenza cases or numerator.

Laboratory confirmation

Ideally, laboratory confirmation for influenza virus should have been conducted on all SARI/ALRI/ILI cases. However, this often is not possible owing to resource constraints. In this situation, clinical specimens are collected from only a proportion or sample of cases. These data can be used for disease burden estimation but the number testing positive will have to be adjusted to account for all of the cases that were not tested but that may be influenza.

If ALL cases in this dataset have been labelled as influenza purely on the basis of a clinical diagnosis (i.e. laboratory confirmation was not conducted even in a proportion of the cases), DO NOT include this dataset.

Date of sample collection

All the cases in the dataset should have the date of sample collection in the calendar year for which data are being analysed.

Exclude cases that do not have the date of sample collection corresponding to the calendar year(s) under analysis.

Residence

For burden estimation for an area, you should only consider cases that are living in the catchment area of the sentinel site or hospital. Defining the area under study can be somewhat complicated and will depend in part on the administrative level at which you can define where cases live. See section 3.4.2 for more information on defining a catchment area.

Exclude cases that reside outside the catchment area of the hospital.

2.3.4. Assessing the potential for bias

Bias is the "deviation of results or inferences from the truth or processes leading to such deviation." [27] Thus, bias is an error caused by systematically favouring some outcomes over others. There are many forms of bias and these can arise as a result of error at any of the phases related to a study design, data collection, data analysis, data interpretation, reporting, or publication. In the context of surveillance, biases are often present due to the selection of cases for testing, and the resulting data may not be representative of the population. For example, if testing is only done on cases coming to clinic or admitted to hospital early in the morning on weekdays, one will get a different picture of the kinds of people most affected by influenza because of differences in the usual timing of when children or non-working adults seek care compared to working adults. As described below, data from influenza surveillance can be limited by several biases.

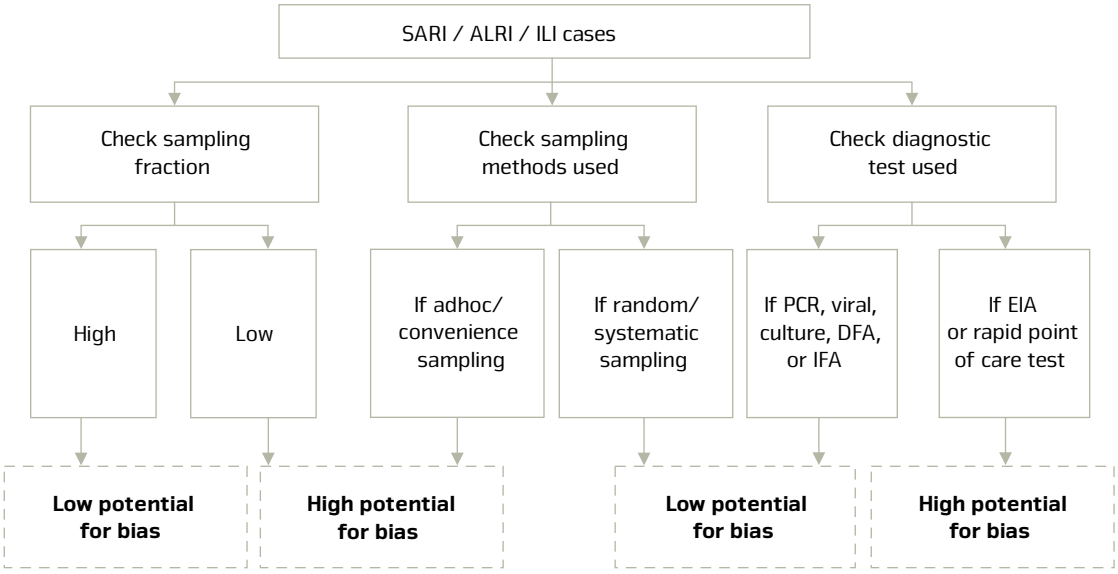
Bias resulting from sampling schemes

SARI/ALRI/ILI cases that are influenza positive constitute the numerator (or the upper half of the fraction) for estimating incidence rates. Although it is recommended that diagnostic samples be collected from all SARI/ALRI/ILI cases, so that we can have an accurate case count, very often a proportion of eligible cases are excluded from virological sample collection because:

1. the patient is very sick and the physicians want to avoid any further trauma collecting specimens
2. the patient does not consent to specimen collection
3. the patient is admitted out of office hours and dies before the specimen is collected
4. the patient is admitted out of office hours and leaves before the specimen is collected
5. specimens are collected only in a proportion of cases due to limited resources
6. the physician does not order the test or doesn't report the case
7. the physician may selectively choose patients for specimen collection based on clinical symptoms (e.g. those with severe respiratory illness perceived to be influenza)

All the above-mentioned scenarios may result in a selection bias. Ideally, a sampling scheme for selection of patients for testing has been adopted that will minimize biases in the data. Even so, it is important to be aware of the likelihood of bias and the effect it will have on disease burden estimates. Generally, if the sampling fraction is low (i.e. clinical specimens were collected from only a small portion of SARI/ALRI/ILI cases), there is a higher potential for bias. If the sampling fraction is high (i.e. clinical specimens were collected from a high proportion >90% of cases), then the potential for bias is lower. Figure 4 outlines the likelihood of bias resulting from sampling schemes and diagnostic assays used at the SAR/ILIl sentinel site.

Figure 4: Assessing for bias resulting from case selection and diagnostic tests



Example

Systems interested primarily in collecting virological data often select the first two cases of the day for testing. However, it is well recognized that patients reporting early to outpatient clinics are very different from the rest (e.g. diabetics often come to clinic early in the morning to have blood sugar tested). This method of case selection will result in a systematic bias in the types of individuals from whom diagnostic specimens and data are collected. While this kind of convenience sampling will likely not create a bias in the resulting virological data, it may bias the disease burden estimates in unpredictable ways. It will also present a skewed picture of the risk factors for influenza and the general demographics of influenza cases. For more information on sampling strategies to avoid bias, please refer to the "WHO Global Epidemiological Surveillance Standards for Influenza".

Bias resulting from diagnostic assays used

Additionally, the diagnostic assay used is likely to have an influence on the case count (Figure 4). It has been shown that rapid point-of-care diagnostic tests and immunofluorescence assays have a much lower sensitivity compared to viral culture or molecular techniques like polymerase chain reaction (PCR) (Table 3).[35-39]

Thus, with a less sensitive test SARI/ALRI/ILI cases that actually have influenza will be falsely identified as being influenza free. Such a bias is called misclassification bias. Clinical specimens tested using assays having low sensitivity and high specificity will bias the result in a downward direction leading to underestimation of the disease burden. Apart from the diagnostic assay, the sensitivity of each test is influenced by the quality of the specimen, how well it is stored, how it is shipped, the specificity of the reagents used, and the level of experience of those performing, reading, and interpreting the tests. (For definitions of sensitivity and specificity, refer to Appendix A7).

Table 3: Comparison of the sensitivity and specificity of various diagnostic assays against viral culture (gold standard)

Diagnostic Assay	Sensitivity (%)	Specificity (%)
Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)**[40]**	100-110	93
Direct immunofluorescence (DFA)**[41]**	70-100	80-100
Indirect immunofluorescence (IFA)***[37]**	90-100	100
Enzyme Linked Immunoassay (EIA)**[41]**	70-75	90-95
Rapid Point of Care (POC) Tests		
Quick vue / Directigen**[36, 42]**	47-78	94-99
Z-stat Flu**[37]**	65-77	77-97

*Comparing IFA to RT-PCR, IFA will only identify 50% of cases. However, this table compares the IFA to viral culture

Bias resulting from case definitions

A related concept is the sensitivity and specificity of precise case definition used for SARI and ILI. The sensitivity and specificity of the current WHO case definition varies across age groups and across study sites (for details refer to section 8.1.3). This again would result in a misclassification bias and have a bearing on the disease burden estimates.

- **What is the sampling technique used at your site(s)?**
- **What diagnostic assays are used at your site to confirm infection with influenza virus?**
- **What is the likelihood and the likely direction of this bias?**
- **What is the health seeking behaviour in the community**

Summary

In this chapter, we have described how to identify the key data sources and relevant data for extraction and how to review the data for quality and relevance. We have identified certain minimal quality criteria failing which the data are unsuitable for disease burden analysis. Some degree of bias is inevitable with any kind of surveillance data. It is important to be aware of these biases while analysing data and interpreting the results.

If you are working at a SARI sentinel site, please go to Chapter 3.

If you have hospital data that are not from a SARI sentinel site, please go to Chapter 5.

If you are working at an ILI sentinel site, please go to Chapter 6.

If you are working at the national level, please go to Chapter 7 (after familiarizing yourself with the tools and concepts in previous chapters).

Now go to checklist in Appendix WS3 and check your data and list your biases.

03

Disease burden estimation using SARI sentinel surveillance data

Sentinel surveillance systems collect epidemiological and/or virological data from a limited number of selected healthcare facilities in the country. Sentinel surveillance is the recommended method for performing influenza surveillance. It is the most efficient way to collect quality data in a timely manner and to obtain high-quality data on relatively common conditions from a manageable number of locations.

After completing this chapter you will be able to:

1. *Make adjustments (using statistical techniques) for missing data*
2. *Define the catchment area and conduct a hospital admission survey*
3. *Estimate the denominator population (i.e. population at risk)*
4. *Estimate the influenza disease burden in a population using data from SARI surveillance*
5. *Estimate the 95% confidence interval for the influenza disease burden estimates*

3.1. Finalising data for disease burden estimation

In Chapter 2, we discussed the general principles of identifying a data source and relevant data for extraction and reviewing the available data for quality and relevance. Applying these principles to SARI sentinel sites, you will be:

Reminder	
Identifying data sources	1. SARI sentinel site
Screening for available data	2. Data availability by suggested age groups* a. 0 to <2 years b. 2 to <5 years c. 5 to <15 years d. 15 to <50 years e. 50 to <65 years f. ≥65 years 3. Data availability by gender 4. Data availability by risk groups
Reviewing the data for quality and relevance	5. Checking for Representativeness 6. Checking for Accuracy a. Laboratory confirmation b. Date of sample collection c. Residence 7. Assessing for potential bias and under-ascertainment from a. Sampling schemes b. Diagnostic assays used c. Case definition

* These are recommended age groups, but countries should use appropriate age groups for their data and that make sense for their population dynamics.

Once you have identified your data sources, screened for available data and assessed the data for quality and relevance, you will need to **extract the relevant available data**.

3.2. Extracting data

Extract the following data **by week or month and gender for each age group:**

Essential data

- Total number of inpatients admitted to the sentinel site all wards
- Total number of new SARI cases admitted to the sentinel site (includes all cases that were not tested for influenza virus) in wards where SARI cases are likely to be admitted. (*Note that some SARI cases may be admitted to wards that are not typical for respiratory illness cases*)
- Number of SARI cases from whom clinical specimens were collected (for laboratory confirmation of influenza)
- Number of SARI cases which are influenza-positive (for each type and sub-type of influenza virus)

Desirable data

- Number of SARI deaths occurring at the sentinel site (includes SARI deaths that are influenza negative or where influenza testing was not carried out)
- Number of influenza-positive SARI deaths occurring at the sentinel site (for each type and sub-type of influenza virus)
- Total number of SARI cases in pregnant women
- Number of influenza-positive SARI cases in pregnant women
- Number of influenza-positive SARI deaths in pregnant women occurring at the sentinel site
- Number of SARI cases, influenza-positive SARI cases, and fatal influenza-positive SARI cases with chronic medical conditions such as those defined in the WHO surveillance guidelines:
  - Chronic obstructive pulmonary disease
  - Asthma
  - Diabetes
  - Chronic cardiac disease
  - Chronic liver disease
  - Chronic renal disease
  - Immunodeficiency, including HIV
  - A severe genetic anaemia such as sickle cell disease or thalassemia major

Include only those cases that are residents of the catchment area for the sentinel site. If you are not sure of the catchment area, then define the catchment area as described in 3.4.3. For some sentinel sites (e.g. large tertiary hospitals and teaching hospitals in large cities) a catchment area may be challenging to define in which case incidence calculation may not be possible.

3.3. Defining the numerator: Case count

The first step for estimating the disease burden due to influenza-associated SARI is to have an accurate numerator (the number of influenza-associated SARI cases). The influenza-associated SARI cases in the numerator must be from the same geographical area as the population in the catchment area that will serve as the denominator for the incidence calculation. Therefore, it is important to **exclude SARI cases that are living outside the catchment area** (e.g. living in dwellings outside the administrative areas primarily served by the sentinel site).

There are potentially two scenarios which you may encounter:

- Data are based on all SARI cases; i.e. all SARI cases presenting to the site have been tested for influenza (section 3.3.1.).
- Data are based on a proportion of SARI cases; i.e. only some SARI cases presenting to the site have been tested for influenza (section 3.3.2).

3.3.1. Data are based on all SARI cases

If all SARI cases presenting to the sentinel site have been tested for influenza – that is, no sampling procedure was used to select a subsample of cases for testing – there are two additional steps that are needed.

Step 1: Exclude cases that are admitted from outside the sentinel site catchment area. Sentinel sites that are close to the border of a catchment area or that are well known in the region may receive patients from outside the catchment area. See section 3.4 for information on defining the catchment area.

Step 2: Perform a brief chart audit to insure that significant under-reporting of SARI cases has not occurred. A source of significant under-estimation of disease burden is likely to come from underreporting by clinicians caring for patients with SARI. A brief chart review (e.g. from a random sample of hospital charts during the influenza season) or even a registry of discharge diagnoses can be used as a double check on completeness of reporting. If significant underreporting has occurred, the unreported cases will need to be evaluated for potential bias that may have been introduced by non-systematic reporting. In addition, it will be necessary to extrapolate the influenza-positive cases to the non-tested cases as described in the next section (3.3.2).

Step 3: If the chart audit does not indicate significant under-reporting, proceed to section 3.4. If chart audits or registry data suggest that a large proportion of patients meeting the SARI case definition remain unidentified by routine surveillance, consider reviewing surveillance guidelines with sentinel site staff.

3.3.2. Data are based on a proportion of SARI cases

If only a sample of SARI cases were selected for laboratory confirmation, we will have to estimate the proportion of SARI cases that remained unidentified by routine surveillance.

Step 1: Obtain case counts for influenza-positive SARI cases meeting the case definitions given in Table 1 in the introduction. Only cases from the catchment area of the sentinel site should be counted (see section 3.4 for how to define the catchment area). It is important that cases in the case count are from the same population that will be used as the denominator for incidence calculations.

Step 2: We will assume that the proportion of cases which are positive for influenza would be similar in those who were tested and those who were not tested during a particular epidemiologic week or month. This also assumes that there is no significant bias in the selection of patients for testing. So, if 15% of patients selected in the sampling procedure for testing are positive for influenza, then approximately 15% of the patients that were not selected in the sampling procedure would also have been positive, if they had been tested.

Using these assumptions, the simplest way of adjusting the case count to estimate to true total number of influenza cases at the site each epidemiologic week or month is by scaling up the number of influenza-

positive SARI cases (y) by the proportion of SARI cases tested (x). It is easier to visually appreciate data on proportions if they are expressed as a percentage (which requires the result to be multiplied by 100).

Equation 3: Calculating the proportion of all cases sampled

$$\text{Proportion of all cases sampled (x\%) month/week} = \frac{\text{Number of SARI cases from whom clinical specimen were tested by month/week}}{\text{Total number of SARI cases by month/week}} \times 100$$

Note: if there is significant under-reporting of SARI cases at the sentinel site, it may be necessary to perform a chart audit to know the actual total number of SARI cases to use in the denominator of Equation 3 (see step 2 in the previous section).

AND

Equation 4: Calculating the total number of influenza-associated SARI cases

$$\text{Total number of influenza-associated SARI cases} = \sum_{k=1}^{n} \frac{\text{Number of laboratory positive SARI case by week or month}}{\text{Proportion of all SARI cases sampled by week or month}}$$

n= number of month or weeks available

Note: it is critical to do this scaling up for each epidemiologic week or month and add the total for the annual number rather than to simply scale up the annual figures.

Example

If only 40% (or 0.4 in proportion terms) of all SARI cases admitted to a sentinel surveillance site are sampled, and if in a given month 100 of these cases have laboratory confirmed influenza, then the estimated number of true influenza-positive SARI cases for the month is 100/0.4= 250.

3.4. Defining the denominator: catchment population

To estimate disease burden by incidence rates, reasonably accurate estimates of the denominator population for the sentinel site are required. The denominator population for a sentinel site consists of all the people living in the catchment area of the healthcare facility who would usually seek healthcare at the site when they get sick. Such data might not be readily available, and additional data collection may be required to estimate the denominator population.

There are potentially three scenarios which you may encounter:

- Data on denominator population for the sentinel site are readily available because the facility is the only one providing in-patient care to the population.
- Data on denominator population for the sentinel site are not readily available but can be estimated (where catchment area can potentially be defined).
- Data on denominator population for the sentinel site are very challenging to obtain.

3.4.1. Data on denominator population are readily available

If the population of the catchment area of the facility is known, then check if age and sex stratified data on the population at risk are available.

- If **YES**, proceed to section 3.5 for disease burden estimation.
- If **NO**, proceed to section 3.4.3 to estimate age-stratified population data before disease burden estimation.

3.4.2. Data on denominator population can be estimated

Selecting the age-stratified denominator population is a multi-step process. First, the catchment area of the surveillance sentinel site needs to be defined, and then the denominator population (i.e. those accessing healthcare at this site) needs to be estimated. There are several methods to estimate the population. One, the Health Admission survey will be describe more in detail below 3.4.4. An alternate and perhaps more robust method to estimate the denominator population is to undertake a healthcare utilization survey, which requires a house-to-house survey in a random sample of representative households to ask which healthcare facility the family uses. There are several survey methods which have been developed and used in low-income settings.[44-47] Sentinel sites and Member States who are interested in undertaking a formal healthcare utilization survey may want to adapt one of these protocols to their individual settings.

3.4.3. Defining a catchment area

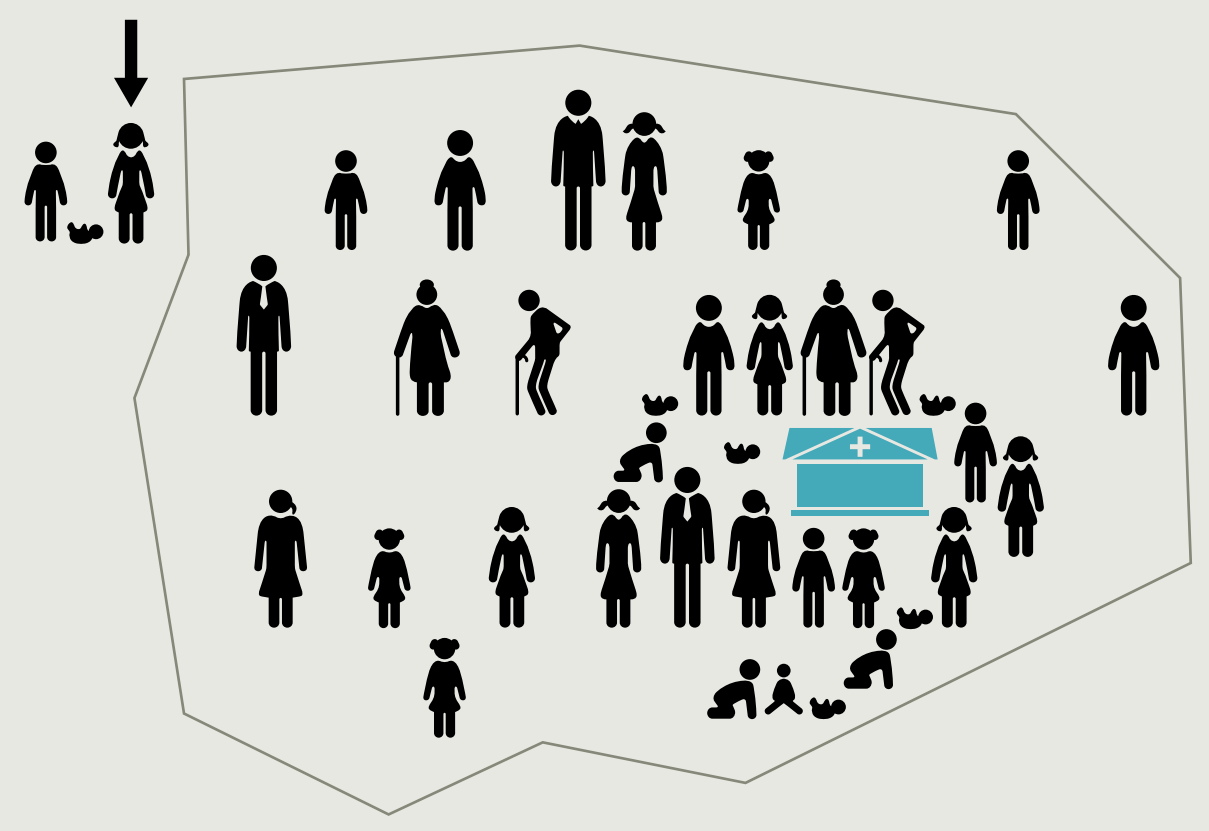
Step 1

Obtain a **map** of the area showing the **location of the sentinel site**.

Step 2

Review the hospital admission records, hospital registries, billing datasets, or other administrative datasets that have patients' address of your SARI cases for the time period of your burden analysis or for the period of time for your incidence estimation and prepare a **spot map of where the cases live**. While preparing the spot map, take note of the lowest administrative level for which data on residence of the cases was recorded. This could be the village or it could be the sub-district (tehsil/taluka/union council/county/parish/census block). If data for only the district of residence are available, then the cacthment area will have to be the district. However, it is preferable to use smaller administrative level area when possible. Note, administrative terms such as "district" will vary by country but the principle is to use the smallest area which can be defined for a facility.

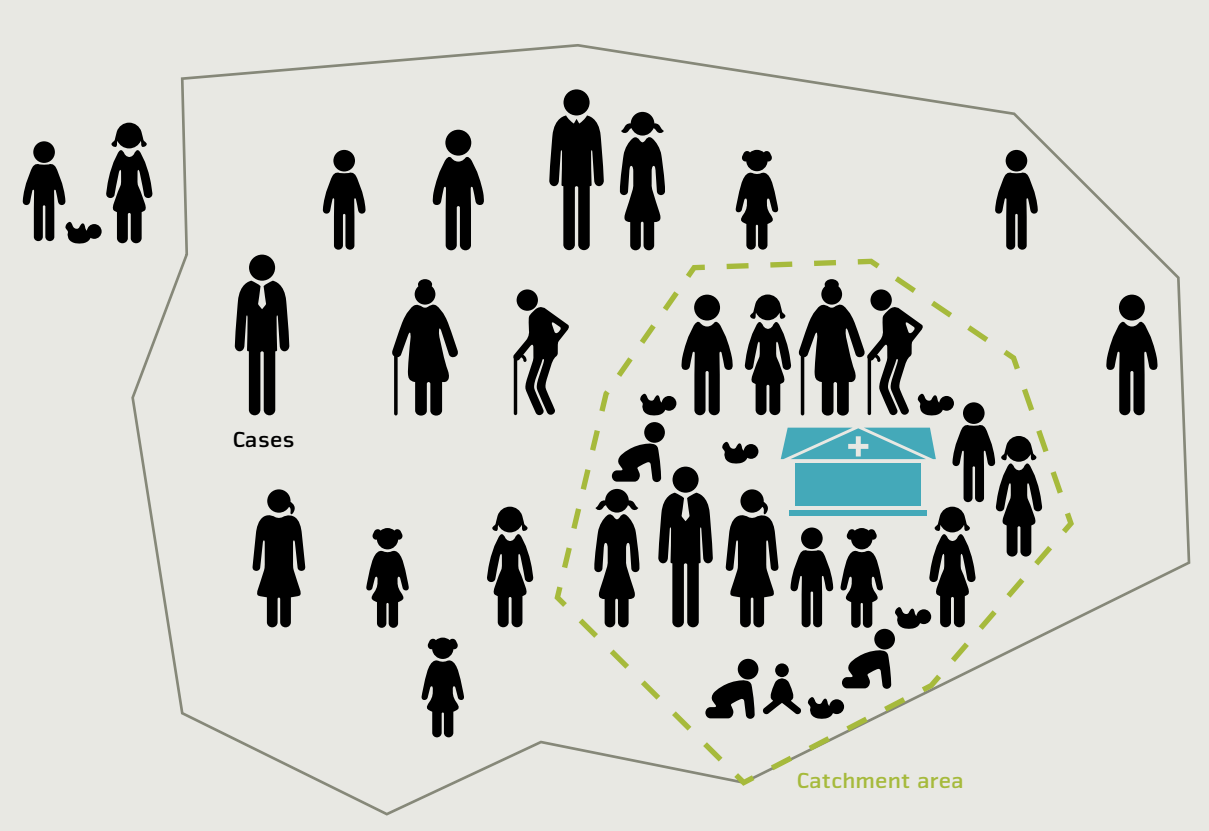
Some cases are from outside the district.



Step 3

Identify the area where the majortity of the cases seeking care at the sentinel site reside (e.g. ≥80%) [43]. This is the **catchment area** of the sentinel site. In the accompanying figure, this area is marked by a green dashed line.

Catchment area of sentinel site (Boundary based on the lowest administrative unit for which population data are available)



Step 4

Obtain **age- and gender-stratified population data** for this area from census or municipal records. When feasible, obtain such data for each year you plan to estimate an influenza-associated rate.

If **this sentinel site is the ONLY hospital in this area** and all cases of pneumonia seek care here, then this is the catchment population for this site. However, this is often not the case as there may be multiple healthcare facilities in an area. In such cases, the catchment population will need to be estimated.

As noted above in section 3.3, SARI cases that reside outside of this catchment area should be excluded from the numerator; the numerator and denominator cases should all come from the same catchment area.

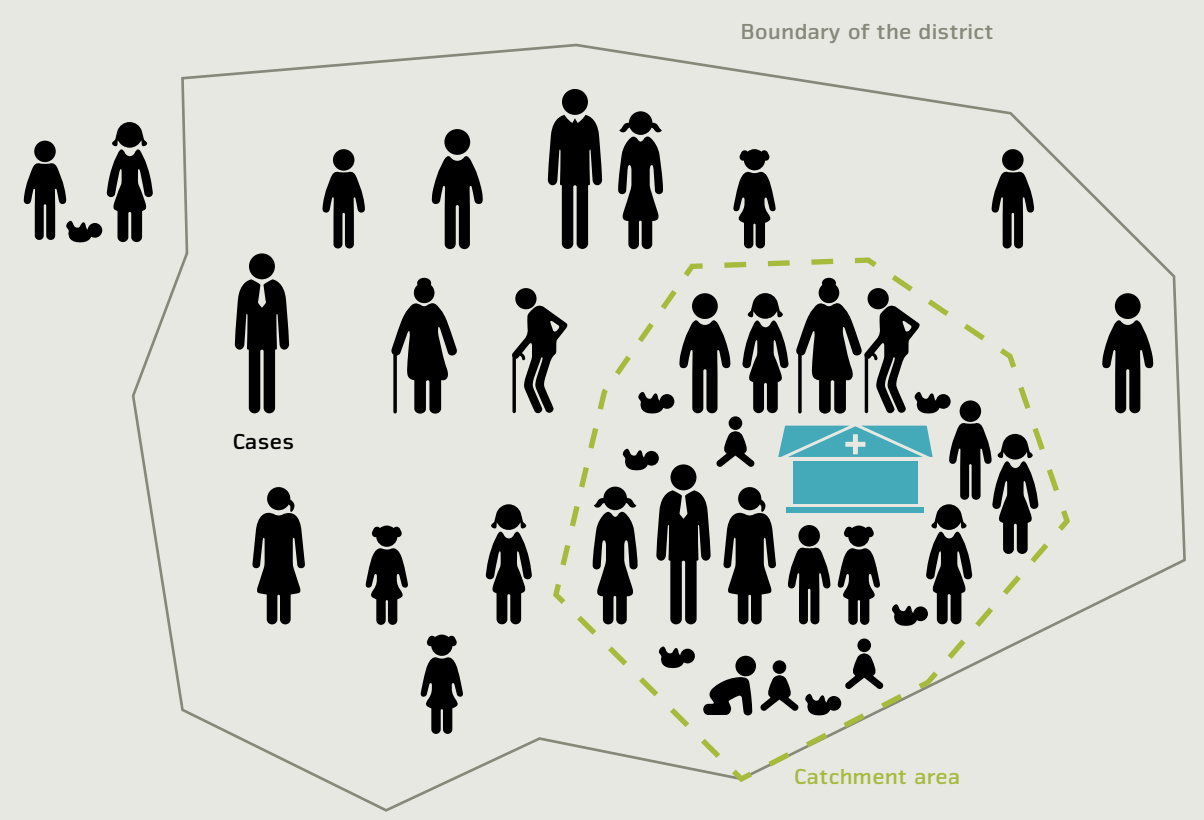
3.4.4. Estimating the denominator catchment population for the sentinel site

If multiple healthcare facilities provide inpatient care for respiratory disease patients within the same area as the sentinel institution, then it is necessary to determine what portion of the total population receives care at the sentinel institution to determine the size of the population denominator for that facility. There are several ways one can do this. Some are more resource intensive than others. The easiest method is what we will call a Hospital Admission Survey (HAS).

Step 1

Identify the catchment area of the sentinel site which is the lowest administrative level for which accurate population data are available as described in the previous section.

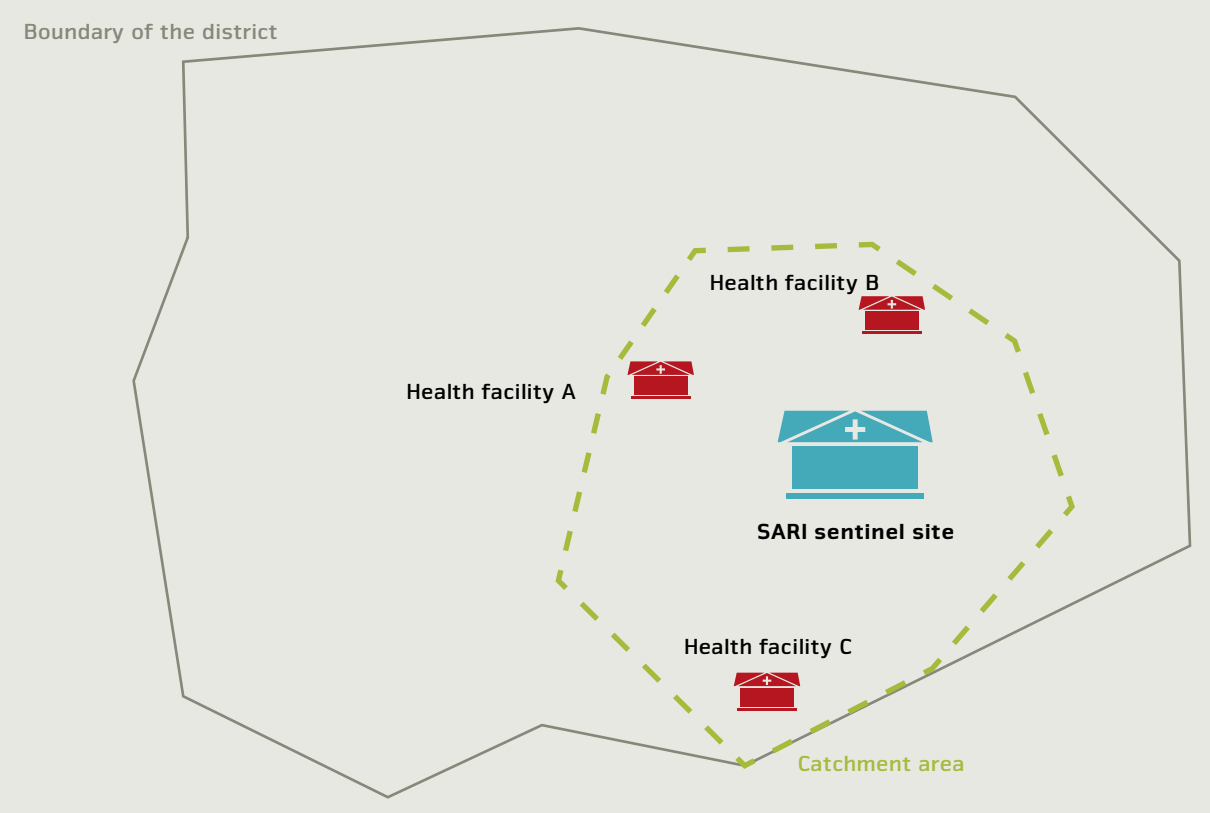
Catchment area of SARI sentinel site



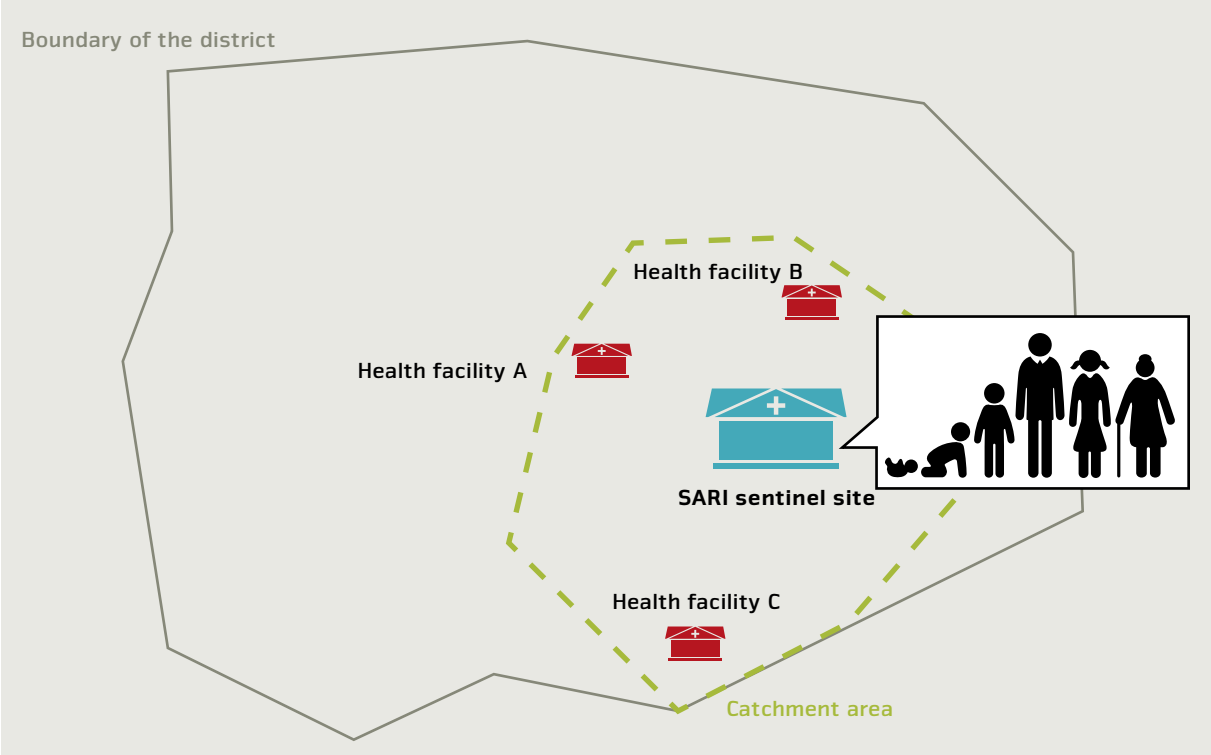
Step 2

Step 2a: Identify the other health facilities in this catchment area where cases with pneumonia are likely to seek care.

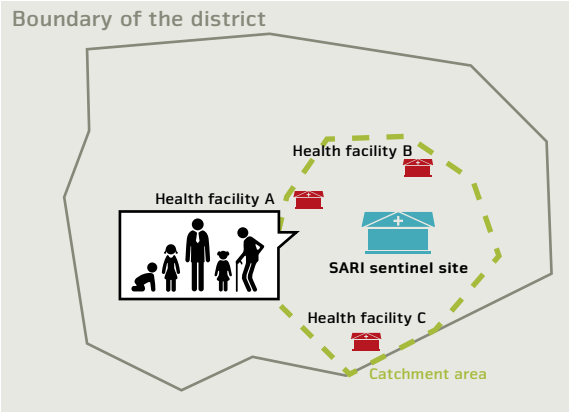
Let us, for example, assume that in the catchment area of the SARI sentinel site there are three other health facilities that admit a substantial number of pneumonia patients every year, which we have labeled health facilities A, B, and C.

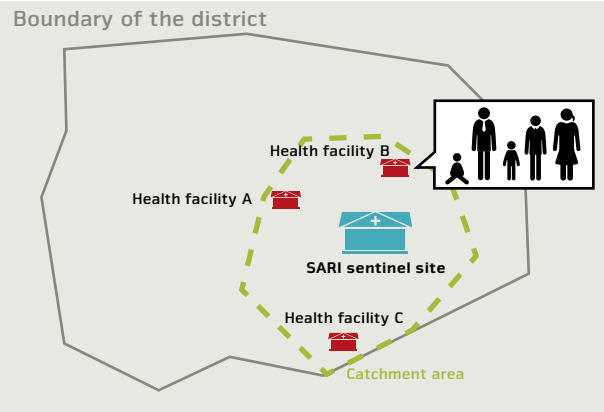


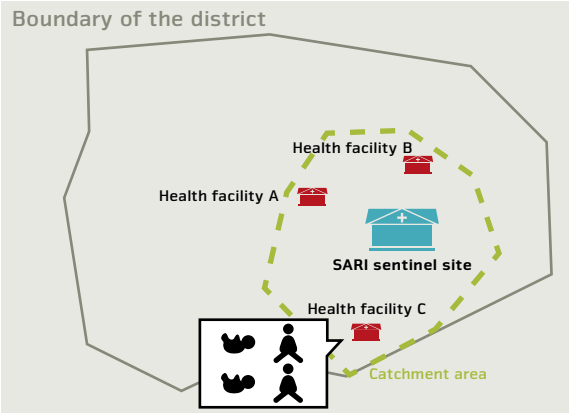
Step 2b: Visit the surveillance sentinel site. **Using the hospital discharge register or similar data source, count the number of patients from within the catchment area who were hospitalized with pneumonia** for each of the age groups for the time period being used for your burden estimation or your incidence calculations. Only patients that reside inside the designated catchment area of the sentinel site should be counted. Record these data on the data template provided in Appendix WS4.



Step 2c: Now visit the other health facilities located in catchment areas A, B, and C and repeat the process, counting and recording the number of pneumonia admissions for each facility. Record also these data on the data template provided in Appendix WS4.

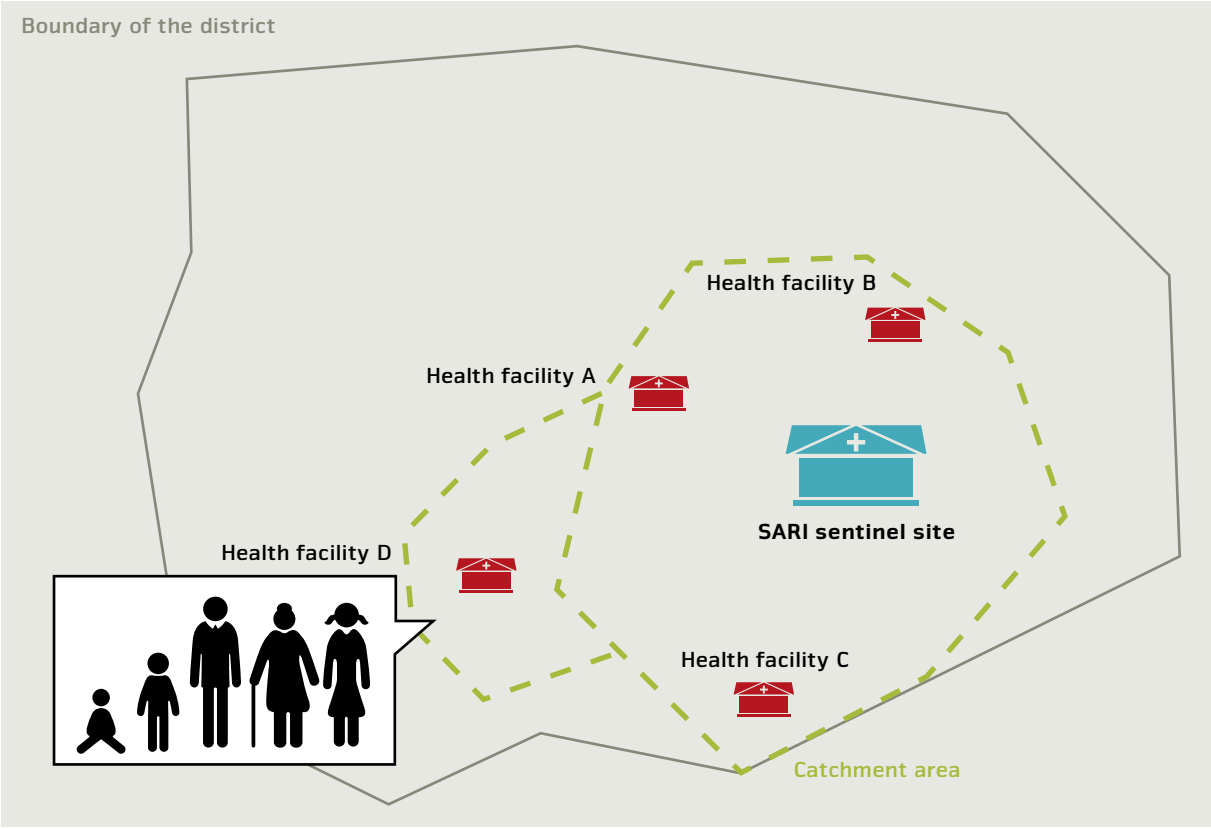






Step 2d: If there is a **health facility** (let us call it D) **just outside the catchment area** which has a **high volume of inpatients with pneumonia**, and if many people from the catchment area are likely to visit this facility, then you will need to include this facility in the survey. Record also these data on the data template provided in Appendix WS5.

Note: If you extend the catchment area to include this health facility, then you will need to include pneumonia cases from the extended area while counting and recording pneumonia cases in other above mentioned health facilities including the sentinel site. Also, you will need to include cases from the extended catchment area while recording SARI cases (numerator) for the sentinel site.



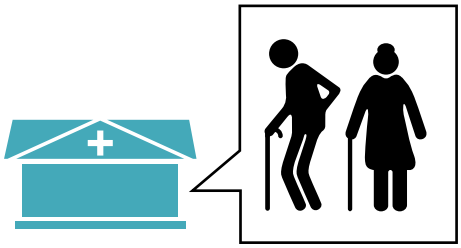
Step 3

Obtain **age and gender population data** for this area from census or municipal records.

Step 4

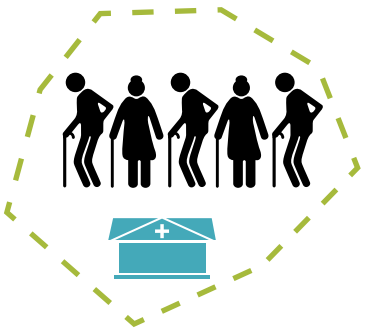
Step 4a: Calculate the proportion of pneumonia (ICD-10 codes: J9-J18) patients in this catchment area that are admitted at sentinel site *in each age group*.

Equation 5: Calculating the proportion of pneumonia patients



$$P_{SS\_g1} = \frac{\text{SARI sentinel site: Cases of pneumonia that are admitted to the SARI sentinel site}}{\text{Total cases of pneumonia for the catchment area}}$$

P_{SS_g1}
Proportion of population admitted at SARI sentinel site *in a given age group*



Step 4b: Estimate the **denominator population** *for each age group and gender* for the sentinel site using the formula:

Equation 6: Estimating the denominator population

Estimated denominator population *for each age group* = Proportion of pneumonia cases *of that age group from the catchment population*, that were admitted at the SARI sentinel site from all pneumonia cases in the catchment area X Total population *of that age group*, living in the catchment area (from census records)

Now do this for each of the other age groups. The population for the individual age groups can then be added to estimate the overall denominator population for the catchment area.

Example 1

For the age group <2 years old, there were a total of 300 pneumonia admissions at sentinel site S and hospitals HA, HB, and HC over three years; 60 of these were admitted at sentinel site S. In this area then, 20% of the pneumonia cases for this age group were admitted at sentinel site S (60/300). Thus, the *denominator population* for sentinel site S is 20% of the total population of the catchment area for this age group. If the total population in the age group <2 years in this catchment area is 10 000 then the denominator population for <2 years for site S is 2000. Follow the same procedure for each age group (see example 2).

Example 2

During the study period, the population of the district where sentinel site S is located is 100 000 and the distribution by age group as shown in Table 4.

Table 4: Population distribution by age group in District

Age group	Population (males)	Population (females)
<6 months	1000	900
6 months to <1 year	980	870
1 year to <2 years	1970	1700
2 to <5 years	5550	5030
5 to <15 years	13 500	12 500
15 to <50 years	24 000	25 000
50 to <65 years	1800	2200
≥65 years	1300	1700

The hospital admission survey (HAS) data finds that 50% of all pneumonia admissions in the last 3 years were admitted to the sentinel site S, which would suggest that the catchment population for the site is 50% of the total population, *but* there are differences in access by age and gender (Table 5).

Table 5: Data from Hospital Admission Survey (HAS) of sentinel site S and other hospitals in district where site is located.

Age group	Proportion of population accessing sentinel site S for pneumonia (males)	Proportion of population accessing sentinel site S for pneumonia (females)
<6 months	59%	37%
6 months to <1 year	62%	34%
1 year to <2 years	54%	44%
2 to <5 years	65%	37%
5 to <15 years	65%	35%
15 to <50 years	55%	45%
50 to <65 years	50%	50%
≥65 years	50%	50%

Now if we apply the HAS data to the census population, we can estimate the population for the catchment area (stratified by age group and gender) as shown in Table 6.

NOTE: If age and gender data are not available for the catchment area, the age and gender distribution for the smallest available administrative area that contains the catchment area can be used as an approximation. The exception to this would be if there are facilities in the area that provide care to a specific age group, such as a paediatric hospital. This should be noted in the initial survey of hospital discharge data as the proportions of cases admitted at each facility will vary markedly by age group. In this situation, if age data are not available for the catchment area population, then only total denominator can be calculated and age specific incidence will not be possible.

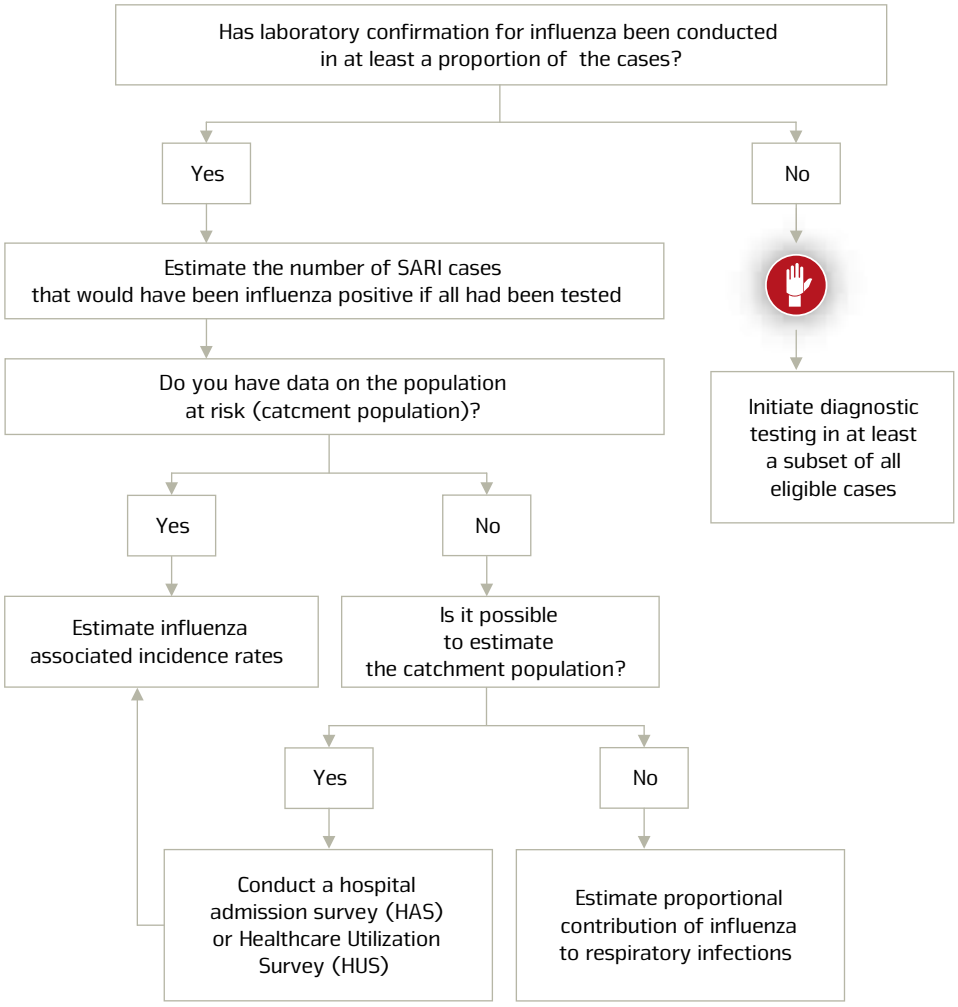
Table 6: **Estimated population for sentinel site S based on district census population and Hospital Admission Survey in the population**

Age group	(a) Population of males in district where sentinel site is located	(b) Proportion of male pneumonia patients who would be admitted to sentinel site	(a x b) Estimated (male) catchment population for sentinel site	(c) Population of females in district where sentinel site is located	(d) Proportion of female pneumonia patients who would be admitted to sentinel site	(c x d) Estimated (female) catchment population for sentinel site
<6 months	1000	59%	590	900	37%	330
6 months to <1 year	980	62%	608	870	34%	292
1 year to <2 years	1970	54%	1069	1700	44%	751
2 to <5 years	5550	65%	3608	5030	37%	1852
5 to <15 years	13 500	65%	8775	12 500	35%	4375
15 to <50 years	24 000	55%	13 200	25 000	45%	11 250
50 to <65 years	1800	50%	900	2200	50%	1100
≥65 years	1300	50%	650	1700	50%	850
Total			29 400			20 800

3.5. Estimating disease burden

As discussed above, it may or may not be practical to estimate denominator population for a SARI sentinel site. It may be, for example, that hospital discharge data are not available to do the HAS and resources are not available to do a healthcare utilization survey. In this situation, burden may be described in terms of the proportion of disease caused by influenza or the percentage of all admissions that are related to influenza. We will discuss disease burden estimation in both these scenarios.

Figure 5: Schematic diagram outlining the possible influenza disease burden estimates based on availability of data on the denominator population



3.6. Estimating disease burden with population denominator

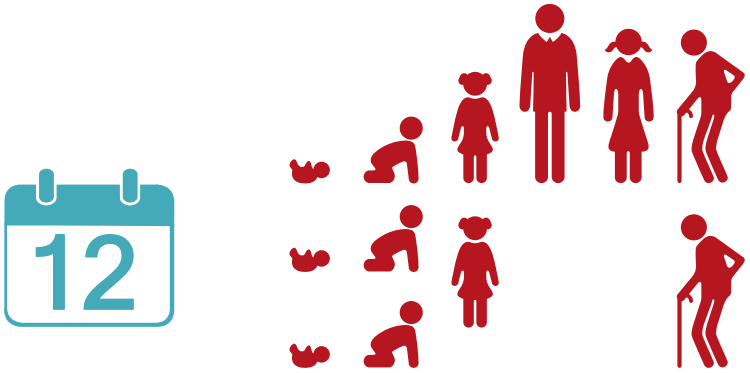
In situations where the data on denominator population are available, the best measure of disease burden in the population is the annual incidence of influenza-associated SARI (for more information on incidence rate see section 1.1.1).

Since the incidence of influenza varies with age, ideally age-specific incidence rates are calculated and reported.

Step 1

Obtain **case counts of influenza-associated SARI for a calendar year**, having adjusted for cases that were not selected for diagnostic testing (as described in section 3.3.2), if diagnostic specimens were collected only in a proportion of SARI cases.

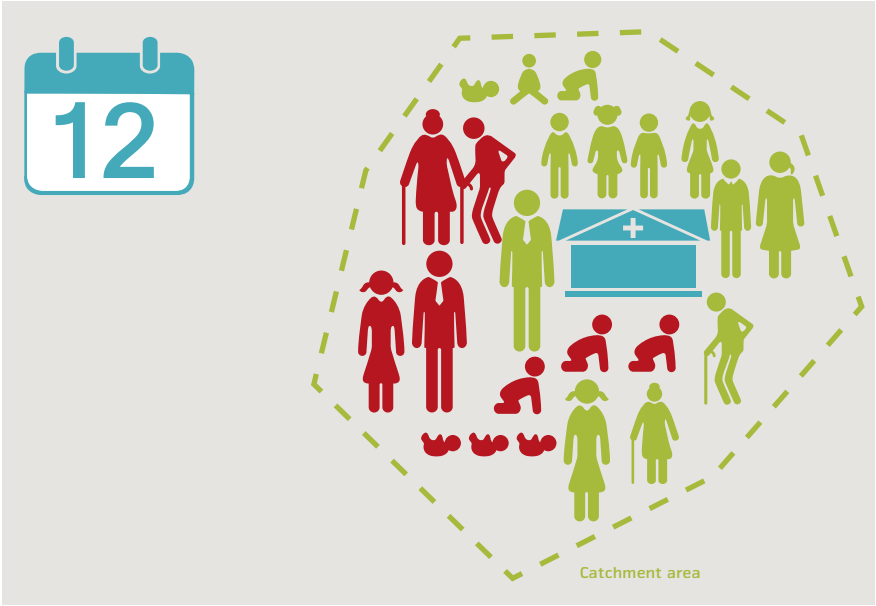
Case count: total number of influenza-associated SARI cases by age group and gender (after adjustment, if any).



Step 2

Obtain or estimate mid-year catchment population for the sentinel site by age group, (and ideally by gender) as detailed above in section 3.4.

Denominator population: Mid-year catchment population for the sentinel site



Step 3

Calculate the annual incidence rate of influenza-associated SARI using the formula:

Equation 7: Calculating annual incidence rates

$$\text{Annual influenza-associated SARI incidence rate (IR)} = \frac{\text{Total number of influenza-associated SARI cases}}{\text{Mid-year catchment population for the sentinel site}} \times 100\,000$$

If the gender-specific incidence rates and gender-specific population data from the census are available, then the number of new cases of influenza-associated SARI (by gender) can be calculated.

If data on the population denominator are not available by the age ranges specified in this manual, then you may have to calculate incidence rates by the age ranges for which data are available.

Example

At a sentinel surveillance site, 100 cases of influenza-associated SARI cases were identified between 1 January 2010 and 31 December 2010. The distribution of cases is shown in Table 7. The population denominator for sentinel site S has been estimated in Table 6 previously. The annual incidence of influenza-associated SARI at sentinel site S for year 2010 is then calculated as shown in Table 7.

Table 7: Estimation of incidence rate of influenza-associated SARI at sentinel site S catchment area

Age group	<6 months	6 months to <1 year	1 to <2 year	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of influenza-associated SARI for A(H1N1)	11	8	11	5	4	2	3	8
(b) Number of cases of influenza-associated SARI for A(H3N2)	6	4	7	2	1	1	2	6
(c) Number of cases of influenza-associated SARI for influenza B	5	3	4	1	0	1	1	4
(d) Number of cases of SARI positive for other human influenza viruses	0	0	0	0	0	0	0	0
(e) Total number of cases of influenza-associated SARI for all human influenza viruses = (a)+(b)+(c)+(d)	22	15	22	8	5	4	6	18
(f) Estimated catchment population for sentinel site S	920	900	1820	5460	13 150	24 450	2000	1500
(g) Incidence rate of influenza-associated SARI in catchment population of sentinel site S in year 2010 (per 100000 population) = [(e)/(f)] x 100 000	2391	1667	1209	147	38	16	300	1200

In this example, for simplicity we have not calculated the gender-specific incidence rates (i.e. incidence rates separately for males and females) although these can be done in a similar manner if gender-specific case counts and gender-specific population data are available. To calculate this information by gender, create the same table for males and females to carry out the calculations of incidence.

If the catchment population for sentinel site S is representative of the population in the district where the site is located (i.e. the population accessing healthcare at sentinel site S is not very different in

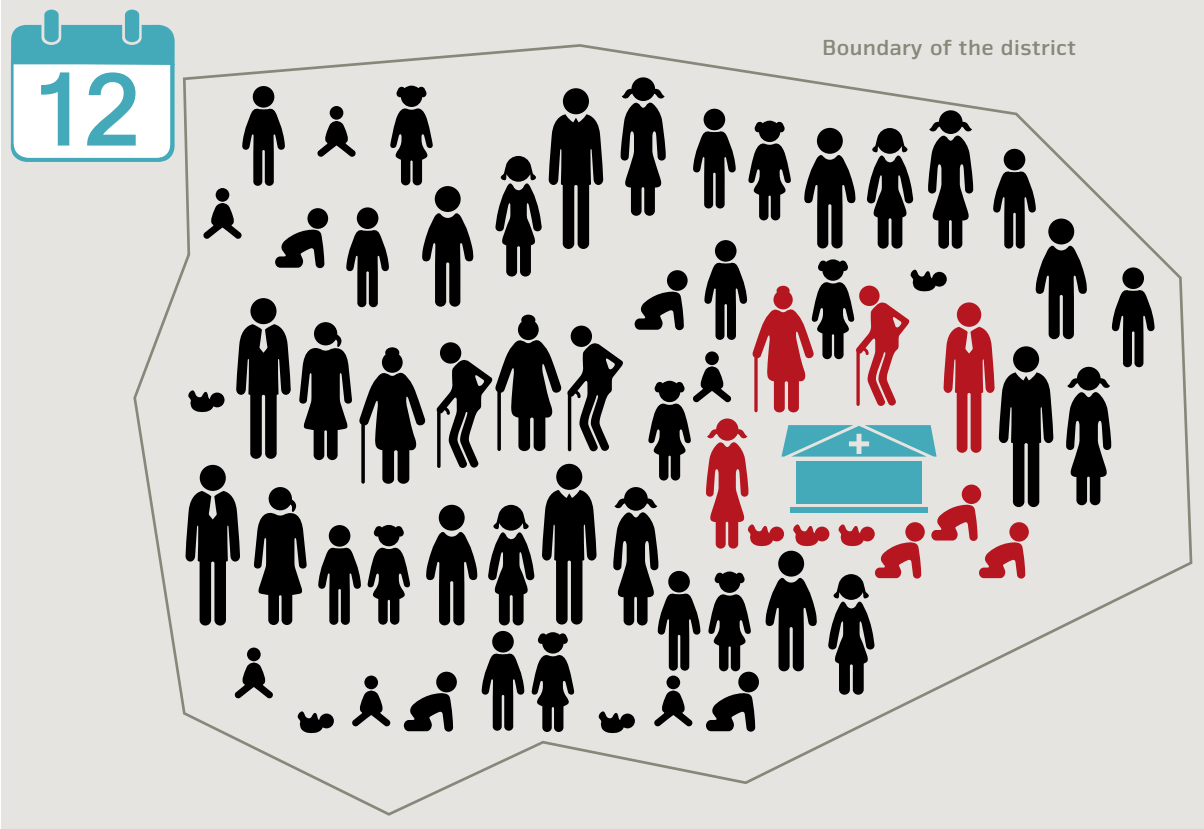
your opinion to the remaining population in the district with regard to demographic characteristics and risk factors), then we can assume that this rate is the same throughout the district.

Step 4

In step 4, we estimate the actual number of new cases of influenza-associated SARI in the district, based on the incidence rate in the catchment area of the sentinel site, by extrapolating to the whole district.

Obtain the **data for the population of the district** in which the sentinel site is located from the census records by age group, (and ideally by gender) as detailed in step 4 of section 3.4.3.

Census population:



Step 5

Estimate the **number of new cases in the district** for the year by using the formula in Equation 8.

Equation 8: Estimating number of new cases

Annual estimated number of new cases of influenza-associated SARI	=	Incidence rate (IR) of influenza-associated SARI for sentinel catchment area	X	District Population at midyear

If the gender-specific incidence rates for influenza-associated SARI are very different, what could be the possible reasons? Does this finding make sense for the population? Is it possible that there is a gender bias for hospitalization in your area?[48]

Continuing further with this example, the number of new cases of influenza-associated SARI in the entire district where the sentinel site is located for the year 2010 can then be calculated on the basis of the district population given in Table 6 and the incidence rates for the catchment population of the surveillance site calculated in Table 8.

Table 8: Estimating the number of new cases of influenza-associated SARI for entire district

Age group	0 to <6 months	6 months to <1 year	1 to <2 year	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(g) Incidence rate of influenza-associated SARI in catchment population of sentinel site S in year 2010 (per 100000 population) = [(e)/(f)] x 100 000 (from Table 7)	2391	1667	1209	147	38	16	300	1200
(h) Population of whole district where sentinel site is located	1825	1775	3600	10 800	26 000	49 000	4000	3000
(i) Number of new cases of influenza-associated SARI in whole district in year 2010 = (g x h)/100 000	44	30	44	16	10	8	12	36

Now, apply the checklist in Appendix WS3 to the data from your SARI sentinel site to assess it for quality and relevance.

If the data are suitable, then input the data for your sentinel site in Appendix WS6 and estimate the incidence rates of influenza-associated SARI for your site.

3.7. Estimating the proportion of SARI cases attributable to influenza when denominator population is not available

Very often, the data on the denominator population for a sentinel site cannot be estimated because the catchment area cannot be defined, discharge data are not available, or there may be a very large number of healthcare providers in the area thus making it extremely difficult to conduct a HAS. In such situations, we may be **unable** to calculate an incidence rate accurately. However, we can calculate the proportion of all hospital admissions that are influenza-associated.

Step 1:

Calculate the proportion of SARI cases that are influenza-associated by dividing the number of influenza-positive SARI cases by the total number tested each epidemiologic week or month during a calendar year:

Equation 9: Calculating the proportion of influenza-associated SARI (%)

$$\text{Proportion of influenza-associated SARI (\%) month or week} = \frac{\text{Number of influenza-positive SARI cases by month or week}}{\text{Total number of SARI cases tested by month or week}} x100$$

Step 2:

Obtain number of **all SARI cases admitted to the sentinel site in the same year from a chart review**. This will include SARI cases that may not have been selected by the sampling procedure for testing.

For these data, hospital records from **all the wards where SARI cases are likely to be admitted or where surveillance was being carried out** (e.g. paediatric wards, adult general medicine wards, adult respiratory medicine wards, geriatric medicine wards, paediatric ICU, respiratory ICU etc.) would be needed. Where possible, count the cases based on their unique hospital identification number allotted at the time of admission so as to avoid double counting.

Step 3:

Calculate the annual number of influenza-associated SARI cases among all admissions at the facility by multiplying the influenza-associated proportion times all SARI cases admitted. Where possible these calculations should be carried out by epidemiologic week or month. This assumes that there has been no bias in the selection of cases for testing and that all untested cases have similar demographic and other characteristics as those that were tested.

Equation 10: Calculating total number of influenza-associated SARI cases

$$\text{Total number of influenza-associated SARI cases} = \sum_{k=1}^{n} \text{Proportion influenza-associated SARI by month or week} \times \text{Total SARI cases admitted by month or week}$$

n=number of month or weeks available

Step 4:

Calculate the percentage of all hospital admissions that are influenza-associated by dividing the number of SARI-associated admissions by the total number of admissions at the facility each epidemiologic week or month for the same calendar year or time period for burden estimation. Another way to think about this percentage is the "**proportional contribution of influenza-associated SARI to all hospital admissions"**

Equation 11: Calculating the proportional contribution of influenza-associated SARI to all hospital admissions

$$\text{Percentage of all admissions that are influenza-associated} = \frac{\text{Total number of influenza-associated SARI cases}}{\text{Total number of hospital admissions among all wards in same year}} x100$$

Example

In a district, 19 cases of influenza were identified in SARI cases at sentinel site S between 1 January 2010 and 31 December 2010. The population for sentinel site S is not known. The annual proportion of influenza-associated SARI at sentinel site S and the proportional contribution of influenza-associated SARI to all hospital admissions are then calculated as shown in Table 9.

Table 9: Proportion of Influenza-associated SARI cases at sentinel site S in the year 2010

Age group	0 to <6 months	6 months to <1 year	1 to <2 year	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Total number of cases of SARI positive for human influenza viruses (all types and subtypes)	4	3	2	1	1	1	2	5
(b) Total number of SARI cases tested for influenza	22	15	22	8	5	4	6	18
(c) Proportion of influenza-associated SARI cases in year 2010 (%) = [(a)/(b)] x 100	18%	20%	9%	12%	20%	25%	33%	28%
(d) Total number of SARI cases (from all hospital wards likely to admit SARI cases and includes those cases not tested for influenza or negative for influenza in laboratory tests)	500	510	800	400	700	1200	600	800
(e) Estimated number of influenza-associated SARI cases = [(c) x (d)]	91	102	72	50	140	300	198	224
(f) Total number of hospital admissions at sentinel site S in 2010	2500	2800	4000	5000	10 000	15 000	8000	3000
(g) Proportional contribution of influenza-associated SARI to all hospital admissions in 2010 = [(e)/(f)] x 100	4%	4%	2%	1%	1%	2%	3%	7%

In this example, we have not calculated proportions separately for males and females. These can be done in a similar manner if gender-specific case counts and gender-specific inpatient data on SARI are available, however as the numbers of cases get smaller, the results may be less meaningful. Combining several years' data will help to keep the data robust. If several cells have very small numbers or 0's adding strata to have larger numbers before extrapolating might be necessary.

Now, apply the checklist in Appendix WS3 to the data from your SARI sentinel site to assess it for quality and relevance.

If the data are suitable, then input the data for your sentinel site in Appendix WS7 and estimate the proportion of influenza-associated SARI for your site.

What are the limitations of disease burden estimation using data lacking a population denominator?

One major limitation of this sort of burden estimate is that it is not possible to quantify and report an estimated number of cases of influenza-associated SARI as could be done if the denominator population was unknown. However, these data are nevertheless valuable. You can estimate the proportional contribution of influenza-associated SARI to all-cause hospitalization and compare that with the burden of other diseases.

Can you think of a possible way to estimate the number of cases of influenza-associated SARI from these data?

If country specific rates for SARI (or their proxy: e.g. hospitalized severe ALRI and pneumonia and influenza ICD-10 J codes 9–18) are available, then it is possible to estimate the number of cases of influenza-associated SARI from these estimated proportions.

Equation 12: Calculating number of estimated new cases of influenza-associated SARI in a calendar year.

Number of estimated new cases of influenza-associated SARI in a calendar year in a country	=	Proportion of laboratory confirmed influenza- SARI cases in the calendar year	X	Estimated annual number of new SARI cases in the country

3.8. Calculating a confidence interval for the estimates

The estimates for incidence of influenza-associated SARI or proportion of influenza-associated SARI discussed above are based on cases identified at a sentinel site/hospital which is by definition a sample of the total population and not the entire population in the catchment area. However, we are extrapolating the results based on this sample population to the entire population of the catchment area. The true rate or proportion in the population is likely to be different from what we have estimated. Though we cannot identify the true incidence or proportion in the population, we can put an uncertainty range around our estimates, within which the mean true incidence is likely to lie if this variation from the true incidence was due to random chance alone. The most common way of defining the uncertainty range is by expressing the 95% confidence interval (CI). If we conducted repeated **random** sampling from the same population over and over again, then 95% of the time, the estimated rate or proportion in the sample population would lie within two standard errors above or below the true rate in the population. This interval of two standard deviations above and below the estimated rate or proportion is called a 95% CI. This means that there is a 95% probability that this interval contains the true population rate, but a 5% probability that it does not.[49]

There are however, other sources of error which contribute to the difference in the estimated rate in the sample population and the true rate in the population, such as confounding, measurement errors, selection biases etc. For example, it is possible that some had falsely negative results on the laboratory tests or were not reported as SARI because of a misunderstanding of the case definition by the healthcare worker. On the other hand, it is also possible that we may have misclassified some cases not having influenza as having the disease because of a false positive test.

The 95% CI accounts only for the random sampling variation and does not account for misclassification errors and other biases we have discussed before. Thus, the true uncertainty in our estimated rates or proportions is greater than what can be expressed in a standard 95% CI.

Step 1: Identify the number of cases of influenza-associated SARI (i.e. the case count). We will call this 'd'.

Step 2: Calculate the square root of 'd'.

Step 3: Calculate the error factor (EF)[49, 50] by taking the exponentiation of 1.96 divided by the square root of 'd'.

Equation 13: Calculating the error factor

$$\mathbf{EF} = e^{(1.96/\sqrt{d})}$$

"e" indicates an exponentiation function

Step 4: Calculate the range of the 95% CI by dividing the rate or proportion by the error factor to the rate or proportion and multiplying that value by the error factor.

Equation 14: Calculating the 95% confidence interval

95% CI = [(rate (or proportion) / EF) to (rate (or proportion) x EF)]

Lower 95% CI Bound: rate (or proportion) divided by the error factor (EF)

Upper 95% CI Bound: rate (or proportion) multiplied by the error factor (EF)

Example

In a district, 100 cases of influenza were identified in SARI cases at sentinel site S between 1 January 2010 and 31 December 2010. The distribution of cases and the annual incidence of influenza-associated SARI at the sentinel site for the year 2010 have been shown in Table 7. Now, calculate the 95% CI for the incidence rate using the above-mentioned formula (Table 10).

Table 10: Calculating confidence interval for the incidence of influenza-associated SARI at sentinel site S1

Age group	0 to <6 months	6 months to <1 year	1 to <2 year	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Total number of cases of SARI positive for influenza viruses (all types and subtypes), denoted as 'd' above	22	15	22	8	5	4	6	18
(b) Estimated population in the catchment area for sentinel site S	920	900	1820	5460	13 150	24 450	2000	1500
(c) Annual incidence rate of influenza-associated SARI (per 100 000 population) = [(a)/(b)] x 100 000	2391	1667	1209	147	38	16	300	1200
(d) EF = $e^{(1.96/\sqrt{a})}$	1.5	1.7	1.5	2	2.4	2.7	2.2	1.6
(e) Lower 95% confidence limit for annual incidence rate of influenza-associated SARI (per 100 000 population) = (c)/(d)	1574	1005	796	74	16	6	135	756
(f) Upper 95% confidence limit for annual incidence rate of influenza-associated SARI (per 100 000 population) (c) x(d)	3631	2765	1836	294	91	43	668	1905

While estimating the uncertainty range, we have assumed that there is no bias in the sampling technique. If the sample was biased in some way, then the calculated rate or proportion would be false and the CI will be meaningless with the calculated rate or proportion for the total population being too high or too low as a result of the bias. The problem of sampling bias is in no way solved by adding a confidence interval to the figure. The confidence interval only shows the possible influence of chance or sampling error. It cannot deal with the methodological issues in sampling.

Now input the data from your surveillance site in Appendix WS12 and calculate the confidence interval for your estimates.

Summary

In this chapter, we have demonstrated how to estimate the disease burden when the denominator population is available, as well as when it is not. Although the strength of the evidence for disease burden and interpretation of the results differs by the kind of data used, any data which has a reasonably stable base over time can help in making valuable inferences regarding influenza disease

burden. Since all burden estimates are built on extrapolating results based on data from a sample population, it is advisable to express an uncertainty range (e.g. 95% CI) for these estimates to account for random error in sampling. The true uncertainty range is considerably larger than what is expressed in a 95% CI as this is influenced by the various biases in the included data and extrapolating from a small sample to a larger population.

04

Burden estimation for specific risk groups

In Chapter 3, we discussed how to estimate disease burden from SARI surveillance data. There, we had only focussed on influenza morbidity in the general population. Often, it is important to estimate and report the disease burden for groups which are more vulnerable for severe disease outcomes. While in the previous chapter, we have discussed how to report disease burden estimates stratified by age groups, and thus covered two of the most vulnerable populations, young children and the elderly, we have not discussed how to estimate and report the burden estimates for other vulnerable populations (e.g. pregnant women; persons with chronic medical conditions like diabetes, asthma, chronic liver disease, chronic kidney disease, chronic liver disease, COPD; and HIV etc.). Persons with these pre-existing conditions have independent risk factors for complications as a result of influenza illness.

After completing this chapter you will be able to:

1. *Estimate the influenza disease burden among pregnant women*
2. *Assess the strength of association between hospitalisation in influenza-associated SARI cases and presence of chronic disease conditions*
3. *Assess the strength of association between mortality in influenza-associated SARI cases and presence of chronic disease conditions*

4.1 Influenza-associated SARI in pregnant women

Along with young children and the elderly, pregnant women constitute an important vulnerable population for influenza. Influenza in a pregnant woman not only affects the mother but also the foetus. Maternal influenza has been demonstrated to result in preterm deliveries.[51] Premature babies are at an increased risk for a number of severe childhood morbidities (especially in the early years of life). Estimation of the incidence of influenza-associated SARI in pregnant women will assist in informing national maternal influenza vaccination policy which can reduce disease burden in both mother and child.[34]

Method

Step 1: Obtain the number of cases of influenza-associated SARI among pregnant women in a given year (12-month period).

Step 2: Estimate the total number of pregnant women in the catchment area in a given year. This is based on the number of live births and assumes that the woman is pregnant for about 40 weeks. Note that these calculations do not take into account multiple births (twins and triplets), miscarriages, abortions, still births, and premature deliveries. As such it is an approximation. Overall, this estimate is likely to be a reasonable one.

Step 2a: Obtain data on the total population in the catchment area. See section 3.4.2 for details on determining catchment population. Let us denote this as 'a'.

Step 2b: Obtain data on the crude birth rate (per 1000 population) in the area. *If local data are not available, use state / province/ region or national data and assume the rate is the same in the catchment area.* Let us denote this as 'b'.

Step 2c: Then the number of live births in a year.

Equation 15: Calculating number of live births

$$\mathbf{c} = \frac{(a \times b)}{1000}$$

Step 2d: Then the estimated number of total pregnancies in a year[2].

Equation 16: Estimating the number of total pregnancies

$$\mathbf{d} = c \times 0.77$$

Step 3:

Equation 17: Incidence of influenza-associated SARI in pregnant women

$$\text{Incidence of influenza-associated SARI in pregnant women (per 100000 population)} = \frac{\text{Annual number of cases of influenza-associated SARI in pregnant women}}{\text{Estimated number of total pregnancies in the year}} \times 100\,000$$

Example

In a district, 100 000 people access healthcare at sentinel site S. The crude birth rate (CBR) of the state in which district is located is 45 per 1000 population. Ten cases of influenza-associated SARI were identified among pregnant women in the year 2010. The incidence of influenza-associated SARI in pregnant women in 2010 is approximately 289 per 100 000 pregnant women (Box 1).

Box 1: Estimation of influenza burden in pregnant women

(a) Crude birth rate per 1000 population	45
(b) Population of catchment area	100 000
(c) Estimated number of live births in a year = (a) x (b)	4500
(d) Estimated number of pregnant women in the catchment area in a year = (c) x 0.77	3465
(e) Number of cases of influenza-associated SARI in pregnant women in 2010	10
(f) Incidence of influenza-associated SARI in pregnant women in 2010 (per 100 000 pregnant women) = [(e) / (d)] x100 000	289

Now input the data from your surveillance site in Appendix WS13 and calculate the incidence of influenza-associated SARI in pregnant women for your site.

A useful comparison to understand the risk associated with pregnancy is to do the same calculation for non-pregnant women of child-bearing age. Calculate the incidence of influenza-associated SARI for non-pregnant women in the same age range as the pregnant women in the SARI cases. The calculation would be the same as for pregnant women except the denominator is the total number of women in the population of that age (typically, age 15–50 years is a useful group) less the number of pregnant

2 We have used an adjustment factor of 0.77 to acknowledge that the period at risk (pregnancy) is only for (a maximum of) 40 of the 52 weeks in a year.

women calculated using Equation 16 above. The ratio of incidence in pregnant women to incidence in non-pregnant women is called the Relative Risk or Risk Ratio and essentially describes the magnitude of increased risk of severe influenza associated with pregnancy. The population denominator of non-pregnant women, however, must come from the same catchment population as the estimated number of pregnant women.

Equation 18: Calculating incidence of influenza-associated SARI in non-pregnant women

$$\text{Incidence of influenza-associated SARI in non-pregnant women} = \frac{\text{Annual number of cases of influenza- associated SARI in women aged 15-50 years}}{\text{Total number of non-pregnant women aged 15-50 years in the catchment population of the surveillance site}}$$

AND

Equation 19: Calculating relative risk of severe influenza associated with pregnancy

$$\text{Relative risk of severe influenza associated with pregnancy} = \frac{\text{Incidence of influenza-associated SARI in pregnant women}}{\text{Incidence of influenza-associated SARI in non-pregnant women}}$$

4.2 Influenza-associated SARI with co-morbidities

Influenza is known to be more likely to have a severe outcome in those with certain pre-existing chronic medical conditions.[52-56] A list of select chronic medical conditions, which are established or suspected risk factors for severe influenza, is provided in Appendix A5. These include diabetes, asthma, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), immunodeficiency including HIV, and severe genetic anaemias such as sickle cell disease or thalassemia major.

A simple tabulation of the percentage of influenza-associated SARI cases with each of the risk factors is a useful way to summarize and review the data. However, it is more informative to understand the magnitude of the increased risk associated with the condition in a similar way as was done for pregnancy in the example in section 4.1.

To accomplish this, a comparison group is needed to understand how frequently these conditions occur in the general population so as to be able to know if they are occurring more frequently in severely ill influenza patients. There are two possibilities for comparison. One would be to compare the proportions of each chronic condition among influenza-associated SARI cases to the rates at which the conditions occur in the same population.[33] However, these population data are often not available. Alternatively, the rates of these conditions in non-severe influenza, influenza-associated ILI, can be used as a comparison, if the information on chronic conditions has been collected on the ILI cases in the same way as in SARI cases. If a condition occurs much more commonly in SARI cases than it does in the general population or in ILI cases, that indicates that persons with that condition are at increased risk of severe disease. The ratio of the rate at which a condition occurs in each of these two groups

is known as an odds ratio (OR) and essentially provides the same measure of risk associated with a condition as the relative risk described above for pregnancy.

4.2.1 If co-morbidity status has not been determined in all cases

One way to identify the importance of a risk factor in severe disease associated with influenza would be to look at the distribution of the risk factor among influenza-associated SARI cases compared to the population of the SARI sentinel site. This can be done by analysing the prevalence of the risk factor among SARI cases (in a given age group) positive for influenza and comparing this with the prevalence of this risk factor (e.g. diabetes) in the general population.

Equation 20: Calculating the proportion of influenza-associated SARI cases having a risk factor

$$\text{Proportion of influenza-associated SARI cases having a risk factor (e.g. diabetes)} = \frac{\text{Number of SARI cases positive for influenza with diabetes}}{\text{Total number of all SARI cases positive for influenza}}$$

Now compare this with the prevalence of the risk factor (diabetes) in the population at the SARI sentinel site.

Example

For example, if 0.25 (or 25%) of all SARI cases (in the age group ≥ 65 years) positive for influenza had diabetes, and the prevalence of diabetes in the general population in the age group ≥ 65 years was 0.1 (or 10%), then having diabetes may place a person at an increased risk of influenza-associated severe disease.

The limiting factor for this analysis is usually the absence of data on risk factor prevalence in the general population by age group. Even then, data on the proportion of influenza-associated SARI cases having the risk factor would help us appreciate the importance of the risk factor in influenza-associated SARI compared to other risk factors and will help in planning targeted interventions for high-risk groups.

4.2.2 If frequency of co-morbidity condition is known in ILI cases

As an alternative, when population prevalence of a risk factor is not known, mild influenza cases from the ILI surveillance system can be used as a comparison group if these data have been collected in the same way as for SARI cases. This involves calculating an odds ratio to estimate the magnitude of the association between the risk factor and hospitalization for severe disease. The odds ratio can be used to understand risk in the same way as the relative risk of incidence described in the previous section on pregnancy.

Odds Ratio The odds ratio (OR) for severe disease in the presence of a risk factor is the ratio of odds of having the risk factor given severe disease relative to the odds of having the risk factor given mild disease. This would indicate the degree of increased risk of severe influenza associated with having a chronic medical condition. For example, we could look at the odds of having diabetes in those with severe disease (influenza-associated SARI) compared to the odds of having diabetes in those who do not have severe disease (influenza-associated ILI).

It is often easier to understand odd ratios by drawing a standard 2x2 table. Such tables are commonly used in epidemiology. To construct such a table for diabetes,

Step1: Identify number of cases of influenza-associated SARI with diabetes (a)

Step 2: Identify number of cases of influenza-associated ILI with diabetes (b)

Step 3: Identify number of cases of influenza-associated SARI without diabetes (c)

Step 4: Identify number of cases of influenza-associated ILI without diabetes (d)

Step 5: Place all of these data in a 2x2 table as shown below

	With diabetes	Without diabetes
Influenza-associated SARI	*a*	*b*
Influenza-associated ILI	*c*	*d*

Equation 21: Calculating odds ratio (using diabetes as an example)

$$\text{OR for diabetes in influenza-associated SARI} = \frac{\text{Number of influenza-associated SARI cases with diabetes}}{\text{Number of influenza-associated ILI cases with diabetes}} \Big/ \frac{\text{Number of influenza-associated SARI without diabetes}}{\text{Number of influenza-associated ILI without diabetes}} = \frac{(a/b)}{(c/d)}$$

An odds ratio that is equal to 1 with a p-value that is greater than 0.05 indicates that there is no association between your risk factor of interest and the severe outcome (influenza-associated SARI). An odds ratio that is greater than 1 and with a p-value that is less than 0.05 indicates that your risk factor of interest is statistically associated with the more severe outcome and implies that the risk factor results in a higher risk of the outcome. An odds ratio that is less than 1 and with a p-value that is less than 0.05 indicates that your risk factor of interest is statistically associated with the severe outcome, but in this case it infers that the risk factor results in a lower risk of the outcome.

Now input the data for influenza-associated SARI in those with chronic diseases at your sentinel site in Appendix WS14.

In order to use influenza-associated ILI as a comparator group for non-severe disease it is important that the following criteria are met:

8. **ILI cases be selected for specimen collection using a nonbiased sampling scheme (as advised in the *WHO Global Epidemiological Surveillance Standards for Influenza*. If convenience sampling schemes are used, those with chronic diseases like diabetes may be more likely to be selected for specimen collection.**
9. **The ILI cases must be from approximately the same catchment area as the SARI cases.**

4.3 Mortality in influenza associated SARI

Comprehensive disease burden estimation requires estimating the burden associated with mortality as well as morbidity (Chapter 1). However, it is extremely challenging to estimate mortality associated with influenza. As discussed earlier, the nonspecific clinical syndrome associated with influenza infection requires that testing be done to be sure that a case is truly due to influenza. Trying to count the number of deaths occurring in patients who have tested positive for the disease requires a huge number of patients to be followed. Traditionally, countries in the temperate region have relied on modelling approaches that relate the seasonal occurrence of deaths from vital statistics registers to the seasonal occurrence of influenza viruses from surveillance data rather than direct counting of the fatal cases.[57, 58] However, these methods are not as useful in areas where the influenza viruses circulate throughout the year during a less demarcated and predictable epidemic period of viral activity. Assessments based solely on peak epidemic periods will underestimate the burden of influenza with these methods [59]. Modelling methods are beyond the scope of this manual, therefore we will limit ourselves to analysing the in-hospital case fatality ratio among SARI cases positive for influenza.

4.3.1 In–hospital case fatality ratio

In-hospital case fatality ratio (hCFR) is the proportion of hospitalized cases that are fatal. As a large proportion of influenza deaths may occur outside the hospital, any mortality estimate based on hospital-based case fatality ratio for influenza-associated SARI is likely to be a significant underestimate of total deaths attributable to influenza. Nevertheless, hCFR data are helpful to:

1. Assess the relative virulence of the circulating influenza viruses
2. Identify vulnerable population groups (by age, gender, or risk factor status)
3. Provide an evidence base for improving patient management protocols and developing new therapeutic regimens
4. Provide baseline data, if tracked over a period of time, with which to compare the severity of different seasons or the behavior of new viruses
5. Provide additional information about the risk associated with underlying medical conditions
6. Describe the relative severity of influenza compared to other causes of SARI by comparing the hCFR of influenza positive and SARI cases associated with other pathogens

First, we will estimate hCFR in influenza-associated SARI cases.

Step 1: Identify the number of deaths in cases with influenza-associated SARI

Step 2: Identify the number of cases of influenza-associated SARI

Step 3: Calculate hCFR

Equation 22: Calculating the in-hospital case fatality ratio

$$\textbf{hCFR (\%)} = \frac{\text{Number of deaths in cases with influenza-associated SARI}}{\text{Number of cases of influenza-associated SARI}} \times 100$$

It would be useful to analyse and report age-specific hCFR for influenza-associated SARI. Again, it is recommended that hCFRs be reported for the following age groups: 0 to <6 months, 6 months to <1 year, 1 to <2 year, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years and ≥ 65 years, however some age groups can be combined based on availability of sufficient age-specific data. If you would like to calculate a CI for this estimate, please refer to the formulas in section 3.8.

Example

At a sentinel site S, 150 cases of influenza-associated SARI were hospitalized in 2010. Ten of these cases died in hospital. While the overall hCFR is 6.7%, the age-specific hCFR is highly variable (Table 11).

Table 11: **In-hospital case fatality ratio for influenza-associated SARI at sentinel site S2**

Age group	Number of deaths in cases with influenza-associated SARI (a)	No. of cases of influenza-associated SARI (b)	hCFR (%) (a/b) x 100
0 to <6 months	2	10	20
6 months to <1 year	1	10	10
1 to <2 year	1	20	5
2 to <5 year	0	10	0
5 to <15 years	0	20	0
15 to <50 years	0	20	0
50 to <65 years	2	40	5
≥65 years	4	20	20
Overall	10	150	6.7

Now, input the data from your surveillance site in Appendix WS15 and calculate the hCFR for influenza-associated SARI for your site.

As noted above, this hCFR only reflects the proportional mortality in hospitalized cases at the sentinel sites. This will be different from the true CFR, especially if a large proportion of deaths occur at home. As with hospital burden estimates, it will also not reflect deaths due to other severe influenza presentations such as acute myocardial infarction or other chronic health conditions that may be triggered by influenza.

4.3.2 Proportional contribution of influenza to SARI mortality

Another useful measure could be to look at the proportional contribution of influenza to SARI mortality. These data would be helpful in informing:

1. The relative importance of influenza in SARI mortality which would be useful while setting priorities for disease burden reduction
2. Assessing the impact of vaccination programs

Equation 23: Calculating the proportion of SARI mortality associated with influenza

$$\text{Proportion of SARI mortality associated with influenza (\%)} = \frac{\text{Number of deaths in cases with influenza-associated SARI}}{\text{Number of deaths in all SARI cases}} \times 100$$

4.3.3 Comparison of case fatality ratios in vulnerable groups with the healthy population

It would be useful to compare the hCFRs in those with special conditions (e.g. pregnancy and chronic medical conditions like diabetes, COPD etc.) and positive for influenza against healthy individuals with influenza in the same age range. When the risk group under consideration are pregnant women, the comparison would be with non-pregnant women.

Equation 24: hCFR for influenza-associated SARI in pregnant women (%)

$$\text{hCFR for influenza-associated SARI in pregnant women (\%)} = \frac{\text{Number of deaths from influenza-associated SARI in pregnant women}}{\text{Number of cases of influenza-associated SARI in pregnant women}} \times 100$$

Equation 25: hCFR for influenza-associated SARI with diabetes (%)

$$\text{hCFR for influenza-associated SARI with diabetes (\%)} = \frac{\text{Number of deaths in influenza-associated SARI cases with diabetes}}{\text{Number of cases of influenza-associated SARI with diabetes}} \times 100$$

Equation 26: hCFR for influenza-associated SARI in healthy individuals (%)

$$\text{hCFR for influenza-associated SARI in healthy individuals (\%)} = \frac{\text{Number of deaths in influenza-associated SARI cases without diabetes}}{\text{Number of cases of influenza-associated SARI without diabetes}} \times 100$$

For these data to be reflective of the true risk of mortality, it is important that the chronic medical condition status is systematically assessed in ALL cases. If this were not the situation and only the very severe cases were checked for the presence of chronic medical conditions, then this would falsely inflate the hCFR.[60]

Summary

It is important to estimate the increased risk for hospitalization and mortality due to influenza-associated SARI in special population groups (e.g. pregnant women, individuals with co-morbidities etc.) who are vulnerable to severe influenza disease. The disease burden in these populations is likely to be much higher than in the general population. This will assist in initiating appropriate targeted interventions (preventive and curative) in these populations and thus provide a cost-effective option to reduce the overall influenza disease burden.

05

Using hospital discharge data for disease burden

It is possible that some hospitals conducting laboratory tests for influenza virus are not designated as sentinel sites for influenza surveillance. Data from these hospitals can be potentially very useful for influenza burden estimation. However, there are a few characteristics of the data that deserve special consideration. This section will describe the special considerations that need to be kept in mind when using hospital data from non-sentinel sites to estimate disease burden.

5.1 Special considerations for using hospital data

In Chapter 2, we discussed the general principles of identifying a data source and relevant data for extraction and reviewing the available data for quality and relevance. Applying these principles to hospitals, you will find that in addition to identifying an appropriate source of data, it will also be necessary to use standard diagnoses groups as assigned by clinicians rather than cases that were identified as SARI in a surveillance system.

Reminder

Identifying data sources	Appropriate hospitals for influenza data • Are there any large hospitals in my area which have good electronic data coding systems and have not been designated as sentinel surveillance sites? • Do any of these hospitals routinely test for influenza virus among their eligible patients? • Do they record these data consistently and completely? If answers to all three questions are YES, then data should be collected from these hospitals.
Mapping case definitions	Hospitals which are not designated as SARI sentinel sites are unlikely to record a diagnosis of SARI. The cases that conform to the syndromic diagnosis of severe ALRI may be reasonable approximations to the case definitions for SARI. Severe ALRI would generally include pneumonia and, in the case of children, bronchiolitis. For hospitals that use ICD coding and have electronic databases of case data, a reasonable substitute for SARI would be to include all cases admitted to hospital with a respiratory disease code (ICD-10 J09-J22, ICD-9 480-488) as a primary cause for admission. (Appendix A3). (http://www.icd9data.com/2011/Volume1/460-519/480-488/default.htm, http://apps.who.int/classifications/icd10/browse/2010/en#/J09-J18) In order for ICD-9 and ICD-10 coded data to be comparable between themselves as well as to data from influenza sentinel surveillance, it is important that these data are mapped to current WHO case definitions (Appendix A4). This will help in harmonization and interpretation of data.
Screening for available data	• Data availability by suggested age groups – 0 to <2 years – 2 to <5 years – 5 to <15 years – 15 to <50 years – 50 to <65 years – ≥65 years • Data availability by gender • Data availability for risk groups

Reviewing the data for quality and relevance	• Check for Completeness
	• Check for Representativeness
	• Check for Accuracy
	  – Laboratory confirmation
	  – Date of sample collection
	  – Residence
	• Assess for potential Bias
	  – from sampling schemes
	  – from diagnostic assays used
	  – from case definition

5.2 Extracting data

Extract the following data **by month and gender for persons from the hospital catchment area within each age group**:

Essential data

- Total number of all inpatients admitted to the hospital (excluding short stays i.e. admission <24 hours).
- Total number of new severe ALRI cases admitted to the hospital (includes all cases that were not tested for influenza virus)
- Number of severe ALRI cases from whom clinical specimens were collected (for laboratory confirmation of influenza)
- Number of severe ALRI cases which are influenza positive (for each type/sub-type of influenza virus)

Desirable data

- Number of severe ALRI deaths occurring at the hospital (includes severe ALRI deaths that are influenza-negative or where influenza testing was not carried out)
- Number of influenza-positive severe ALRI deaths occurring at the hospital (for each type/sub-type of influenza virus)
- Number of severe ALRI cases among pregnant women
- Number of influenza-positive severe ALRI cases among pregnant women
- Number of influenza-positive severe ALRI deaths among pregnant women occurring at the hospital
- Number of severe ALRI cases, influenza-positive severe ALRI cases, and influenza-positive severe ALRI deaths with at least one of the following chronic medical conditions (based on a physician's diagnosis)
  - Chronic obstructive pulmonary disease
  - Asthma
  - Diabetes
  - Chronic cardiac disease
  - Chronic liver disease

- Chronic renal disease
- Immunodeficiency, including HIV
- A severe genetic anaemia such as sickle cell disease or thalassemia major

Include only those cases that are resident of the catchment area of the hospital. If you are not sure of the catchment area, then define the catchment area as described in section 3.4.3.

5.3 Estimating disease burden

It is very likely that only a portion of admissions for respiratory disease belonging to the ICD categories listed previously will have been tested unless the hospital from which the data are being extracted is a study site. Therefore the most appropriate method for defining the numerator is described in section 3.3.2.

If the hospital is the only one providing care in the catchment area and the catchment population is known, then section 3.5 can be used for disease burden estimation without further adjustment. However, if the catchment population denominator has to be estimated, start with section 3.4.3.

Once the case count has been determined for the numerator and the catchment population for the denominator, calculate incidence of influenza-associated severe ALRI as described in section 3.6.

If it is not possible to estimate the population catchment area, then section 3.7 can be used to describe the proportion of severe ALRI admissions that are influenza associated.

Now, apply the checklist in Appendix WS3 to the data from your hospital to assess it for quality and relevance.

If the data are suitable, then input the data for your sentinel site in Appendix WS8/ WS9 and estimate the incidence or proportion of influenza-associated severe ALRI respectively for your site.

06

Disease burden estimation using ILI sentinel surveillance data

ILI is the milder end of the spectrum of influenza disease and is non-specific for influenza (for detailed description and case definition see Introduction). ILI sentinel surveillance is commonly conducted as part of influenza surveillance and sometimes is the only surveillance in some countries. As ILI sentinel data are the only influenza surveillance data available in some WHO Member States, we will briefly discuss how these data could contribute to influenza disease burden estimation.

What are the characteristics of ILI sentinel surveillance data?

Data from ILI sentinel surveillance are generally from patients seeking ambulatory care and are often based on a presumptive clinical diagnosis with little or no laboratory confirmation for influenza virus being conducted, except in a small proportion of patients. Since ILI is a fairly common condition, there are likely to be many providers of care in the community and at individual sites. In addition, it will likely be difficult to know with any degree of confidence what proportion of ILI cases are being captured by a sentinel site.

What are the limitations of ILI sentinel surveillance data?

- It is likely that the majority of mild influenza-associated disease will not report to any health facility for treatment and will either self-medicate or not use any treatment at all. Thus, ILI sentinel surveillance sites underestimate the ILI disease burden in the community. ILI surveillance data is more appropriately thought of as the burden of *medically attended* mild influenza-associated disease.
- Since the ILI symptoms are not specific for influenza (infection with other respiratory viruses results in similar symptoms), data from ILI surveillance in the absence of virological diagnosis are hard to interpret in terms of influenza-associated disease. Outside of the period of high transmission of influenza virus in a community, most ILI will be caused by another pathogen. Even in the period of influenza transmission, other viruses such as RSV will account for substantial portions of ILI in children, if the two viruses overlap in their respective seasons.
- In most situations, the population denominator for an ILI sentinel site may be challenging to estimate because of the large number of care providers in the community. Thus, only rarely can incidence rates of influenza-associated ILI be estimated. In most situations, burden estimation will need to be restricted to analysing the proportion of influenza-associated ILI.[61]

What are the possible uses of ILI sentinel surveillance data?

Though data from ILI sentinel surveillance have major limitations, nevertheless, these are useful for certain purposes; namely, to:

- Gauge the relative importance of ILI on ambulatory healthcare services
- Delineate the influenza season
- Identify unusual patterns of influenza
- Create a base for influenza-associated economic burden and influenza vaccine effectiveness estimates

After completing this chapter you will be able to:

1. *Use statistical techniques to adjust for missing data*
2. *Estimate the denominator population*
3. *Estimate the influenza disease burden in a population using data from ILI sentinel sites*

6.1 Identify data for disease burden estimation

In Chapter 2, we discussed the general principles of identifying a data source and relevant data for extraction and reviewing the available data for quality and relevance. Applying these principles to ILI sentinel sites, you will obtain the following:

Reminder

Identifying data sources	• ILI sentinel site
Screening for available data	• Data availability by suggested age groups – 0 to <2 years[3] – 2 to <5 years – 5 to <15 years – 15 to <50 years – 50 to <65 years – ≥65 years • Data availability by gender • Data availability for risk groups
Reviewing the data for quality and relevance	• Check for Completeness • Check for Representativeness • Check for Accuracy – Laboratory confirmation – Date of sample collection – Residence • Assess for potential Bias – from sampling schemes – from diagnostic assays used – from case definition

Once you have identified your data sources, screened for available data and assessed the data for quality and relevance, you will need to **extract the relevant available data**.

6.2 Extracting data

Extract the following data for each of the age groups and by gender (if desired):

Essential data

- Total number of outpatient visits at the sentinel site by week

3 Where available, age groups can be further broken down

- Total number of ILI cases diagnosed among outpatients by week
- Number of specimens submitted for laboratory confirmation of influenza virus by week
- Number of ILI cases with positive laboratory test for influenza virus by week

6.3 Estimating disease burden

6.3.1 Defining numerator and denominator

Reminder

Step 1: Obtain the numerator (case count)	• Data on case count are complete because all ILI cases have been tested for influenza. *Proceed to Step 2.* • Data on case count are incomplete because clinical specimens for laboratory diagnosis of influenza virus have not been collected from all the eligible ILI cases. *Adjust your case count to obtain the estimated number of ILI cases attributable to influenza if not all ILI cases were tested for influenza.*
Step 2: Obtain the denominator (population at risk)	• In some situations, it may not possible to estimate the denominator population for ILI sentinel surveillance site (catchment area cannot be defined). *Proceed to 6.3.3.* • Data on denominator population for the ILI sentinel surveillance site are readily available. *Estimate age and gender stratified population data if not available and if necessary, then proceed to 6.3.2.* • Define the catchment area by estimating the denominator catchment population for the clinic or hospital. Then estimate the age and gender stratified population data if necessary, then proceed to 6.3.2 • Data on denominator population for the ILI sentinel surveillance site are not readily available but can be estimated (where catchment area can potentially be defined)

As noted previously, ILI surveillance is carried out in ambulatory patients in outpatient/primary care clinics. **In most cases, the ILI sentinel surveillance sites may not have a population denominator that is known or knowable**. In such cases, we are unable to calculate an incidence rate. However, we can calculate the proportion of influenza-positive cases among all ILI cases if laboratory confirmation for influenza virus is conducted in at least a proportion of the ILI cases.

It is possible that many ILI sentinel surveillance sites select cases for testing using a convenience sampling strategy, such as choosing the first two ILI cases that come in each day. In this situation, the percentage of specimens testing positive for influenza will reflect the level of influenza activity in the community at the time and can be followed over time to establish seasonal baselines. However, the epidemiological characteristics of the cases selected are likely to be biased (see section 2.3.4) and not necessarily representative of the population at large.

6.3.2 Estimating disease burden with population denominators

In the case that data on denominator population for the ILI sentinel surveillance site are available or can be estimated using the technique described in section 3.4.3., the method for estimating incidence of influenza-associated ILI would be similar to that for estimating the incidence of influenza-associated SARI (as discussed in 3.5).

Use Appendix WS11 to input the data for your sentinel site and estimate the incidence of influenza-associated ILI at your site.

6.3.3 Estimating the proportion of ILI cases attributable to laboratory-confirmed influenza illness without population denominators

Step 1: Obtain data on case counts (i.e. number of ILI cases positive for influenza virus using laboratory tests) by the following age groups: 0 to <6 months, 6 months to <1 year, 1 to <2 year, 2 to <5 years, 5 to <15 years, 15 to <50 years, 50 to <65 years, ≥ 65 years.

Step 2: Obtain data on the number of ILI cases from whom clinical specimens were collected for diagnostic testing.

Step 3: Calculate the proportion of influenza-positive ILI. For convenience, we will express this proportion as a percentage (%).

Equation 27: Proportion of influenza associated ILI (%)

$$\text{Proportion of influenza-associated ILI (\%) by month or week} = \frac{\text{Number of influenza-associated ILI by month or week}}{\text{Number of ILI cases from whom clinical specimens were collected by month or week}} \times 100$$

Step 4: Obtain the number of total outpatient visits and ILI outpatient visits (from all clinics) at the ILI sentinel site in the same year. For this data, clinic records must be searched for the outpatient clinics where ILI cases are likely to seek care (e.g. paediatric outpatient department, adult general medicine outpatient department, adult respiratory clinic, paediatric respiratory clinic, geriatric clinic, etc.)

Step 5: Estimate the annual number of influenza-associated ILI cases at the sentinel site.

Equation 28: Estimating the number of influenza-associated ILI

$$\text{Estimated number of influenza-associated ILI} = \sum_{k=1}^{n} \text{Proportion influenza-associated ILI by month or week} \times \text{Total Number of ILI cases by month or week}$$

n=number of month or weeks available

Step 6: The burden of influenza on the ambulatory healthcare system can be gauged by estimating the proportion of influenza-associated ILI cases among all outpatient visits.

Equation 29: Proportional contribution of influenza-associated ILI to annual outpatient load

$$\text{Proportional contribution of influenza-associated ILI to annual outpatient load (\%)} = \frac{\text{Estimated number of influenza-associated ILI visits in a calendar year}}{\text{Total number of outpatient visits at the sentinel site in the same year}} \times 100$$

Example

We will now illustrate this using a numerical example.

In a district (D), 5000 cases of ILI were seen at sentinel site S between 1 January 2010 and 31 December 2010. Of these, clinical specimens were collected for laboratory confirmation of influenza virus in a proportion of the cases. The distribution of ILI cases with laboratory confirmed influenza is shown in Table 12. The population for sentinel site S is not known. The estimated annual number of influenza-associated ILI cases at the sentinel site and proportional contribution of influenza-associated ILI to the annual outpatient load at sentinel site S is then calculated as shown in Table 12.

Table 12: Proportion of Influenza-associated ILI cases at sentinel site IS1 in the year 2010

Age group	0 to <6 months	6 months to <1 year	1 to <2 year	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
Number of cases of ILI positive for Influenza A(H1N1)pdm09 (a)	1	1	4	4	1	1	5	9
Number of cases of ILI positive for Influenza A(H3N2) (b)	0	0	2	3	0	1	5	6
Number of cases of ILI positive for Influenza B (c)	0	0	1	1	0	0	4	4
Number of cases of ILI positive for other human influenza viruses (d)	0	0	0	0	0	0	0	0
Total number of cases of ILI positive for human influenza viruses (all types and subtypes) (e) = (a)+(b)+(c)+(d)	1	1	7	8	1	2	14	19
Total number of ILI cases from who clinical specimens were collected (f)	10	15	30	50	91	100	100	100
Proportion of ILI cases from whom clinical specimens were collected for laboratory confirmation of influenza virus (%) (g) = [(e)/(f)) x100	10%	6.6%	23.4%	16%	1.1%	2%	14%	19%
Total number of ILI outpatient visits (from all clinics and includes those cases not tested for influenza or negative for influenza in laboratory tests) at sentinel site IS1 (h)	100	150	300	500	950	1000	1000	1000
Estimated number of number of influenza-associated ILI cases (i) = (g) x (h)	10	10	70	80	10	20	140	190
Total number of all outpatient visits at sentinel site IS1 (j)	1000	800	3000	4000	10 000	15 000	14 000	9500
Annual proportion of influenza-associated ILI to outpatient load at sentinel site (%) (k) = [(g)/(j)] x 100	1%	1.3%	2.3%	2%	0.1%	0.1%	1%	2%

Again, in this example, we have not calculated the gender-specific proportions (i.e. proportions separately for males and females) although these can be done in a similar manner if gender-specific case counts and gender-specific data on ILI and total outpatient visits (by different age strata) are available.

Now, input the data for your sentinel site in Appendix WS10 and estimate the proportion of influenza-associated ILI of all ILI cases and proportion of influenza-associated ILI seeking ambulatory care at your site.

What are the limitations of disease burden estimation using data lacking a population denominator?

One major limitation of this sort of burden estimate is that it is not possible to quantify and report an estimated number of cases of influenza-associated ILI as could be done if data on denominator population were available. Nevertheless, these data are still valuable. You can estimate the proportional contribution of influenza-associated ILI to ambulatory care and compare that with the burden of other diseases. Over time, baseline values for this proportion will also be established allowing a near real-time comparison of the severity or level of influenza activity to average previous seasons. A more detailed description of methods to establish baselines can be found in the *WHO Global Epidemiological Surveillance Standards for Influenza*.

Summary

In this chapter, we have learnt how to estimate the disease burden when data from ILI sentinel sites on the denominator population are not available. Though data from ILI sentinel surveillance have major limitations, nevertheless, these are useful for certain purposes; e.g. gaging the relative importance of ILI on ambulatory healthcare services; delineating "influenza season" (refer to section 8.3); and early identification of unusual patterns of influenza activity.

07

Estimating disease burden using data from multiple sentinel sites

In Chapters 3 to 6, we have discussed how to estimate influenza disease burden in a population using data from a single sentinel surveillance site or hospital. However, if there are multiple sentinel surveillance sites or hospitals in your country, you would want to utilize data from all sites to estimate the disease burden for the entire country.

7.1 Identifying data sources for national influenza disease burden estimates

For burden estimation at the national level, segregate the data from the three main sources- SARI sentinel surveillance, hospitals not designated as SARI sentinel sites, and ILI sentinel site. Though both SARI sentinel surveillance and hospital data provide estimates for the burden of severe respiratory disease associated with influenza, it would not be advisable to pool the hospital data with data from SARI sentinel surveillance as they might be using differing case definitions and protocols for sampling eligible cases.

7.2 Eligibility for pooling the burden estimates from different SARI sentinel sites or hospitals

Before pooling the disease burden estimates you will need to decide whether it is indeed advisable to pool these data.

Figure 6: **Flowchart for assessing eligibility of data for pooling disease burden estimates**

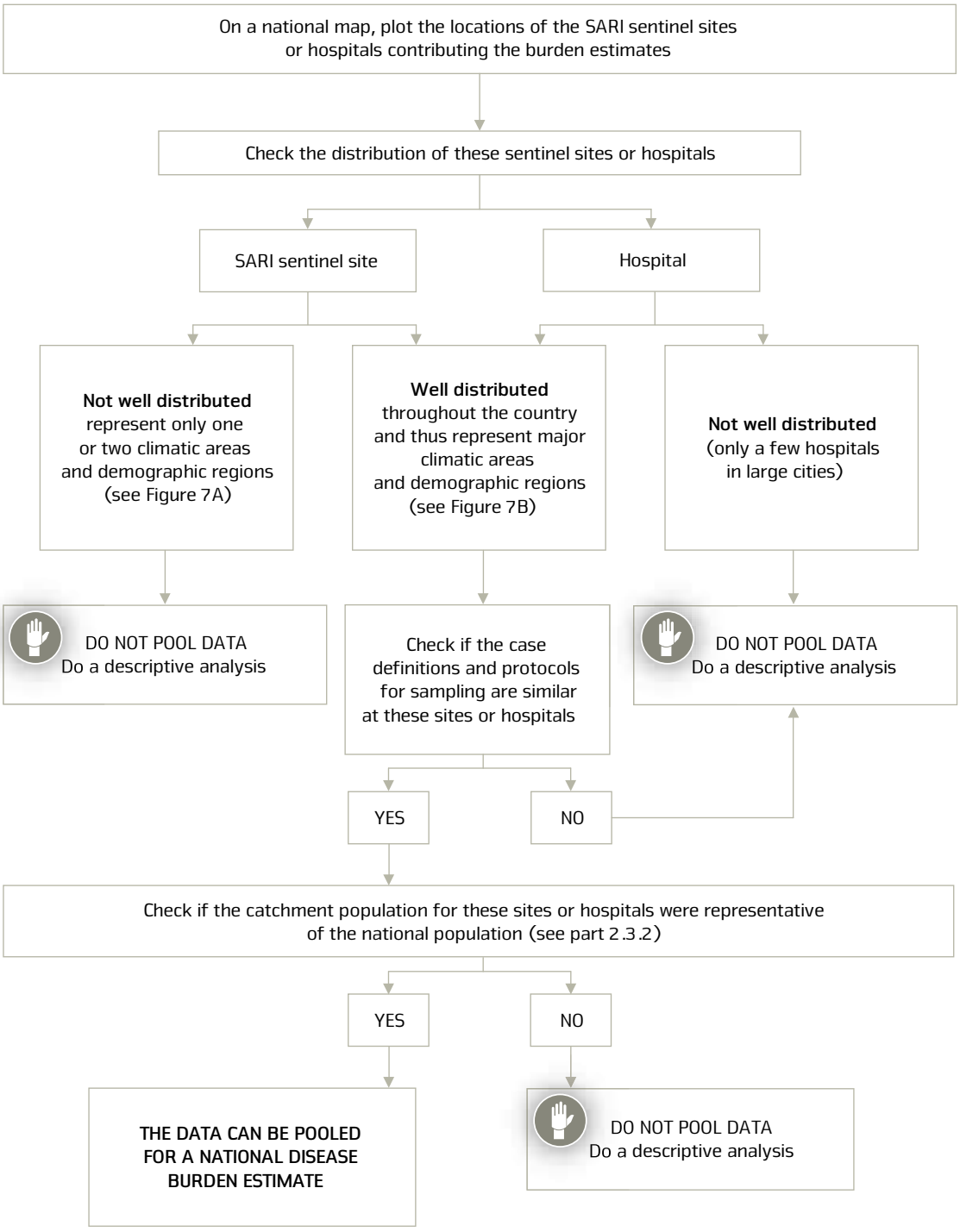
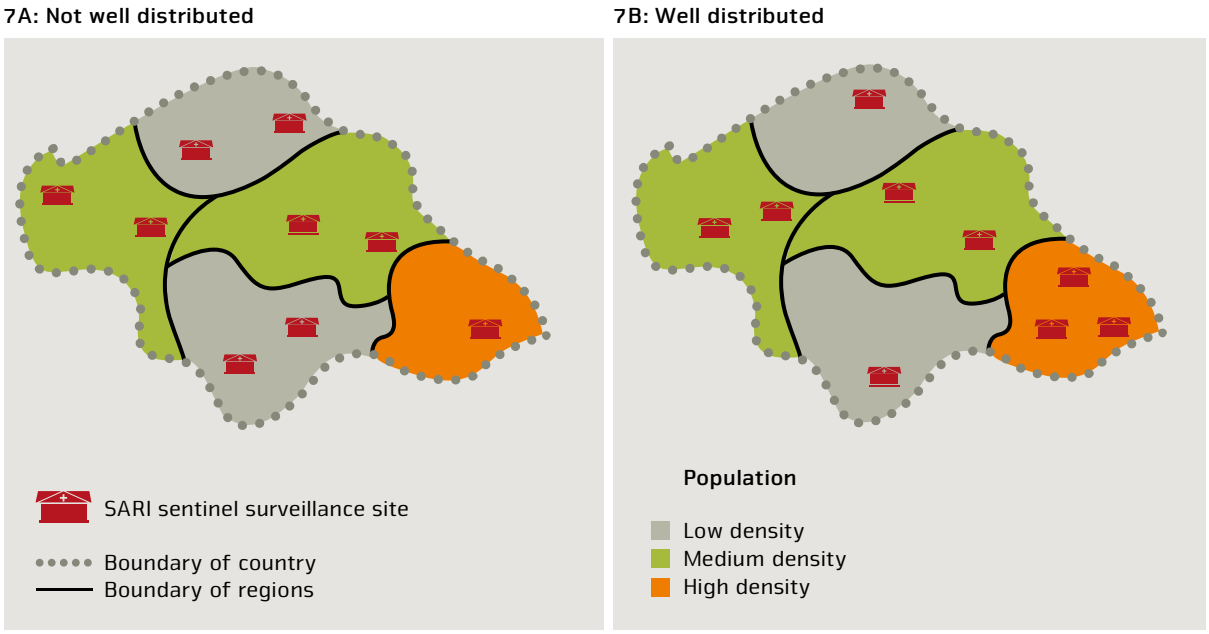


Figure 7: **Examples of distribution of SARI sentinel surveillance sites in a country**



7.3 With data from SARI sentinel sites

7.3.1 Generating national incidence estimates

Once the incidence rate data which can be pooled are identified, then a pooled national estimate can be generated as described below.

7.3.1.1 Method

Step 1: Compare the incidence rates from the various SARI sentinel sites. It is likely that the incidence rates across the sites are highly variable. The incidence rates for influenza-associated SARI will be influenced by:

- Underreporting at the sentinel site
- Sampling techniques and the biases introduced by them
- Access to the sentinel site and healthcare seeking behaviour: if the sentinel site is not easily accessible or the local population seeks healthcare from informal providers, then it is likely that the estimated annual incidence of influenza-associated SARI at the sentinel site might be an under-ascertainment.
- Missing epidemiological and demographic data. If only a proportion of eligible SARI cases are considered for collection of clinical specimens, then it is possible that complete epidemiological and demographic information is not recorded from cases not considered for diagnostic testing. In such case, many of the cases with missing data may have been excluded.
- Errors in classification and coding of cases
- Difference in the sensitivity and specificity of diagnostic assays used

- Underlying risk factors and ethic differences in different regions. Some vulnerable population groups have a much higher rate of severe influenza.

Step 2: Calculate the age-specific median incidence rates by pooling the data from all surveillance sites. The procedure for calculating median is described in Appendix A7. In practice, this can be done easily using the spread sheet model accompanying this manual. However, we will illustrate the principle by using an example.

Example

The incidence rates for influenza-associated SARI (in children aged 5 - <15 years) from five SARI sentinel sites S1 to S5 in a Country C in the year 2010 are as shown in Table 13.

Table 13: Incidence of influenza-associated SARI (per 100 000 persons) across 5 sentinel sites in Country C in 2010

Age group (yrs)	S6	S7	S8	S9	S10
5 to <15	15	25	18	36	8

The median estimated incidence rate for influenza-associated SARI in Country C is 18 per 100 000

Step 3: Apply the median incidence rates to the census population for the country. This will provide you with the estimated annual number of cases of influenza-associated SARI in the country.

Equation 30: Calculating the estimated number of cases of influenza-associated SARI in Country C

$$\text{Estimated number of cases of influenza-associated SARI in country C} = \text{Median incidence rate} \times \text{Census population}$$

Continuing with the above example, if the estimated population of 5-<15 year olds in Country C in 2010 was 1 million, then we estimate, after substituting the values in Equation 30, that there were 180 new cases of influenza-associated SARI in this age group in Country C in the year 2010.

7.3.1.2 Limitations of this approach

This is a very simplistic approach to estimating the influenza disease burden at the national level and there are several key limitations that need to be borne in mind while interpreting the results.

- An incidence meta-estimate using a meta-analysis approach[4] would have been better than median incidence rate. However, meta-analysis is complex and beyond the scope of this manual. We have found that, in practice, median incidence rates and incidence meta-estimates can be quite similar.[62]
- The national disease burden estimates are based on incidence rates for severe disease in those seeking healthcare. Unless the incidence rates are adjusted for the healthcare seeking behaviour in the population, these rates do not account for those cases with severe disease who do not seek healthcare. Hence, the disease burden will, in such cases, be an underestimate with the degree of underestimation related to the proportion of population not seeking formal healthcare.

- This approach does not permit us to estimate influenza disease burden by province/state/region. The process of generating state- or provincial-level estimates from the estimates from a single SARI sentinel surveillance site/hospital is complex and requires a more sophisticated modelling approach, which is beyond the scope of this manual. This is because the distribution of social and demographic factors are usually not uniform across a state and thus the catchment population for a sentinel site or hospital are not comparable with the remaining population in a state, thus making it difficult to extrapolate an incidence rate at a given site to the entire state or province. However, the more homogenous the population and the more representative the site is of the general population, the more generally representative estimates from the site will be of the entire population of the province/state/region where the site is located.
- These estimates are limited by the biases in the surveillance data that were pooled to generate the national estimates (see section 2.3.4 for details).

7.3.2 Generating national disease estimates for proportion of influenza-associated SARI

Once the data which can be pooled are identified, then a pooled national estimate for the proportion of SARI that is influenza associated can be generated as described below. The process is the same as that described in the previous section for pooling influenza-associated SARI incidence rates.

7.3.2.1 Method

Step 1: Compare the proportions of influenza-associated SARI from the various SARI sentinel sites. It is very likely that the proportions of influenza-associated SARI across the sites are highly variable. The proportion of influenza-associated SARI would be influenced by:

- Sampling techniques and the biases introduced by them.
- Access to the sentinel site and healthcare seeking behaviour. If the sentinel site is not easily accessible or the local population seeks healthcare from informal providers, then it is likely that the estimated annual proportion of SARI associated with influenza at the sentinel site will be an under-ascertainment.
- Missing epidemiological and demographic data. If only a proportion of eligible SARI cases are considered for collection of clinical specimens, then it is possible that complete epidemiological and demographic information has not been recorded from cases not considered for diagnostic testing. In such case, many of the cases with missing data are likely to be excluded.
- Errors in classification and coding of cases.
- Differences in the sensitivity and specificity of diagnostic assays used.

Step 2: Calculate the age-specific median proportions by pooling the data from all surveillance sites. The detailed procedure for calculating median is described in Appendix A7. In practice, this can be done easily using the spread sheet model accompanying this manual. However, we will illustrate the principle by using an example.

Example

The proportion of influenza-associated SARI (in children aged 5-<15 years) from five SARI sentinel sites S6-S10 in a Country C in the year 2010 are as shown in Table 14.

Table 14: **Proportion of influenza-associated SARI (%) across five sentinel sites in Country C in 2010**

Age group	S6	S7	S8	S9	S10
5 to <15	7	12	10	15	4

The median proportion of influenza-associated SARI in children aged 5-<15 years in Country C is 10%.

7.3.2.2 Limitations of this approach

Apart from the limitations discussed in section 7.3.1.2, these results cannot be used to estimate the number of cases of influenza-associated SARI that seek care at health facilities in a country (unless the estimated annual number of SARI/pneumonia hospitalizations in a country is known). At best, these provide a sense of the relative importance of influenza vis-à-vis other diseases resulting in hospitalization in the given population. As with ILI, following this proportion over time will establish a baseline for the relative impact of influenza that can allow the evaluation of current seasons to average previous seasons. See the ***WHO Global Epidemiological Surveillance Standards for Influenza*** for more information on establishing baseline values.

7.4 With data from hospitals

The method for estimating the disease burden at the national level from hospital data (i.e. incidence of influenza-associated severe ALRI and proportion of influenza-associated severe ALRI) are similar to those discussed in sections 7.3.1 and 7.3.2, respectively.

Summary

In this chapter, we have learnt how to identify data sources, assess eligibility of data for pooling disease burden estimates, and combine data from SARI sentinel sites to generate national disease burden estimates for incidence rates and for proportion of influenza-associated SARI using data from SARI sentinel sites and hospitals.

08

Interpreting the results

Until now, we have discussed what data sources are available for estimating influenza disease burden, what adjustments need to be made in the numerator and denominator fractions if the data are not complete, and how to estimate the annual disease burden using these data sources. This chapter deals with carrying out some finer analyses and interpreting the results.

After completing this chapter, you will be able to:

1. *Critically analyse and comment on the disease burden estimates*
2. *Delineate the influenza season*
3. *Relate seasonal influenza patterns to seasonal patterns in SARI/severe ALRI hospital admissions*
4. *Analyse time trends over the years*

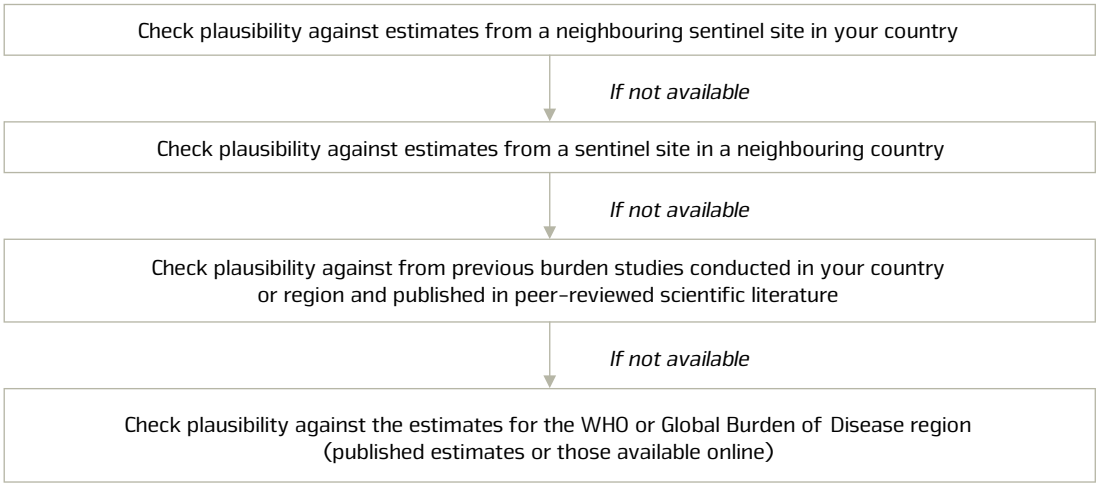
8.1 Critical analysis of disease burden estimates

Once you have estimated the influenza disease burden, you will need to analyse critically if these results are indicative of the true disease burden in the population and, if not, perhaps comment on the degree of uncertainty in these estimates.

8.1.1 Conducting a plausibility check

Now that you have estimated the influenza disease burden in your population, you may want to critically analyse whether or not these estimates are at all plausible. Figure 9 lists the possible options and outlines an algorithm for conducting a plausibility check.

Figure 9: Algorithm for conducting a plausibility check on the influenza disease burden estimates



While conducting your plausibility check, you will need to assess how your estimates compare with the estimates from other sources (e.g. fall within the 95% CI of others' findings). For example, there are other methods like Capture-Recapture[63] and Lot Quality Assurances [64], details of which are beyond the scope of this manual. Both these methods have their own advantages and disadvantages. However, if used properly, these could be used for validating the disease burden estimates calculated using the methods provided in this manual. If the comparator data do not use the same measure of disease burden (e.g. you can only compare incidence with incidence and proportion with proportion), then you should calculate the proportion of influenza-associated SARI for the site and then compare. It

is important to note that at any given site, the incidence and mortality associated with influenza varies markedly from year to year depending upon the strain of the circulating influenza virus, immunity in the population, and other host and environmental risk factors. Similarly, in any given year, there may be considerable variation in incidence and mortality across different sites even within a country again owing to the same factors as well as to the demographics and health utilization patters of the population living in the sentinel site's catchment area, the operationalization of case definitions, method of case identification, and the assays used to confirm influenza illness.

Since these estimates are from a different site and were collected using a different methodology at a different point in time (if comparing against published estimates), we should expect some variability. If your disease burden estimates are consistent with your comparator estimates, you should proceed to the next step; i.e. critically interpret the results for error, chance, and bias.

If you find that your estimates are markedly different from the comparator estimates, then you should be alert to the possibility of error during data entry and computation, or significant underreporting of cases. Once these are ruled out, assess the possibility of chance and bias in the estimates. Alternatively, it may be that you are comparing data from different years in which the severity of influenza was markedly different.

Example

In Table 15, we have estimated the incidence of influenza-associated SARI for the year 2010 across different age strata based on data from sentinel site S1. Let us assume that sentinel site S1 is located in Viet Nam. From our literature search we have identified one published estimate from a study in Nha Trang, Viet Nam, conducted in 2008.[65] However, the study was limited to children aged <5 years. Therefore, we can only check the plausibility of our estimates with those reported in the paper for the 0 – <5 year age range. Our plausibility check indicates that the estimates from sentinel site S1 in Viet Nam are largely consistent with the published estimates from the same country for the same period.

Table 15: Assessing plausibility of estimates based on data from sentinel surveillance with other published estimates from same country

	Data from sentinel site S1 Jan 2010 – Dec 2010			Data from published estimate for NhaTrang, Vietnam[65] Mar 2007 – Feb 2008		
	0 to <1 year	1 to <2 years	2 to <5 years	0 to <1 year	1 to <2 years	2 to <5 years
Number of cases of influenza-associated SARI	37	22	8	38	45	39
Estimated population	1820	1820	5460	2250	2442	9260

	Data from sentinel site S1 Jan 2010 – Dec 2010			Data from published estimate for NhaTrang, Vietnam[65] Mar 2007 – Feb 2008		
	0 to <1 year	1 to <2 years	2 to <5 years	0 to <1 year	1 to <2 years	2 to <5 years
Annual incidence rate of influenza-associated SARI (per 100000 population) (c) = [(a)/(b)] x 100 000	2033	1209	147	1689	1843	421
$EF^{(d)} = e^{(1.96/\sqrt{a})}$	1.4	1.5	2	1.4	1.3	1.4
Lower 95% confidence interval (LCI) (e) = (c)/(d)	1473	796	73	1229	1376	308
Upper 95% confidence interval (UCI) (f) = (c) x(d)	2806	1836	293	2321	2468	576
Incidence rate of influenza-associated SARI (per 100 000 population) (95% Confidence Interval)	2033 (1473 to 2806)	1209 (796 to 1836)	147 (73 to 293)	1689 (1229 to 2321)	1843 (1376 to 2468)	421 (308 to 576)

8.1.2 Evaluating the role of chance

A principal assumption underlying the disease burden estimates (and indeed in all of epidemiology) is that we can draw an inference about the experience of an entire population based on an evaluation of only a sample of this population. One of the major limitations in drawing such an inference is the role chance plays, which may affect the results simply because of random variation from sample to sample. One of the major determinants of the degree to which chance affects the findings in any particular study is the sample size.

Example

For example, in an obesity survey in a community, if we were to measure the hip and waist circumference in a random sample of 10 men aged 35 to 45, the resultant estimate might differ substantially from the frequency of obesity among all men of that age in the community as a whole, simply a result of chance. If we had data from a random sample of 1000 men, there would be less variability in our estimate, and we would consequently be more likely to draw a valid inference about the experience of the total population. Thus, in general, the smaller the sample from which our inference is made, the more variability there will be in the estimates and the less likely the findings will reflect the experience of the total population. The effects of sample size can be determined from the width of the confidence interval. The narrower the confidence interval, the less variability was present in the disease burden estimate, reflecting a larger sample size.

8.1.3 Evaluating the role of bias

As discussed in section 2.3.4, some degree of bias is inevitable in any study. Although it is very difficult to determine precisely the impact a potential source of bias actually has on the disease burden estimate, it remains crucial to attempt to identify the magnitude as well as the direction of the bias for any estimate. There are several sources of bias in the numerator data. Table 16 provides a list of possible scenarios resulting in bias in influenza case counts and the effect these would have on influenza disease burden estimates. While using these examples to identify the potential sources of bias in your data and interpret the direction (and the effect they would have on your overall estimate), you should also attempt to quantify what you think is the likely magnitude of the bias. This is helpful while interpreting the overall result when many biases are operating and are likely to influence the estimates in opposite directions.

Table 16: Scenarios resulting in various biases and their result on disease burden estimation

S. No	Example	Scenario (if…)	Direction of bias	Result on influenza disease burden estimates
Selection bias				
1	SARI cases admitted out of office hours and on weekends are *not* considered for collection of clinical specimen	Patients coming into the office out of normal working hours are working adults.	⇧ ⇔	More likely to result in overestimation of burden as working adults generally have lower rates of severe disease than children or the elderly. However, the biggest effect will be on the description of risk groups.
2	Surveillance is conducted only for a limited period in a year in tropical and subtropical areas	Influenza virus circulates throughout the year	⇩	Under estimation of influenza burden as only a portion of cases will be captured
3	Only the first two SARI cases admitted to a hospital ward are considered for collection of clinical sample	Patients are admitted more often from outpatient clinics than emergency department.	⇔	Probably will have no impact on overall burden estimate but will markedly distort the demographics and risk factors.
4	Critically ill patients are not tested	Critically ill cases are *more likely* to be influenza positive	⇩	Under estimation of influenza burden
5	Clinical specimens are only collected from SARI cases in paediatric wards	Children are *more likely* to be influenza positive	⇧	Over estimation of influenza burden, distortion of risk groups and age distribution
7	ILI cases are sampled from specialised clinics (diabetes clinic, heart disease clinic etc.)	Those with chronic diseases are *more likely* to be influenza positive	⇧	Over estimation of influenza burden, distortion of risk groups and age distribution

S. No	Example	Scenario (if…)	Direction of bias	Result on influenza disease burden estimates
Misclassification bias				
8a	Error in coding cases	Those who *have SARI* are not reported as such	⇩	Under estimation of influenza burden
8b	Clinical samples are tested using diagnostic assays with low sensitivity and high specificity (e.g. immunofluorescence, rapid tests)	Those who *have* influenza are *not coded* as influenza cases	⇩	Under estimation of influenza burden (sometimes up to -40%)

8.1.3.1 Effect of the sensitivity of case definition on disease burden estimates

As discussed in section 2.3.4, the sensitivity of the precise case definition for SARI/ILI will have an effect on the overall disease burden estimate. Various studies have demonstrated that the WHO case definition used from 2006 through 2014 has an overall sensitivity ranging from 42% to 67% (median 55%), depending on the study location. However, data from a proportion of studies that have stratified the sensitivity by age reveal that while the case definition is highly sensitive (70% to 96%) in children aged below 5 years, the sensitivity is lower in older children and adults (13% to 33%). This means that SARI/ILI cases provide a reasonably accurate reflection of the true influenza burden among young children. The WHO case definition was changed in late 2014 to improve its sensitivity and specificity for all age groups. When analysing several years of surveillance data, it is useful to consider the potential impact of changes in case definitions on influenza-associated illness estimates. For example, the WHO SARI/ILI case definition typically used during 2006-2014 is likely to systematically identify a proportion of all cases that would be identified with the current version of the WHO SARI/ILI case definition.

WHO Member States wishing to identify the proportion of hospitalized influenza cases that are not captured using the current SARI/ILI case definition might want to initiate further studies to gather evidence. One method is to test all (or a random sample of) hospital admissions irrespective of signs and symptoms at admission for a period of time. In this way, one could determine the sensitivity and specificity of the case definition at that institution. However, this does not guarantee that the sensitivity and specificity of this case definition would be the same at other institutions in the country as local practice and interpretation would affect it a great deal. The new WHO SARI/ILI definition still is targeted towards influenza presenting as respiratory disease and will likely miss cases that present with other clinical syndromes that overshadow respiratory complaints, such as acute myocardial events.

As it is not feasible to adjust for the sensitivity of the SARI/ILI case definition in most settings, it is likely that we are underestimating the overall influenza burden. Many patients, especially adults, present with a clinical picture that is not recognized as being due to a primary respiratory infection, such as an acute myocardial event triggered by an influenza infection. It is important to keep this in mind while interpreting and communicating your results.

8.1.3.2 Effect of healthcare seeking behaviour on disease burden estimates

In most low- and low-middle income countries, a large proportion of the population may not seek formal healthcare. This is true even in cases of severe disease and, as a result, the majority of deaths often occur outside a health facility. Data on access to healthcare are not routinely available unless a formal healthcare utilization survey (HUS) has been carried out. In the absence of an HUS, it is not possible to make numerical adjustments to the disease burden estimates. In addition, it may be difficult to compare cases detected in an HUS to those actually admitted to hospital. That is, there is a potential for recall bias when asking about health-seeking behaviours and hospitalization for a respiratory illness in a retrospective interview. In addition, heath utilization varies from month to month and year to year. Ultimately, the SARI/ILI burden is, in fact, the burden on the healthcare system and should be viewed as such. However, it is possible to get some understanding of the degree of underestimation based on your qualitative judgement of the proportion of health seeking cases-patients of the totally who may have similar symptoms but may choose to seek care or self-treat (Box 2).

What are the key biases in your data? Critically analyze the disease burden estimates from your sentinel site and comment biases that are likely to have an impact on the disease burden estimates on the worksheets in the Appendix WS3.

Box 2: Case study on interpreting influenza-associated SARI burden estimates

At a sentinel site, the influenza-associated SARI disease burden estimate among adults aged ≥65 years is estimated to be 150 per 100 000 persons per year. The estimates from a neighbouring sentinel site for the same age range are 300 per 100 000 persons per year. Both sites use the current WHO case definition for SARI. All SARI cases are eligible for specimen collection and diagnostic testing using rapid point-of-care (POC) tests. The data on health-seeking behaviour for severe respiratory disease are not available for the sentinel site. However, past surveys have demonstrated that 40% to 50% of adults who have been severely ill do not go to hospitals. An epidemiologist has been asked to interpret this estimate and provide his comments.

The epidemiologist concludes:

- There are limited data available to interpret these findings. The available data suggest that the disease burden estimates are plausible but are possibly an underestimate of the true disease burden because:
- The rapid POC diagnostic assays used have poor sensitivity (47-77%).
- The SARI case definition in adults does not reflect the true total influenza disease burden because it is not designed to readily capture case patients that primarily manifest as exacerbations of circulatory diseases (e.g. persons with congestive heart failure precipitated by an influenza illness).
- Since 40-50% of those with any severe disease do not seek care at hospitals, this is probably true for influenza as well.
- It is not possible to precisely quantify the magnitude of the true influenza disease burden in this population; however the SARI burden is the portion of influenza that is likely to have the greatest impact on costs to the healthcare system.

8.2 Placing the influenza disease burden estimates in the context of burden estimates for other diseases

Ideally, in order to interpret and appreciate the influenza disease burden estimates, we should compare them with estimates for other diseases. However, it is very likely that such estimates are not

available for other diseases in local or even national contexts. In such cases, you may want to consider the burden of influenza-associated SARI/hospitalised severe ALRI in the context of other diseases resulting in hospitalization.

- **What is the proportion of influenza-associated SARI in all-cause hospitalization? What proportions of SARI cases are positive for influenza?**
- **What is the proportion of influenza-associated SARI mortality?**
- **What is the proportional contribution of influenza-associated SARI to all-cause hospital mortality?**
- **How does this compare with the hospitalization and mortality for other leading infectious diseases? (E.g. malaria, bacterial pneumonia, HIV, meningococcal meningitis, hepatitis B etc.)?**
- **What is the proportion of ILI cases seeking outpatient care?**
- **How does this compare with other infectious diseases seeking outpatient care?**

8.3 Delineating the influenza season

An influenza season is a period of influenza activity wherein influenza virus is circulating in a sustained manner as opposed to periods when influenza cases are occurring sporadically with no sustained community transmission. There is a usual or expected level of influenza activity that occurs during a hypothetical average influenza season. This is referred to as the influenza average epidemic curve and is based on average illnesses per epidemiologic week for multiple years. For details, please refer to the *WHO Global Epidemiological Surveillance Standards for Influenza*. Using average epidemic curves as a point of reference, we can determine the relative severity of the current season.

8.3.1 Method

There are several methods that have been used to define the onset of influenza season and no single method will be useful for every member state. The simplest technique is the visual method outlined in the WHO Global Epidemiological Surveillance Standards for Influenza. In this method, an average epidemic curve, or baseline, for influenza activity is determined and based on this, a seasonal or epidemic threshold can be established for identifying the start of the influenza season. This value is meant to distinguish when influenza is circulating in a sustained manner, indicating that an influenza season has started, from periods when cases are occurring sporadically with no sustained community transmission. The same parameters that define baseline values (ILI or SARI numbers; proportions or rates; percentage of specimens testing positive for influenza; etc.) can also be used to define the seasonal threshold, and experience in country will determine the most useful parameter to use. In some cases, it may be a combination of parameters. For example, a seasonal threshold could be defined as the week in which the ILI rate crosses a certain value and the percentage of specimens testing positive reaches a certain point. The epidemic threshold needs to be set low enough to signal the start of the season in a timely manner but high enough to avoid false signals. Tropical countries may find it particularly difficult to define an epidemic threshold as influenza seasons may not be as clearly distinguished from non-seasons and indeed in some tropical countries it has been observed that sustained low-level community transmission can occur during inter-seasonal periods (see Figure 2).

8.3.2 Public health utility of delineating the influenza season

Identifying an influenza season will help in triggering public health action such as:

- Raising awareness of influenza and severe disease caused by influenza among the general public and encouraging them to seek care
- Stimulate case detection and clinical diagnosis
- Initiate control measures in vulnerable population groups by identifying appropriate timing for administering influenza vaccine and ensuring availability of diagnostic kits, antivirals, and antibiotics for secondary bacterial infections.

8.4 Analysing time trends over the years

Once you have influenza surveillance data for a minimum of three years, you can start analysing trends in influenza disease over time. Influenza is a seasonal disease and there is considerable variation in the disease burden from year to year.

- **Identify which weeks of the year were included in the influenza season each year.**
- **How much is the year-to-year variation in what can be labelled as influenza season?**
- **Look for the predominant circulating virus type/subtype in each season.**
- **Is the severity of disease burden (incidence of influenza-associated SARI or proportion of influenza-associated SARI or mortality attributable to influenza) related to any particular type or subtype?**

Comparison with data from previous years is helpful in determining the severity of the seasonal influenza activity in a particular year. It also helps to identify and label any unusually severe activity and (if picked up early) initiate public health control measures.

Summary

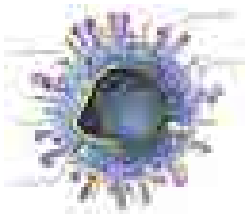
In tropical climates where the influenza virus activity continues throughout the year, it may be difficult to delineate the influenza season. Prior knowledge of the influenza season helps prepare for the seasonal influenza epidemic. It is usual to notice a higher rate of hospital admission for SARI during influenza weeks. Prior knowledge of the timing of the influenza season can assist in better patient management by augmenting hospital capacity and ensuring a stockpile of antivirals, antibiotics, and oxygen supplies in the lead up to the influenza season. A good epidemiologist should always check the plausibility of their estimates with other estimates based on data from the same country/region.

Appendices

Additional information

Worksheets

A1: Influenza virus



Influenza viruses belong to the family *orthomyxoviridae* and are classified as A, B, or C. Influenza A and B viruses are responsible for seasonal epidemics of what we generally think of as influenza illness, while influenza C viruses cause mild cold-like illness. Influenza A viruses are further categorized into subtypes (e.g. H1N1 or H3N2) on the basis of surface glycoproteins, hemagglutinin (HA), and neuraminidase (NA). While antigentically distinct B strains are currently circulating globally, these are not different enough from each other genetically to be called subtypes. Influenza B viruses are currently grouped into two lineages (Victoria and Yamagata) but are not subtyped. Influenza A viruses circulate among a diverse range of host species, including birds, swine, horses, and humans, but B viruses only infect humans. The large pool of genetically distinct influenza A viruses circulating among animal species serves as a source of *novel* viruses to which humans have little or no immunity. The introduction of these viruses into human populations is responsible for periodic worldwide influenza pandemics. At the level of individual patients, both influenza A and B viruses cause clinically indistinguishable disease.

Antigenic change is one of the hallmarks of influenza viruses and occurs through one of two distinct mechanisms: antigenic drift and antigenic shift. Antigenic drift refers to a process by which point mutations in the RNA genome of the influenza virus result in antigenic variants. When these changes result in a survival advantage for the virus, the new antigenic variant can become the predominant circulating strain. As an increasing number of individuals within the population develop antibody against the new circulating strain, selective pressure favours the emergence a new variant, which then becomes the next predominant strain in an on-going global process. Each new antigenic strain typically circulates for a very few years before it is displaced by the next emerging strain.

Antigenic shift resulting in a global pandemic occurs by one of the two mechanisms: genetic reassortment between animal and human influenza viruses or a direct jump from animal to human of a virus that has acquired the ability to easily spread from human-to-human. In the former, genetic reassortment can occur if a suitable host, such as swine, is co-infected by both human and non-human (animal) influenza viruses allowing the two viruses to intermingle their genetic material. The second mechanism is less well understood but likely occurs when animal influenza viruses that generally do not infect humans develop mutations that allow them to more easily infect humans. Antigenic shift occurs relatively infrequently.

A2: Mapping previous WHO case definitions for influenza disease to current WHO case definitions

Age group	Criteria from previous WHO case definitions	Classification as per current WHO definition
All ages	• Sudden onset of fever ≥38°C, AND • Cough or sore throat, AND • Absence of other diagnoses	ILI
Age <5 years	IMCI criteria for pneumonia Cough or difficulty breathing with: • Respiratory rate >50 breaths/ minute (if child 2–11 months old) • Respiratory rate >40 breaths/ minute (if child >1 year old) AND • Requires hospitalisation	SARI
Age <5 years	IMCI criteria for severe pneumonia Cough or difficulty breathing with: • Respiratory rate >60 breaths/ minute (if child <2 months old) Chest wall indrawing in child <5 years AND Requires hospitalisation	SARI
Age <5 years	IMCI criteria for very severe disease Cough or difficulty breathing with: • Any of the danger signs (if child is >2 months old) – Unable to drink or breast feed – Vomits everything – Convulsions – Lethargy or unconsciousness, AND • Requires hospitalisation	SARI
Age ≥5 years	• Sudden onset of fever >38°C, AND • Cough (or sore throat, AND • Shortness of breath or difficulty breathing, AND • Requires hospitalization	SARI

A3: ICD 9 and ICD 10 codes for influenza

ICD-10 code	Description
J09.01	Influenza due to identified avian influenza virus (A/H5N1) with pneumonia
J09.02	Influenza due to identified avian influenza virus (A/H5N1) with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion)
J09.03	Influenza due to identified avian influenza virus (A/H5N1) with gastrointestinal manifestations
J09.09	Influenza due to identified avian influenza virus (A/H5N1) with other manifestations (acute myocarditis, encephalopathy, otitis media etc.)
J09.11	Influenza due to identified influenza A(H1N1)pdm09 virus with pneumonia
J09.12	Influenza due to identified influenza A(H1N1)pdm09 virus with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion)
J09.13	Influenza due to identified influenza A(H1N1)pdm09 virus with gastrointestinal manifestations
J09.19	Influenza due to identified influenza A (H1N1) pdm09 virus with other manifestations (acute myocarditis, encephalopathy, otitis media etc.)
J10.0	Influenza with pneumonia, other influenza virus identified
J10.1	Influenza with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion), other influenza virus identified
J10.2	Influenza with gastrointestinal manifestations, other influenza virus identified
J10.8	Influenza with other manifestations (acute myocarditis, encephalopathy, otitis media etc.), other influenza virus identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion), virus not identified
J11.2	Influenza with gastrointestinal manifestations, virus not identified
J11.8	Influenza with other manifestations (acute myocarditis, encephalopathy, otitis media etc.), virus not identified

ICD-9 code	Description
487	Influenza with pneumonia
487.1	Influenza with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion)
487.8	Influenza with other manifestations (gastrointestinal, acute myocarditis)
488.01	Influenza due to identified avian influenza virus A/H5N1 with pneumonia
488.02	Influenza due to identified avian influenza virus A/H5N1 with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion)

ICD-9 code	Description
488.09	Influenza due to identified avian influenza virus A/H5N1 with other manifestations (gastrointestinal, acute myocarditis, encephalopathy etc.)
488.11	Influenza due to identified influenza A(H1N1)pdm09 virus with pneumonia
488.12	Influenza due to identified influenza A(H1N1)pdm09 virus with other respiratory manifestations (acute upper respiratory infections, laryngitis, pharyngitis, pleural effusion)
488.19	Influenza due to identified influenza A(H1N1)pdm09 virus with other manifestations (gastrointestinal, acute myocarditis, encepaholpathy etc.)
488.8	Influenza due to novel influenza A (excludes avian influenza, influenza A/H5N1, influenza A(H1N1)pdm09)

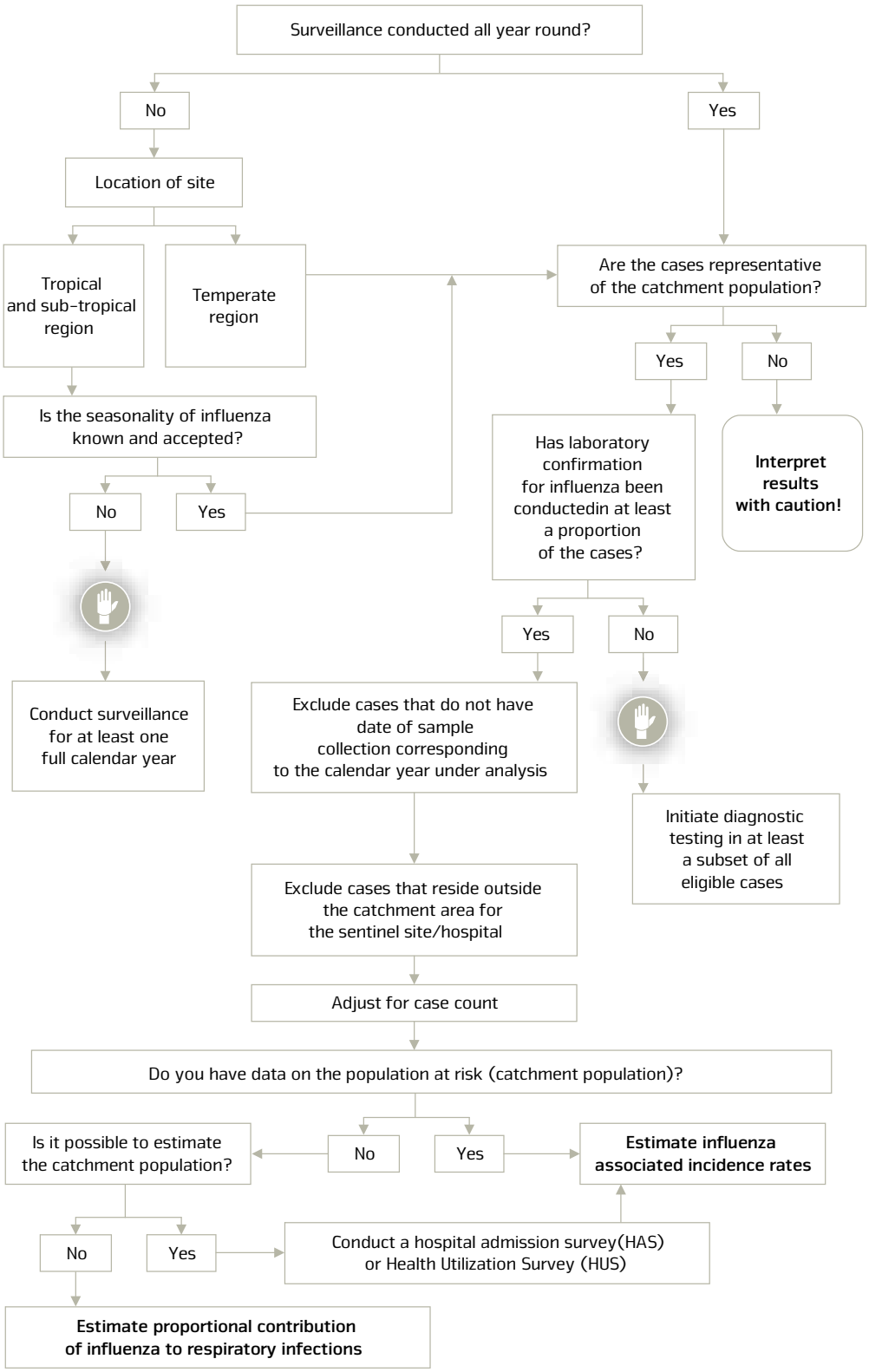
A4: Mapping ICD codes to case definitions

ICD-9 code	ICD-10 code	WHO sentinel surveillance classification	Classification for Influenza burden estimation
487, 488.01, 488.11,	J09.01, J09.11, J10.0, J11.0	SARI	
487.1, 488.02, 488.12	J09.02, J09.12, J10.1, J11.1	ILI	
488.01, 488.11	J09.01, J09.11, J10.0		Influenza-associated SARI
488.02, 488.12	J09.02, J09.12, J10.1, J11.1		Influenza-associated ILI
487.8, 488.09, 488.19	J09.03, J09.09, J09.11, J09.13, J09.19, J10.2, 10.8, J11.2, J11.8		Influenza-associated non-respiratory manifestations

A5: List of select co-morbidities and their ICD codes associated with increased risk of severe influenza

Co-morbidity	ICD 9 codes	ICD 10 codes
Chronic Respiratory Disease (COPD)	490-492, 496	J 40-44
Asthma	493	J 45
Diabetes Mellitus	250	E 08-13
Chronic cardiac disease	393-398, 410-417, 420-429	I 05-09, I20-25, I26-28, I30-52
Chronic liver disease	571	K 70-77
Chronic kidney disease	585	N18
HIV	042	B 20
Other immune deficiencies	279	D 80-89
Hereditary haemolytic anaemias	282	D 55-59

A6: Flow chart outlining the key steps in influenza disease burden estimation



A7: Glossary

Case Fatality Ratio The proportion of cases of a specified condition which are fatal within a specified time period.

Incidence Rate The rate at which new events occur in a population. The numerator is the number of new events that occur in a defined period; the denominator is the population at risk of experiencing the event during this period, sometimes expressed as person-time.

Median A measure of central tendency used to represent the average when the data are not normally distributed. It is the point which has half the values above and half the values below. If the data are arranged in an ascending or descending order, then in the case of

i) odd number of observations- median is the (n+1)/2 th observation, where n denotes the number of observations. For example, if there are 5 patients aged 52, 55, 58, 61 and 63 then median age is 58.

ii) even number of observations- median is the mean of n/2 th and (n+1)/2 th observation, where n denotes the number of observations. For example, if there are 6 patients aged 52, 55, 58, 61, 63 and 67 then median age is (58+61)/2 i.e. 59.5 years.

Sensitivity Is the probability of correctly diagnosing a case with a test or clinical criteria in a case definition.

Specificity Is the probability of correctly identifying a non-infected person with a test or clinical criteria in a case definition.

WS1: Mapping local case definitions to current WHO case definitions for influenza disease

***Instructions*:**
List the case definitions for SARI and/or ILI at your surveillance site/country and compare with the current WHO case definition

SARI[4]

Case definition at surveillance site	WHO case definition
	Acute respiratory illness, AND
	History of fever, or measured fever ≥38°C, AND
	Cough, AND
	Onset in last seven days, AND
	Requires hospitalisation

ILI[4]

Case definition at surveillance site	WHO case definition
	Acute respiratory illness, AND
	Measured fever ≥38°C, AND
	Cough, AND
	Onset in last seven days

4 WHO Global Epidemiological Surveillance Standards for Influenza at WHO website (www.who.int/influenza)

WS2: Identifying data sources

***Instructions*:**
List the data sources you think are available for influenza disease burden estimation at your sentinel site/country

Sentinel site

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. etc _____

Country level

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____

WS3: Checklist to assess relevance and quality of data for influenza burden estimation

Instructions:

1. ***Where the response to a question is YES/NO, put a check mark against the appropriate response***
2. ***Use this check list in combination with the flowchart in Appendix A6***

Assessing data for quality and relevance	
Completeness 1. Are the data for a full calendar year? If YES, go to 2 If NO, refer to Appendix A6, and if the seasonality of influenza is not well known and accepted for this location, then STOP.	☐YES / ☐NO
Representativeness 2. Do all cases of the catchment area have equal possibility to go to this site? Consider demographic and socioeconomic characteristics.	☐YES / ☐NO
Accuracy 3. Has laboratory confirmation for influenza been conducted in at least a proportion of the cases? If YES, go to 4. IF NO, then STOP.	☐YES / ☐NO
4. Are all of the cases from the calendar year for which data are being analysed (i.e. is the date of sample collection corresponding to the year under analysis)? If NO, then include only those cases which have a date of sample collection in the year for which data are being analysed.	☐YES / ☐NO
5. Are all the cases from the catchment area of the sentinel site? If NO, then identify and exclude cases that are from outside the catchment area of the sentinel site.	☐YES / ☐NO
Bias 6. Was clinical specimen for virological diagnosis required to be collected from all eligible cases? If YES, go to 7. If NO, go to 8.	☐YES / ☐NO
7. Were some cases excluded from specimen collection for some reason (refusal, too sick, admitted out of office hours or weekend)?	☐YES / ☐NO

Assessing data for quality and relevance	
8. What was the proportion of cases in who clinical specimens were not collected?	_____
9. What sampling technique was used to identify eligible cases for clinical specimen collection? (Check the appropriate sampling technique.)	☐Random sampling ☐Systematic sampling ☐Convenience sampling ☐Adhoc sampling
10. Is there a possibility of error in coding cases? If yes, comment _____	☐YES / ☐NO

11.Identify the diagnostic assay used for virological confirmation of influenza and the sensitivity and specificity of the assays.

Diagnostic assay	Sensitivity	Specificity

12. Could incomplete recording have led to such data being treated as missing and cases being excluded?	☐YES / ☐NO
Adjusting for missing data 13. Have you adjusted for incomplete case count?	☐YES / ☐NO
14. Do you have accurate data on denominator population (population at risk in the catchment area)? If YES, go to Appendix WS5. If NO, go to 15.	☐YES / ☐NO
15. Can you identify the catchment area for your sentinel site? If YES, go to 16 If NO, go to Appendix WS6	☐YES / ☐NO
16. Are population data available for the catchment area? If YES, obtain a list of health service providers in your catchment area, and conduct a hospital admission survey and estimate the catchment population for the sentinel site, respectively. Then go to Appendix WS5. If NO, go to Appendix WS6.	☐YES / ☐NO

Interpretation of results

17. Review the answers for questions 1 to 14 and list all possible sources of potential bias in the data and the result it could have on the disease burden estimate.

Assessing data for quality and relevance

Potential sources of bias	Likely direction of bias (⇧ or ⇩)	Likely scale of bias (high or low)	Result on disease burden estimation

WS4: Estimating the proportion of cases (from catchment area) accessing SARI sentinel site/ hospital for treatment of SARI/ALRI

Instructions:

Complete this table with your own data and adjust the age and gender categories as needed for your data

Name of health facility	Total number of cases of ALRI in the previous 12 months from catchment area																Proportion of ALRI cases (accessing sentinel site for treatment from catchment area) (a/b)															
	0 to <6 months		6 m to <1 year		1 to <2 years		2 to <5 years		5 to <15 years		15 to <50 years		50 to <65 years		≥65 years		0 to <6 months		6 m to <1 year		1 to <2 years		2 to <5 years		5 to <15 years		15 to <50 years		50 to <65 years		≥65 years	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Sentinel site / hospital (a)																																
Other health facilities																																
Overall Total (b)																																

WS5: Estimating the denominator population using data from hospital admission surveys and census population

Instructions:

Complete this table with your own data

Age group	(a) Census population of males in catchment area	(b) Proportion of male population accessing sentinel site/hospital for treatment of pneumonia	(a x b) Estimated catchment population (males) for sentinel site/ hospital	(c) Census population of females in catchment area	(d) Proportion of female population accessing sentinel site/hospital for treatment of pneumonia	(c x d) Estimated catchment population (females) for sentinel site/ hospital
<6 months						
6 months to <1 year						
1 to <2 years						
2 to <5 years						
5 to <15 years						
15 to <50 years						
50 to <65 years						
≥65 years						
Total						

WS6: Estimating incidence and number of new cases of influenza-associated SARI in a population using data from sentinel surveillance when data on catchment population for the sentinel site are available

Instructions:

Complete this table with your own data and adjust the age categories to meet your country needs.

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of SARI positive for Influenza A(H1N1)pdm09								
(b) Number of cases of SARI positive for Influenza A(H3N2)								
(c) Number of cases of SARI positive for unsubtyped Influenza A								
(d) Number of cases of SARI positive for Influenza B								
(e) Number of cases of SARI positive for other human influenza viruses								
(f) Total number of cases of SARI positive for human influenza viruses (all types and subtypes) = (a)+(b)+(c)+(d)+(e)								
(g) Number of SARI cases in who clinical specimens were collected for laboratory confirmation of influenza								
(h) Total number of SARI cases (from all hospital wards likely to admit SARI cases and includes those cases not tested for influenza or negative for influenza on laboratory tests)								
(i) Proportion of SARI cases from who clinical specimens were collected for laboratory confirmation of influenza (%) = (g)/(h)								
(j) Estimated number of number of cases of SARI positive for influenza viruses (all types and subtypes) after adjusting for the sampling fraction = (f)/(i)								
(k) Estimated catchment population for the sentinel site								
(l) Incidence rate of influenza-associated SARI at sentinel site in year _____(per 100000 population) = [(j)/(k)] x 100 000								
(m) Population of district _____								
(n) Number of new cases of influenza-associated SARI in district _____in year _____ = (l x m)/100 000								

WS7: Estimating the proportion of influenza-associated SARI in a population using data from sentinel surveillance when data on catchment population for the sentinel site are not available

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of SARI cases positive for Influenza A(H1N1)pdm09								
(b) Number of SARI cases positive for Influenza A(H3N2)								
(c) Number of SARI cases positive for unsubtyped Influenza A								
(d) Number of SARI cases positive for Influenza B								
(e) Number of SARI cases positive for other human influenza viruses								
(f) Total number of SARI cases positive for all human influenza viruses = (a)+(b)+(c)+(d)+(e)								
(g) Total number of SARI cases in who clinical specimens were collected for laboratory confirmation of influenza								
(h) Proportion of influenza positive SARI (%) = [(f)/(g)] x 100								
(i) Total number of SARI cases (from all hospital wards likely to admit SARI cases and includes those cases not tested for influenza or negative for influenza on laboratory tests)								
(j) Estimated annual number of influenza-associated SARI cases in the hospital = (i) x (h)								
(k) Total annual number of hospital admissions (all-cause)								
(l) Proportional contribution of influenza-associated SARI to all hospital admissions in year _____(%) = [(j)/(k)] x100								

WS8: Estimating incidence and number of new cases of influenza-associated severe ALRI in a population using data from hospital when data on catchment population for the hospital are available

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of severe ALRI positive for Influenza A(H1N1)pdm09								
(b) Number of cases of severe ALRI positive for Influenza A(H3N2)								
(c) Number of cases of severe ALRI positive for unsubtyped Influenza A								
(d) Number of cases of severe ALRI positive for Influenza B								
(e) Number of cases of severe ALRI positive for other human influenza viruses								
(f) Total number of cases of severe ALRI positive for all human influenza viruses = (a)+(b)+(c)+(d)+(e)								
(g) Number of severe ALRI cases in who clinical specimens were collected for laboratory confirmation of influenza								
(h) Total number of severe ALRI cases (from all hospital wards likely to admit severe ALRI cases and includes those cases not tested for influenza or negative for influenza on laboratory tests)								
(i) Proportion of severe ALRI cases from who clinical specimens were collected for laboratory confirmation of influenza (%) = (g)/(h)								
(j) Estimated number of number of cases of severe ALRI positive for influenza viruses (all types and subtypes) after adjusting for the sampling fraction = (f)/(i)								
(j) Estimated catchment population for the hospital								
(k) Incidence rate of influenza-associated severe ALRI at hospital in year _____(per 100000 population) = [(f)/(j)] x 100 000								
(l) Population of district _____								
(m) Number of new cases of influenza-associated severe ALRI in district _____in year _____ = (k x l)/100 000								

WS9: Estimating the proportion of influenza-associated severe ALRI in a population using data from hospital when data on catchment population for the hospital are not available

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of severe ALRI positive for Influenza A(H1N1)pdm09								
(b) Number of cases of severe ALRI positive for Influenza A(H3N2)								
(c) Number of cases of severe ALRI positive for unsubtyped Influenza A								
(d) Number of cases of severe ALRI positive for Influenza B								
(e) Number of cases of severe ALRI positive for other human influenza viruses								
(f) Total number of cases of severe ALRI positive for all human influenza viruses = (a)+(b)+(c)+(d)+(e)								
(g) Total number of severe ALRI cases in who clinical specimens were collected for laboratory confirmation of influenza								
(h) Proportion of influenza positive severe ALRI (%) = [(f)/(g)] x 100								
(i) Total number of severe ALRI cases (from all hospital wards likely to admit severe ALRI cases and includes those cases not tested for influenza or negative for influenza on laboratory tests)								
(j) Estimated annual number of influenza-associated severe ALRI cases in the hospital = (i) x (h)								
(k) Total annual number of hospital admissions (all-cause)								
(l) Proportional contribution of influenza-associated severe ALRI to all hospital admissions in year _____(%) = [(j)/(k)] x100								

WS10: Estimating the proportion of influenza-associated ILI in a population using data from sentinel surveillance when data on the catchment population for the sentinel site are not available

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of ILI positive for Influenza A(H1N1)pdm09								
(b) Number of cases of ILI positive for Influenza A(H3N2)								
(c) Number of ILI cases positive for unsubtyped Influenza A								
(d) Number of cases of ILI positive for Influenza B								
(e) Number of cases of ILI positive for other human influenza viruses								
(f) Total number of cases of ILI positive for all human influenza viruses = (a)+(b)+(c)+(d)+(e)								
(g) Total number of ILI patients from who clinical specimens were collected for laboratory confirmation of influenza								
(h) Proportion of influenza positive ILI cases (%) = [(f)/g)] x100								
(i) Total number of ILI outpatient visits (from all clinics and includes those cases not tested for influenza or negative for influenza in laboratory tests)								
(j) Estimated number of number of influenza-associated ILI cases = (i) x (h)								
(k) Total number of all-cause outpatient visits in a year								
(l) Proportional contribution of influenza-associated ILI to annual outpatient load (%) = [(j)/(k)] x100								

WS11: Estimating the incidence and number of new cases of influenza-associated ILI in a population using data from sentinel surveillance when data on catchment population for the sentinel site are available

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Number of cases of ILI positive for Influenza A(H1N1)pdm09								
(b) Number of cases of ILI positive for Influenza A(H3N2)								
(c) Number of cases of ILI positive for unsubtyped Influenza A								
(d) Number of cases of ILI positive for Influenza B								
(e) Number of cases of ILI positive for other human influenza viruses								
(f) Total number of cases of ILI positive for human influenza viruses (all types and subtypes) = (a)+(b)+(c)+(d)+(e)								
(g) Number of ILI cases in who clinical specimens were collected for laboratory confirmation of influenza								
(h) Proportion of influenza positive ILI cases (%) = [(f)/g)] x100								
(i) Total number of ILI cases (from all outpatient cases and includes those cases not tested for influenza or negative for influenza on laboratory tests)								
(j) Estimated number of number of influenza-associated ILI cases = (i) x (h)								
(k) Estimated catchment population for the sentinel site								
(l) Incidence rate of influenza-associated ILI at sentinel site in year _____ (per 100000 population) = [(j)/(k)] x 100 000								
(m) Population of district _____								
(n) Number of new cases of influenza-associated ILI in district _____in year _____ = (l x m)/100 000								

WS12: Calculating confidence interval for the estimates

Instructions:

Complete this table with your own data

Age group	0 to <6 months	6 m to <1 year	1 to <2 years	2 to <5 years	5 to <15 years	15 to <50 years	50 to <65 years	≥65 years
(a) Total estimated number of cases of SARI / severe ALRI positive for influenza viruses (all types and subtypes)								
(b) Estimated catchment population for the sentinel site / hospital								
(c) Annual incidence rate of influenza-associated SARI / severe ALRI (per 100000 population) = [(a)/(b)] x 100000								
(d) Error Factor (EF) = exp(1.96/√(a))								
(e) Lower 95% confidence interval (LCI) of the incidence estimate = (c)/(d)								
(f) Upper 95% confidence interval (UCI) of the incidence estimate = (c) x (d)								

WS13: Estimating the burden of influenza-associated SARI in pregnant women

Instructions:

Complete this table with your own data

(a) Crude birth rate per 1000 population	
(b) Population of catchment area	
(c) Estimated number of live births in a year = (a) x (b)	
(d) Estimated number of pregnant women in the catchment area in a year = (c) x 0.77	
(e) Number of cases of influenza-associated SARI in pregnant women in year _____	
(f) Incidence of influenza-associated SARI in pregnant women in year _____ (per 100 000 pregnant women) = [(e) / (d)] x100000	

WS14: Estimating the burden of influenza associated SARI in those with chronic diseases

Instructions:

Complete this table with your own data

	With chronic disease	Without chronic disease
Influenza-associated SARI	*a*	*b*
Influenza-associated ILI	*c*	*d*

OR for chronic disease in Influenza-associated SARI
= ad/bc

WS15: Estimating the in-hospital case fatality ratio due to influenza-associated SARI

Instructions:

Complete this table with your own data

Age group	(a) Number of deaths in cases with influenza-associated SARI	(b) No. of cases of influenza-associated SARI	hCFR (%) (a/b) x 100
0 to <6 months			
6 months to <1 year			
1 to <2 year			
2 to <5 year			
5 to <15 years			
15 to <50 years			
50 to <65 years			
≥65 years			
Overall			

WS16: Identifying the influenza season and correlating influenza season with hospitalization for SARI

Instructions:

Complete this table with your own data

Week #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
(a) Number of reported ILI cases in all age groups																										
(b) Total number of outpatient visits in all age groups																										
(c) Proportion of ILI outpatient visits in all age groups (%) = (a)/(b)																										
(d) Number of influenza positive specimens in all age groups																										
(e) Total number of specimens processed in all age groups																										
(f) Proportion of influenza positive specimens in all age groups (%) = (d)/(e)																										
Number of hospitalised SARI cases in age group 0 to <5 years																										
Number of hospitalised SARI cases in age group ≥65 years																										

Week #	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52
(a) Number of reported ILI cases in all age groups																										
(b) Total number of outpatient visits in all age groups																										
(c) Proportion of ILI outpatient visits in all age groups (%) = (a)/(b)																										
(d) umber of influenza positive specimens in all age groups																										
(e) Total number of specimens processed in all age groups																										
(f) Proportion of influenza positive specimens in all age groups (%) = (d)/(e)																										
Number of hospitalised SARI cases in age group 0 to <5 years																										
Number of hospitalised SARI cases in age group ≥65 years																										

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