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TO THE WHO PUBLICATION

"A manual for estimating disease burden associated with seasonal influenza"

Using a hospital admission survey to determine rates of influenza-associated severe acute respiratory infections



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Table of contents

Acknowledgements	3
Abbreviations	5
1 Background	10
2 Prepare for a hospital admission survey	12
2.1 Ethical approval and research determination	12
2.2 Review surveillance at sentinel sites	12
2.3 Sensitivity analysis	13
2.3.1 Tips for a successful sensitivity analysis	13
2.3.2 Sensitivity analysis steps	14
2.4 Evaluation of influenza proportion positive data	16
2.5 Define the catchment area for each sentinel site	16
2.5.1 Creating a spot map	17
2.5.2 Using a table	17
2.6 Obtain population estimates	18
2.7 Determine which respiratory diagnoses to include in a hospital admission survey	18
3 Conduct a hospital admission survey	22
3.1 Identify currently available data sources	22
3.2 Determine data availability from hospitals within the catchment area	23
3.3 Hospital data collection	24
3.3.1 Training	24
3.3.2 Data collection	25
4 Calculate the catchment population	28
5 Application of hospital admission survey results	30
5.1 Estimate rates of influenza-associated hospitalizations	30
5.2 Calculate confidence intervals for the number of influenza-associated hospitalization	1532
5.3 Calculate confidence intervals for rates of influenza-associated hospitalizations	33
Summary	34
Appendices	36
Appendix 1 Severe acute respiratory infection case definitions	36
Appendix 2 Flowchart for determining the catchment area and catchment population	37
Appendix 3 Example of a data entry form for sensitivity analysis of application of case definition	38
Appendix 4 Example of official letter to participating hospitals	39
Appendix 5 Example of a hospital admission survey data collection form	40
Appendix 6 Denominator population estimate using data from hospital admission surve	
and census population estimates	
Appendix 7 Influenza-associated incidence rate estimate	42
References	43

Using a hospital admission survey to determine rates of influenza-associated severe acute respiratory infections

Abbreviations

ARI acute respiratory infection

CDC United States Centers for Disease Control and Prevention

CI confidence interval

HAS hospital admission survey

HUS healthcare utilization survey

ICD International statistical classification of diseases and related health problems

MOH ministry of health

SARI severe acute respiratory infection

WHO World Health Organization



Background

Background

Influenza is an acute viral infection that has a significant effect on global morbidity (2) and mortality (3), and has serious economic consequences. Annually, CDC estimates that seasonal influenza results in 291 000–646 000 respiratory deaths worldwide (4). Although the burden of influenza has been established in some countries, it is not well understood in most WHO Member States, particularly in low- to middle-income countries (1). Key deliverables in the *Pandemic Influenza Preparedness Framework: Partnership Contribution Implementation Plan 2013–2016* (5), which WHO established to implement a global approach to pandemic influenza preparedness and response, include producing national estimates of influenza morbidity and mortality, impact on health systems, and economic burden. These national estimates can also be used within countries to evaluate the impact of influenza on the population, and to determine appropriate prevention and control measures. For example, age specific estimates of influenza-associated burden could help ministries of health (MOH) determine which populations they could target for seasonal influenza vaccine campaigns (6, 7).

In response to the need for reliable estimates, WHO developed a manual for estimating disease burden associated with seasonal influenza (1) and accompanying training materials. WHO has also used the manual when conducting training workshops on burden of disease estimation in countries in an attempt to enhance the development of country-specific and regional estimates of influenza disease burden. Participants in these trainings were national public health professionals, including epidemiologists, members of rapid response teams and field epidemiology trainees.

Many countries use the WHO global standards for influenza surveillance (8-10). Surveillance of hospitalized acute respiratory infection (ARI) captures hospitalized influenza-associated severe respiratory illness cases. Such surveillance uses a case definition – either recommended by WHO or country specific (Appendix 1) – to identify severe presentations of influenza-associated respiratory disease (11).

Many countries face the challenge of complex health-care seeking behaviour and of numerous health-care providers whose data may not be captured as part of the health system that houses the hospital-based surveillance system. Depending on the context, health-care providers can include, for example, public and private hospitals, health centres, pharmacies and traditional healers. Access to and use of different types of health-care providers may pose a challenge to understanding the health-care seeking behaviour at specific health facilities, and therefore to understanding the catchment populations on which burden estimates are based. To address this, the WHO manual (1) outlines a methodology for estimating influenza-associated hospitalization burden at sentinel sites; it also provides a hospital admission survey (HAS) that can be conducted to establish catchment areas and populations for these sites. WHO developed these HAS methods as a less resource intensive approach to quantifying hospital catchment populations compared to the traditional healthcare utilization survey (HUS) (1). This guide is an extension of the WHO manual, and it should be used in conjunction with the WHO manual — to simplify this process, where appropriate, this protocol cites relevant section numbers from the WHO manual.

Public health officials can use an HAS to determine what proportion of the population living in a hospital's catchment area seeks care at the sentinel site for a severe respiratory illness, compared with other admitting facilities in the area. A hospital catchment area is defined as the geographical area in which 80% or more of ARI case-patients admitted to the sentinel hospital reside (1). Public health officials can then apply the population proportions calculated during an HAS to census population estimates from the catchment area to determine the total catchment population of each hospital. The catchment population will serve as the denominator when calculating rates of influenza-associated hospitalizations for the hospital.



Prepare for a hospital admission survey

2 Prepare for a hospital admission survey

Before undertaking an HAS, it is important to identify all potential data sources and evaluate each data source for completeness and accuracy. Some of the key steps to preparing for an HAS are determining whether ethical approval is needed, evaluating the hospitalized ARI surveillance data for completeness and accuracy, determining the probable catchment area for each sentinel site and determining which hospital diagnoses will be used during the HAS. A thorough evaluation of the surveillance system is recommended before using surveillance data for estimating disease burden (12). A flowchart of the HAS process is given in Appendix 2.

2.1 Ethical approval and research determination

Completing an HAS is often part of reviewing and using routine surveillance data to direct programmes, policies, vaccine introduction and evaluation. Using routine surveillance data is generally not considered as research; nevertheless, it is important to check with the applicable MOH and assisting agency (if any) to determine whether a "non-research determination" is required before proceeding with an HAS. Occasionally, public health officials conduct an HAS to generate generalizable knowledge to further research initiatives, in which case, review by a local ethical review board will be required.

2.2 Review surveillance at sentinel sites

Many countries conduct ARI surveillance to capture severe presentations of influenza and other respiratory viruses that require hospitalized care. The severe acute respiratory infection (SARI) case definition is often used for surveillance purposes. As of 2013, WHO defines SARI as a respiratory infection with measured or history of fever and cough, with onset within the past 10 days that requires hospitalization (13). Case definitions may vary slightly by country, programme or age group (Appendix 1 provides examples of other SARI case definitions). If a surveillance evaluation has not been carried out recently, it can be conducted using the 2001 Updated Guidelines for Evaluating Public Health Surveillance Systems (14), to help describe the components and function of the system. A first and important step of reviewing the surveillance platform is to determine which case definition surveillance staff are using, how long that case definition has been used and whether the definition is being applied uniformly across all sentinel surveillance sites. If a case definition has been used uniformly across sentinel sites for the period of time desired for the HAS, this case definition should be used for the HAS even if it varies from the WHO case definition. If no single case definition has been used consistently or uniformly across all sentinel sites, it may be necessary to first review and strengthen surveillance by adopting a universal case definition across sites. Alternatively, an agreed upon definition could be applied retrospectively; however, this may require review of all medical charts of hospitalized patients in typical surveillance wards at the sentinel sites to determine the number of hospitalized ARI cases that met the newly agreed upon case definition. Different case definitions will have varying levels of sensitivity to influenza virus infections (15). Consult the WHO manual introduction on case definitions (pages 10-12) for additional information. The number of hospitalized ARI cases tested each month for influenza by age group should then be evaluated to determine whether age group specific proportion positives could be used in estimation of disease burden.



Sensitivity analysis is covered briefly in Section 3.3 of the WHO manual (1).

Another important part of reviewing the surveillance platform at the sentinel site is conducting a sensitivity analysis of case-capturing practices. This analysis compares the number of hospitalized ARI cases identified by surveillance officers during a specified time period to the number of hospitalized ARI cases identified by surveillance review staff retrospectively for the same time period, and can be accomplished through a retrospective medical chart review at the sentinel site. Such an analysis should review at least 6 weeks of data, which should ideally be distributed across the year, and should include weeks both inside and outside of the typical influenza season, representing a variety of influenza activity and proportion influenza virus positive. If electronic medical records are available, it may be possible to conduct the review for the entire HAS period.

2.3.1 Tips for a successful sensitivity analysis

A successful sensitivity analysis requires the following, as discussed below:

- prepare for data collection;
- determine type of data source;
- define and communicate terms;
- check quality; and
- check in with health-care providers.

Prepare for data collection

Preparation for data collection is essential. To maximize time and reduce the risk of incomplete data, all medical charts should be collected and organized by week and by ward, if possible, before starting data collection. Also, before beginning data collection, the team leader should ensure that all weeks and all wards are accounted for by enumerating weeks by wards and ensuring that neither weeks nor wards are missing medical charts. For example, if a hospital has two hospital wards where surveillance is conducted and the review will cover 20 weeks of hospital admissions, create a table with two columns (one for each ward) and 20 rows (one for each week). Then place a check mark in each cell where the medical charts have been found for a specific week and ward.

Determine type of data source

It is important to know the type of data source (e.g. electronic, paper or charts) before starting the review process, because this will greatly affect the review method and the time needed to complete the task. For example, electronic data may be easier to access and take less time to filter, allowing the review of a longer time period compared to the use of paper records.

Define and communicate terms

Another important step before beginning data collection is to define all terms in the data collection form and communicate this information to data collectors. It is best to use a one-page reference sheet that clearly defines the case definition being used and all of the terms that are acceptable for identifying desired symptoms. For example, different providers may record fever differently – one may list fever in the history of present illness, whereas another may rely on vital signs to document that a fever was present on examination. All acceptable ways to document fever should be listed on the reference sheet so that everyone on the team is collecting data in the same way.

Check quality

The work of each data collector should be reviewed for quality. One approach is to review 20% of the charts from each data collector. If no errors are found, the quality is acceptable and no further action is necessary. If errors are found, all charts completed by that data collector should be reviewed. This approach is most effective if it is first done early in the data collection and then occasionally repeated throughout the data collection process. It also provides a training opportunity, identifying what was not clear to the team and then reviewing with everyone to ensure that others are not making the same mistake.

Check in with health-care providers

Interviews with surveillance officers at all of the hospital-based sentinel sites should be included, to understand how the officers enroll cases, what criteria they use, how information is recorded and how to interpret the information recorded in the charts. Surveillance staff should also be questioned about the days on which they conduct surveillance (e.g. do they conduct surveillance on the weekend?) and the wards on which they conduct surveillance. This information can be used in the analysis to adjust for possible under-ascertainment of cases.

2.3.2 Sensitivity analysis steps

This section outlines the steps to be taken in a sensitivity analysis.

- 1. Decide how many and which weeks of surveillance data to review. If possible, randomly select weeks to review using a random-number generator (using the week number from both inside and outside the influenza season), and choose the total number of weeks to review based on available time and resources. If this is not possible, supervisors could ask six data collectors to select a number between one and 52, or the supervisors could write the numbers one to 52 on small pieces of paper and have someone blindly choose six of those numbers. The reason for choosing six numbers is to ensure that at least six weeks are included in the chart review. Team members should review all charts during the specified weeks.
- 2. In the week before the site visit, contact the hospital authorities to request access to all of the medical charts for the specified time period and to explain the process that will be taken and what will be required of the hospital staff.
- 3. On the day of the site visit, meet with the hospital and surveillance staff and ask them to provide orientation to the chart files that are available. Ensure that the available charts are sufficient for the review and the HAS. Request additional charts as necessary (if available).
- 4. For each medical chart, review the chart for the following information and record in a table preferably an electronic data entry table, such as one created in Epi Info (see Appendix 3 for an example data collection form):
 - a. Hospital name: write the name of the sentinel site under review.
 - b. Data collection date: write the date of data collection and ensure that the entries are in a consistent format (e.g. DDMMYY).
 - c. Ward: write the name of the hospital ward if applicable (e.g. paediatrics or general medicine).
 - d. Data collector: write the name of the person transferring the data from the chart to the data collection form.

Prepare for a hospital admission survey

- e. N: write the chart number for that data collection sheet, beginning with the number 1.
- f. Week: write the surveillance week of the chart.
- q. Age in years: write the age of the patient in years.
- h. Age in months: write the age of the patient in months (if the patient is aged under 1 year).
- i. District: write the patient's district of residence (or lower administrative unit if available).
- j. Date of admission: write the date on which the patient was admitted to the hospital.
- k. Discharge diagnosis: write the diagnosis reported by the physician at discharge. If International statistical classification of diseases and related health problems (ICD) codes for ICD-9 or ICD-10 (16) are reported, record this information as well. Write all of the discharge diagnoses listed.
- I. Date of symptom onset: write the date on which the patient's symptoms began.
- m. History of fever: review the chart for any mention of fever or fever symptoms (e.g. chills, sweats, skin hot to touch, or measured temperature ≥100.4 F or 38 C) and record yes, no, or unknown.
- n. Measured fever: review the chart for any mention of measured fever (measured temperature ≥100.4 F or 38 C at any point during hospitalization) and record yes, no, or unknown.
- o. Temperature: if measured fever is present, write the highest recorded temperature in degrees Fahrenheit or Celsius.
- *p.* Cough: review the chart for any mention of cough (either reported or observed by the clinician) and record yes, no, or unknown.
- q. Additional symptoms: if the case definition includes additional respiratory or other symptoms, add additional columns to record this information.
- 5. Repeat for all selected medical charts within the specified time period.
- 6. After data collection has been completed, review each recorded patient to determine whether they meet the case definition.
 - a. First, calculate the number of symptom days, by subtracting the date of symptom onset from the date of admission plus one.
 - b. Next, determine whether the patient meets the agreed upon hospitalized ARI case definition for this project. If using the WHO SARI case definition, the hospitalized patient would be a hospitalized ARI case if they had history of fever or reported fever marked yes and a cough marked yes, and the number of symptom days was 10 days or less. If a component of the case definition is unknown based on the information recorded from the medical chart, do not count the patient as a case.
- 7. Count the total identified hospitalized ARI cases by week of the year and age group.
- 8. Obtain the surveillance data captured by the surveillance system (either electronic or paper) and review the number of hospitalized ARI cases captured by the system for the same weeks as the sensitivity analysis.
- 9. Divide the number of hospitalized ARI cases enrolled in the surveillance platform for each given week and age group by the number of hospitalized ARI cases identified through the medical chart review for the same week and age group, and multiply by 100. This gives the percentage of potential cases identified that surveillance staff enrolled in the surveillance platform. Ideally, this number would be 100% for all weeks and age groups.

- 10. If the percentage is less than 100%, this percentage will be used as an adjustment factor during the calculation of influenza-associated hospitalized ARI cases to correct for under ascertainment of cases.
- 11. If the percentage is greater than 100%, then the surveillance system recorded more patients hospitalized with ARI than were found in the sensitivity review (i.e. there was an over enrolment of cases). In this situation, consider back–tracing enrolled cases and examining the patients' charts to find the recorded symptoms and listed diagnoses, to determine whether cases enrolled in the surveillance system meet the case definition. It is possible that there may be some weeks where the percentage is greater than 100% because some components of the case definition may not be recorded in the medical chart, decreasing the number of potential cases identified during the sensitivity analysis chart review.
- 12. Identify any factors that may have either positively or negatively affected enrolment. For example, in Country A, which is predominantly Christian, the proportion of hospitalized ARI patients enrolled in surveillance was lower in December because many surveillance officers took leave around Christmas. In contrast, in Country B, the proportion of hospitalized ARI patients enrolled in surveillance was found to be lower among adults because the surveillance officers spent most of their day in the paediatric ward and did not have as much time to identify and enroll cases in the adult wards.

2.4 Evaluation of influenza proportion positive data

The proportion influenza virus positive is defined as the number of hospitalized ARI cases testing positive for influenza virus, divided by the number of hospitalized ARI cases that had specimens collected and were tested for influenza viruses, by month:

Proportion influenza positive = Number of influenza positive hospitalized ARI case - patients

Number of hospitalized ARI cases tested for influenza

If the number of hospitalized ARI cases tested for influenza viruses is ≤10 in a given month, either overall or by age group, the monthly proportion of influenza virus positive may be unstable. For example, if surveillance staff only collected specimens a few days in a given month due to holidays, and therefore, only a few specimens were collected, these specimens may not represent the true proportion of influenza virus positive specimens for that month. To determine whether age group specific influenza proportion positives should be used in analyses, count the number of hospitalized ARI cases tested for influenza viruses by age groups and by month across the time period of interest. If any months and age groups have 10 or fewer hospitalized ARI cases tested for influenza viruses, consider combining data across age groups (17). Also consider combining age groups for calculating the proportion influenza virus positive cases if most of the hospitalized ARI cases tested for influenza viruses occurred in one age group.

2.5 Define the catchment area for each sentinel site

Information on defining the catchment area of each sentinel site can be found in Section 3.4 of the WHO manual (1).

According to the WHO manual, the catchment area should include the area of residence of at least 80% of surveillance cases for that specific sentinel site over the time period of interest (1).



Prepare for a hospital admission survey

This catchment area can be enumerated either by creating a spot map or by simply sorting data by location of patient residence in a table. This step requires surveillance data with residence information of hospitalized ARI cases for each sentinel site, together with a map of the area surrounding each sentinel site for a defined period of time, ideally for one year so that annual variation can be taken into account.

2.5.1 Creating a spot map

The steps for creating a spot map are as follows:

- 1. Mark on the map the residence of each hospitalized ARI case. If specific addresses are not available, use available district or other smaller administrative unit residence information to map the residences of enrolled cases. This can be done electronically (with mapping software) or by hand.
- 2. Determine the administrative units on the map where the largest number of hospitalized ARI cases resided.
- 3. Rank the administrative units by the number of total hospitalized ARI cases residing in each administrative unit. Calculate the percentage of hospitalized ARI cases residing in each administrative unit.
- 4. Determine the administrative units where, when added together, more than 80% of the hospitalized ARI cases resided. To do this, sum the percentages of hospitalized ARI cases that resided in each administrative unit (see Step 3), starting with the highest percentage, until the sum is over 80%. These administrative units are the catchment area of the sentinel site.

2.5.2 Using a table

The steps for using a table are as follows (1):

- 1. Review data from the surveillance system, the hospital admission records or other administrative datasets that have patient addresses of hospitalized ARI cases to find the lowest administrative level (e.g. district, town or census tract) for which data on residence of hospitalized ARI cases was recorded and for which population data are available.
- 2. Count the hospitalized ARI cases over the defined time period, grouping them by the lowest administrative level identified.
- 3. Rank the administrative units by the number of total hospitalized ARI cases that resided in each administrative unit.
- 4. Calculate the percentage of hospitalized ARI cases that resided in each administrative unit.
- 5. Determine the administrative units where, when added together, more than 80% of the hospitalized ARI cases resided. To do this, sum the percentages of hospitalized ARI cases that resided in each administrative unit (see Step 3), starting with the highest percentage, until the sum is over 80%. These administrative units are the catchment area of the sentinel site.

If information about hospitalized ARI case residence is not available, residence information for all admitted patients or residence information from all patients admitted with a respiratory illness can be used. In this scenario, hospital admissions records or other administrative datasets should be used to determine the lowest administrative level for which data on residence of all admitted patients is available. Complete Steps 2–5 (above) using information on all admitted patients.

2.6 Obtain population estimates

Obtain population estimates by the same administrative unit that was used to determine the catchment area. For example, if the catchment area was delineated by district, then district-level population data are needed. Population estimates need to be age stratified and, ideally, gender stratified; also, they should cover the same time period of interest. Determine the source and quality of these population estimates (e.g. how recently a census was conducted or what portion of the population was surveyed) before beginning an HAS. Obtain population estimates for each administrative unit within the catchment area by age group and gender. Sum these population estimates across administrative units to obtain population estimates by age group and gender for the entire catchment area.

2.7 Determine which respiratory diagnoses to include in a hospital admission survey

Another important initial step of conducting an HAS is to determine which respiratory diagnoses are associated with a hospitalized acute respiratory diagnosis and should be included during data collection at hospitals. The WHO manual suggests using the diagnosis of pneumonia (ICD-10 code J12-J18) for this purpose (1). This approach may be appropriate in some settings; however, there are several other admission and discharge diagnoses that could potentially be used, and typical diagnoses may differ by hospital, admitting provider or age group. Pneumonia diagnoses may not capture all hospitalized ARI cases or all influenza-associated ARI hospitalizations, so consider some alternative diagnoses by reviewing the commonly recorded discharge diagnoses of patients meeting the hospitalized ARI surveillance case definition. Some diagnoses to consider are shown in Table 2.1.

Table 2.1. Respiratory diagnoses to consider for inclusion in a hospital admission survey

Diagnosis	ICD-10 code	ICD-9 code
Pneumonia		
Severe pneumonia	J12-J18	480-486
Bronchopneumonia		
Broncho-asthma	J45	493
Bronchitis	J20	
Bronchiolitis	J21	466
Asthma	J45	493
Pharyngitis	J02	462
Rhino pharyngitis	J31	472
Tonsillitis	J03	463
Laryngitis	J04	464
Lower respiratory tract infection	J22	519.8
Upper respiratory tract infection	J06	465
Influenza	J09-J11	487-488
Respiratory illness	J00-J99	460-519

ICD, International statistical classification of diseases and related health problems



Prepare for a hospital admission survey

When deciding which diagnoses to include when conducting the HAS, consider the diagnoses shown in Table 2.1 and other diagnoses that are commonly identified among patients meeting the surveillance case definition. Depending on the context within the country, all or only some of these diagnoses may be used. For example, before conducting an HAS in Country C, the above diagnoses were compared to medical charts of admitted patients. Forty-one patients met the hospitalized ARI case definition used in Country C. Of these 41 patients, 40 (98%) had an admission or discharge diagnosis consistent with a respiratory illness. The most frequently found diagnoses were pneumonia (16, 39%), pharyngitis (11, 27%), bronchiolitis (6, 15%) and asthma (6, 15%). When Country C's hospitalized ARI case definition was compared to the WHO SARI case definition, 101 hospital admissions were identified that met the WHO SARI case definition. Of these 101 hospital admissions, 90 (89%) had an admission or discharge diagnosis consistent with a respiratory illness. The most common diagnoses were pharyngitis (47, 47%); pneumonia, including severe pneumonia and bronchopneumonia (20, 19%); bronchiolitis (9, 9%); and asthma (6, 6%). Of the 11 patients without a respiratory diagnosis, the following diagnoses were observed: neonatal infection (5), hyperthermia (1), dysentery (1), malnutrition (1), enteritis (1), denque (1) and intoxication (1). Country C used the respiratory diagnoses identified (pneumonia (including severe pneumonia and bronchopneumonia), pharyngitis, bronchiolitis, and asthma) for their HAS.

The situation observed in Country C may not reflect the situation in other countries or regions. The most appropriate diagnoses to include will differ by region, by country, by patient age and sometimes even by hospital. One approach is to determine which respiratory diagnoses are routinely collected by MOH officials, if applicable. Another approach is to use the sensitivity analysis (Section 2.3) as a guide to determine which diagnoses are most commonly associated with a hospitalized ARI case. Depending on data availability and specificity in hospital logbooks or discharge databases, it may be necessary to use all respiratory diagnoses (ICD-10 codes J00-J99). Regardless of the approach used, these diagnoses should be clearly delineated before continuing the HAS.



Conducting an HAS is covered in Section 3.4.4 of the WHO manual (1).

The HAS can begin once the sentinel case definition and ascertainment have been evaluated, the catchment area of each sentinel hospital has been determined, diagnoses for inclusion have been determined and population estimates have been obtained. All hospitals within the catchment area that admit patients overnight should be considered for inclusion in the HAS. The first step is to identify currently available data sources and determine data availability of other hospitals located within the catchment area of the sentinel hospital. An HAS can then be conducted at each hospital within the catchment area (including the sentinel site). Information collected during these surveys will be used to calculate the catchment populations of the sentinel sites. The catchment population for a sentinel site is defined as all the people living in the catchment area of the sentinel site who would usually seek healthcare at the sentinel site when they have a respiratory illness. Ideally collect information by age group and gender. Stratification by these categories is important as care-seeking behavior at specific facilities may be different for different populations (18). For example, if a pediatric hospital is located within the catchment area of one of the sentinel hospitals, many more children may seek care at the pediatric hospital compared to the sentinel hospital, whereas no adults would seek care at the pediatric hospital.

3.1 Identify currently available data sources

Some countries may have a repository of national-level health data. Before undertaking any new surveys, all currently available data sources should be reviewed to determine whether additional surveys are necessary or if something already exists, from which the information needed can be drawn. In some countries, publicly and privately run hospitals may record and keep these data separately. In other countries, these databases may be separated by health insurance type. Colleagues at the MOH may know of additional data sources that the team is not aware of that could be used to calculate influenza-associated hospitalization rates. Where new sources of data are identified for use in calculations, these data may need to be evaluated to understand how they were collected and to determine the quality of the information. When reviewing current data sources, evaluate key information for adequacy (e.g. by answering the following questions).

- 1. Are the data summarized or are they individual patient data?
- 2. If the data are summarized, how are they summarized (e.g. by day, week, month or year)?
- How are hospital diagnoses (at discharge) recorded?
 - Are the data coded using ICD-9 or ICD-10 codes or are diagnoses listed as free text?
 - Can only one diagnosis be reported per patient or might a patient be counted under multiple diagnoses?
- How complete are the data?
 - Does the database only contain information on certain hospitals (public or private) or on all hospitals across the country?
 - b. Are there times when data were not reported or are there any gaps in the dataset?
 - How often are data missing? С.
 - Do all hospitals report into the system?



- e. Is there a record of which hospitals do not report?
- f. How many discharge diagnoses are collected all of them or only the first one?
- 5. Is there any information about patient age? (Note: recommended age groupings are covered in Section 2.2.1 of the WHO manual (1))
- 6. Is there any information about patient gender?
- 7. Is there any information about hospitalization date (day, month or year)?
- 8. Is there any information about patient residence (address, city or district)?
- 9. Is there a standard protocol for data collection?
- 10. How often are the data submitted?
- 11. Have there been any other evaluations of this data source? How is the quality of these data checked by those that maintain this dataset?

An ideal data source would be clean, with no missing data, and would contain information from all hospitals. Information should be able to be summarized by hospital, discharge diagnosis (respiratory diagnoses), age groups, district of residence (or, preferably, smaller administrative unit), gender (if possible) and month of hospital admission. If this summary information is available, this national data source could be used to define catchment populations of the sentinel hospitals without the need to conduct individual HAS surveys in each hospital. If this summary information is available for certain hospitals (e.g. all public hospitals), it could be used to decrease the number of hospitals where primary data collection needs to take place.

3.2 Determine data availability from hospitals within the catchment area

All hospitals within the catchment area that admit patients overnight should be considered for inclusion in the HAS. Data availability from non-sentinel admission facilities may vary based on country, context, facility record-keeping and relationship with local health officials. The availability of hospital records should be determined before the decision to conduct an HAS, because the absence of records may limit or prevent an HAS. A representative from the MOH should contact each facility to explain the proposed project and obtain permission for a site visit. If someone from the MOH is not available, try to identify another government organization that could assist. The person should be equipped with an official letter explaining the project (Appendix 4 provides an example), the desired time frame and data and stated support or permission from the appropriate MOH official. Finally, conduct a site visit at each possible admitting facility, to determine whether they admit patients overnight and, if so, what type of patients are admitted (e.g. trauma or surgical, obstetric only or general medicine). Interviewing someone from the hospital facility or conducting a site visit will provide useful information to guide the development of methods to conduct rate estimation as well as to understand the facility and how the information from the facility would be used during the process. For example, the way hospital admission is defined may vary between countries and during influenza-associated hospitalizations estimation, to the team may want to include individuals that are ill enough to require at least an overnight stay in the hospital. It is also important to determine if hospital staff record only one or more than one discharge diagnosis for each patient. If some hospitals only report one discharge diagnosis for each patient, then only one discharge diagnoses for all patients across all hospitals can be collected. If only one discharge diagnosis from one hospital and multiple discharge diagnoses per patient in other hospitals are reviewed, the number of respiratory patients in hospitals that only report one discharge diagnosis may be underestimated.



Essential questions to ask to help understand the site include:

- 1. Does the facility admit patients overnight?
- 2. How many overnight hospital admissions were recorded in the previous year?
- 3. What types of patients are admitted and in what volume? How frequently is a patient admitted overnight for a respiratory illness?
- 4. How does the facility decide to admit versus refer?
- 5. Where does the facility send referrals?
- 6. Does the facility communicate with the regional or national public health officials? If so, how does the communication happen and what is communicated?
- 7. Will the facility allow access to medical charts, hospital logbooks or hospital admission or discharge databases (if available)? Are any special letters or permissions required in order to access records?
- 8. Are any records in electronic format? If so, which ones?
- 9. Does the facility keep a hospital admission or discharge logbook or a hospital discharge database?
- 10. Does the logbook or database have admission diagnosis or discharge diagnosis?
- 11. Does the logbook or database list the age of admitted patients?
- 12. Does the logbook or database list the gender of admitted patients?
- 13. Does the logbook or database list the admitted patient's residence? If so, how is it reported (e.g. address, district or other)?

When identifying and visiting each hospital, a team member should ask to look at the medical charts, logbooks and discharge databases to determine suitability for an HAS and to adjust data collection methods, if necessary.

3.3 Hospital data collection

At each hospital identified within the catchment area, review discharge registries (either in the form of paper logbooks for hospital admission and discharge or electronic admission and discharge databases) to identify hospitalized patients with at least one respiratory diagnosis residing in the catchment area. Hospitalized respiratory patients from the catchment area will be counted by age group and gender to determine the number of respiratory patients being treated at each hospital of interest over the time period of interest. This information will be used to calculate the proportion of hospitalized respiratory patients that are hospitalized at the sentinel site compared with other hospitals within each catchment area by age group. If national databases (as described above) are available for some or all hospitals, follow the steps for "Data collection – using an electronic database" below.

3.3.1 Training

Data collection training should occur with all team members before data collection. If needed, study documents should be translated and back-translated into the local language. The training should include the data collection methods and, at a minimum, an overview of the background of influenza and severe respiratory infections and the purpose of an HAS. Ample time should be given to practise data collection using the same data and resources that will be used during the HAS.

3.3.2 Data collection

An overview of data collection is given in Section 3.4.4 (Steps 2b and 2c) of the WHO manual (1).

Hospitals should be advised of data collection times in advance to give them ample time to find and prepare the discharge registers or to extract the data from the electronic discharge databases. Data collection teams should be paired with supervisors who can systematically check entries for accuracy. Before data collection begins, each data collection team member should be provided with the finalized list of selected respiratory discharge diagnoses and a list of all districts and administrative units located within the hospital catchment area, to serve as a reference. If possible, electronic data entry forms should be completed using a tablet or laptop rather than paper forms to reduce errors (Appendix 5 provides an example paper data collection form that could be made into an electronic data collection form). When working in teams of two, it is feasible to use a simple data entry tool created in Epi Info or Microsoft Excel, with one person reading the medical chart and the other person recoding information into the electronic form. Whenever possible, hospital staff should be present or on call during data collection to answer questions and interpret information written into the logbook or coded in the electronic databases. The data collection steps are detailed below.

Data collection steps - using paper logbooks

The steps for collecting data using paper logbooks are as follows:

- 1. Obtain access to logbooks for the time period of interest and locate the start of this time period.
- 2. At the top of each data collection sheet record the following:
 - a. Hospital district: write the district of the hospital.
 - b. Hospital name: write the name of the hospital.
 - c. Ward: write the ward of the logbook.
 - d. *Logbook number*: all logbooks for the facility should be numbered sequentially (starting with 1) by the supervisor or hospital staff before data entry begins.
 - e. *Logbook start date:* find the date of the first entry in the logbook and record this date, even if the date is before the data collection period.
 - f. Logbook end date: find the date of the last entry in the logbook and record this date, even if the date is after the data collection period.
 - g. Data collector name: write the name of the HAS data collector.
 - h. Data collector phone: write a working phone number of the HAS data collector.
 - i. Data collection date: write the date of data collection.
- 3. Review the logbook line by line (patient by patient) and do the following:
 - a. First, determine whether the patient resides in one of the districts or administrative units within the hospital catchment area. If not, move on to the next patient.
 - b. If the patient does reside in the catchment area, review all discharge diagnoses for the patient to determine whether any are on the selected list of respiratory diagnoses. If not, move on to the next patient.

Conduct a hospital admission survey

- 4. If the patient resides in the catchment area and has at least one selected respiratory discharge diagnosis, record the following information:
 - a. Age: write the age of the patient in years or months noting the unit (Y: years, M: month).
 - b. Sex: write M for males and F for females.
 - c. Residence: write the lowest administrative unit for the patient's residence.
 - d. Admission diagnoses: write all listed admission diagnoses.
 - e. *Symptom onset date*: some logbooks will record the date of onset. Record this date in DDMMYY format. If missing, leave this variable blank.
 - f. Admission date: write the date of admission in DDMMYY format.
 - g. Discharge date: write the date of discharge in DDMMYY format.
 - h. Discharge diagnoses: write all listed discharge diagnoses.
 - i. *Outcome*: if listed, write the patient outcome:
 - i. Died.
 - ii. Discharged home.
 - iii. Referred to another hospital.
 - iv. Left against medical advice or absconded.
 - v. Unknown.
 - j. Referral to or from: if referred to or from another ward, record that information here.
 - k. *Transfer comment:* add any other written information about transfers or referrals if needed.
- 5. Repeat with the next entry and subsequent entries until all patients for the selected time period have been recorded.
- 6. Once data collection has been completed, count the number of patients recorded by age group, respiratory diagnosis, month of hospital admission and (preferably) gender.

Data collection - using an electronic database

Depending on how the hospitals store their data and the type of system they use to store the data, the approach to obtaining the requisite data may be different for each database. Work with the database manager at the hospital site to obtain the required data in the correct format. This can usually be done by filtering the discharge database first by date ranges so that it contains only patients admitted during the time period of interest. Next, filter the database by residence (to exclude those hospitalized patients who do not reside within the catchment area) and then by discharge diagnoses (to identify those patients residing in the catchment area that also had at least one selected respiratory diagnosis as one of their listed discharge diagnoses). Ideally, obtain counts of hospitalized patients who had at least one of the selected respiratory diagnoses listed as a discharge diagnosis and who lived within the catchment area, summed by age group, respiratory diagnosis, month of hospital admission and (preferably) gender. For identified hospitalized patients who had at least one of the selected respiratory diagnoses, plan to collect information about patient age, sex, residence, admission diagnoses, symptom onset date, admission date, discharge date, discharge diagnosis, patient outcome and other notes, as described above for data collection from a logbook.



Calculate the catchment population

4 Calculate the catchment population

Information on calculating the catchment population is given in Section 3.6 of the WHO manual (1).

Once the HAS has been conducted at each hospital within the catchment area, the results should be summary counts of hospitalized patients by hospital, age group, respiratory diagnosis, month of hospital admission and (preferably) gender for the time period of interest. This information can be used to calculate the catchment population of the sentinel site as follows:

1. Calculate the total number of respiratory hospitalizations by age group and gender (if applicable) across all hospitals in the catchment area for the selected time period.

Total Respiratory Hospitalizations= $\sum_{Hospital=1}^{N} (Number of Respiratory Hospitalizations)_{Hospital N}$

2. Calculate the proportion of all respiratory hospitalizations occurring at each hospital by dividing the number of respiratory hospitalizations for a given age group and gender identified at one hospital by the total number of respiratory hospitalizations for that age group and gender across all hospitals in the catchment area. Repeat this calculation for each age group, gender and hospital.

Proportion of Respiratory Hospitalizations $\frac{1}{S_{entinel}} = \frac{Respiratory Hospitalizations}{Total Respiratory Hospitalizations}$



Example: If 400 respiratory hospitalizations in all hospitals in the catchment area and 100 respiratory hospitalizations at the sentinel hospital were identified, the proportion of respiratory hospitalizations at the sentinel site would be 100/400 = 0.25 (25%).

3. Multiply the proportions calculated above by age group and gender for the sentinel hospital site by the population estimates obtained previously for the entire catchment area by age group and gender (Appendix 6). These adjusted population estimates are the catchment population estimates for the sentinel site. These catchment population estimates will be used as the denominator in the rate calculations.

 $\label{eq:Catchment Population = Proportion Respiratory Hospitalizations} \textsubstitute{Substitute} X \text{ (Population Estimate of Catchment Area)}$



Example: If the proportion of respiratory hospitalizations at the sentinel hospital compared to all hospitals was 25% (or 0.25) and the census population for the catchment area was 32 000 then the catchment population would be $0.25 \times 320~000 = 80~000$.





The HAS provides an estimate of the catchment population of a sentinel site in a surveillance system. With that catchment population and known numbers of ARI case-patients, it is possible to calculate the rate of disease and the burden of disease. The steps below describe one way to estimate the rates of influenza-associated hospitalizations using the number of ARI hospitalizations, the proportion of laboratory confirmed influenza virus positive hospitalized ARI patients, and the hospital's catchment area determined from the HAS.

5.1 Estimate rates of influenza-associated hospitalizations

Data on surveillance case-patients (numerator data) and catchment population estimates (denominator data) can now be used to estimate rates of influenza-associated hospitalizations (Appendix 7).

- 1. Count the number of hospitalized ARI cases by age group, month and gender (if applicable) and the number of influenza virus positive hospitalized ARI cases by age group, month and gender (if applicable).
- 2. Refer to Section 2.4 to determine whether age group specific or all age influenza proportion positives should be used. Next, calculate the monthly proportion of influenza positive hospitalized ARI case-patients by age group (if applicable) by dividing the number of influenza virus positive hospitalized ARI case-patients by the number of hospitalized ARI cases tested for influenza viruses:

 $Proportion \ influenza \ positive \ = \ \frac{\text{Number of influenza positive hospitalized ARI cases-patients}}{\text{Number of hospitalized ARI cases tested for influenza}}$



Example: If there were 200 specimens, of which 20 were positive for influenza virus in January, the proportion positive would be 20 / 200 = 0.10 (10%).

3. If necessary, adjust the number of surveillance case-patients by age group, month and gender (if applicable) by the proportion of underreporting determined during the sensitivity analysis, by multiplying the number of hospitalized ARI case-patients by the inverse of the proportion underreported:

Adjusted hospitalized ARI cases = 1(Number of hospitalized ARI cases enrolled) Xproportion underreported



Example: If 50 hospitalized ARI cases were identified through the sensitivity analysis chart review, but only 35 hospitalized ARI cases were reported through the surveillance platform in the same time period, the proportion underreported would equal 35 / 50 = 0.7 (or 70%). Following the calculation through, if 88 hospitalized ARI cases were reported through the surveillance platform in January, the adjusted number of hospitalized ARI cases for January would be $88 \times (1 / 0.7) = 126$.



4. Calculate the monthly number of influenza-associated hospitalized ARI case-patients by age group and gender (if applicable), by multiplying the adjusted number of hospitalized ARI case-patients by the proportion of influenza positive:

Influenza-associated hospitalized ARI cases = (Adjusted hospitalized ARI cases) X proportion influenza positive



Example: If, in January, 10% (or 0.1) of the specimens were positive for influenza virus and the adjusted hospitalized ARI case count was 126, the number of influenza-associated hospitalized ARI cases would be $126 \times 0.1 = 12.6$.

5. Sum the monthly estimates of influenza-associated hospitalized ARI case-patients by year:

Annual influenza-associated hospitalized ARI cases =

 $\sum_{i=1}^{12}$

Influenza-associated hospitalized ARI cases

6. To calculate the incidence rate of influenza-associated hospitalizations, divide the number of influenza-associated hospitalized ARI case-patients by the appropriate catchment population denominator (determined from an HAS) and then multiply by 100 000:

Rate of influenza-associated hospitalized ARI cases =

annual influenza-associated hospitalized ARI cases catchment population X 100 000



Example: If the annual estimate of influenza-associated hospitalized ARI cases was 400 and the catchment population was 80 000, the rate of influenza-associated hospitalized ARI cases would be $400 / 80\ 000 \times 100\ 000 = 500\ per\ 100\ 000$.

7. Repeat these steps for all age groups and gender stratifications.

More information on estimating rates of influenza-associated hospitalizations, including detailed calculations and table examples, can be found in Chapter 3 of the WHO manual (1).



5.2 Calculate confidence intervals for the number of influenza-associated hospitalizations

The confidence intervals (CIs) for the number of influenza-associated hospitalizations depend on the variance of the proportion of specimens positive for influenza viruses and the variance of the number of ARI hospitalizations.

1. For each month of influenza data, first calculate the variance for the proportion influenza positive assuming a binomial distribution:

Variance for proportional influenza positive = (proportional influenza positive) X (1-proportional influenza positive)

number of specimens tested



Example: If there were 200 specimens, of which 20 were positive for influenza virus (proportion positive = 0.1), the variance would be = $(0.10) \times (1 - 0.10) / 200 = 0.00045$.

2. Then calculate the variance of the monthly hospitalized ARI case count (by age group) assuming a Poisson distribution:

Variance for hospitalized ARI cases = adjusted hospitalized ARI case count



Example: If there were 126 hospitalized ARI cases for January, the variance would also be 126.

3. To calculate the monthly variance for influenza-associated hospitalized ARI case-patients, combine the two calculated variances using the following formula and repeat for each month of available data:

Variance for influenza-associated hospitalized ARI cases =

(variance for hospitalized ARI cases) X (variance for proportion influenza positive) + (variance for hospitalized ARI cases) X (proportion influenza positive)² + (variance for proportion influenza positive) X (adjusted hospitalized ARI case count)²



Example: If there were 126 hospitalized ARI cases for January, the proportion positive was 0.1 and the variance for the proportion positive was 0.00045, the variance for influenza-associated hospitalized ARI cases would be $(126) \times (0.00045) + (126) \times (0.1)2 + (0.00045) \times (126)2 = 8.46$.



To calculate the variance for the annual estimate, sum the variances across the year by adding all monthly variances together. The confidence intervals would then be calculated as:

Lower 95% CI=(annual estimate of influenza"-" associated hospitalized ARI cases) – $1.96 \times \sqrt{\text{annual variance for influenza"-" associated hospitalized ARI cases}}$

Upper 95% CI=(annual estimate of influenza"-" associated hospitalized ARI cases) + $1.96 \times \sqrt{\text{annual variance for influenza"-"}}$ associated hospitalized ARI cases



Example: If the annual estimate of influenza-associated hospitalized ARI cases was 400 and the associated variance was 76.2, the lower 95% CI would be $400 - 1.96 \times \sqrt{(76.2)} = 382.9$, and the upper 95% CI would be 400 + $1.96 \times \sqrt{(76.2)} = 417.1$.

5.3 Calculate confidence intervals for rates of influenza-associated hospitalizations

1. Using the variance for influenza-associated hospitalized ARI cases, calculate the variance for the rate of influenza-associated hospitalized ARI:

Variance for rate of influenza-associated hospitalized ARI = $\frac{\text{annual variance for influenza-associated hospitalized ARI cases}}{(\text{catchment population})^2} \mathbf{X} (100\ 000)^2$



Example: If the annual variance for influenza-associated hospitalized ARI cases was 76.2 and the catchment population was 80 000, the variance associated with the rate would be $76.2 / (80\ 000)2 \times 100\ 0002 = 119.06$.

2. The confidence intervals would then be calculated using the same formulas as above:

Lower 95% CI=(annual estimate of influenza-associated hospitalized ARI cases) –

1.96×√ annual variance for influenza-associated hospitalized ARI cases

Upper 95% CI=(annual estimate of influenza-associated hospitalized ARI cases) + 1.96×√ annual variance for influenza-associated hospitalized ARI cases



Example: If the annual rate was 500 per 100 000 and the associated rate variance was 119.06, the lower 95% CI would be $500 - 1.96 \times \sqrt{(119.06)} = 478.6$ per 100 000, and the upper 95% CI would be $500 + 1.96 \times \sqrt{(119.06)} = 521.4$ per 100 000.



Summary

Understanding burden of disease attributed to seasonal influenza is important for countries in order to evaluate the impact of influenza on their population and determine appropriate prevention and control measures. This guide was designed for use in conjunction with the WHO Manual for Estimating Disease Burden Associated with Seasonal Influenza (1) to help countries evaluate their influenza surveillance data, determine the catchment areas around each sentinel hospital, conduct an HAS to estimate the catchment populations visiting each sentinel hospital, and estimate rates of influenza-associated hospitalized ARI. This guide is not meant to serve as a replacement to any WHO manual and is not inclusive of all challenges countries might experience while conducting an HAS. If you have any further questions, please contact the WHO Global Influenza Programme at WHOinfluenza@who.int.



Appendices

APPENDICES

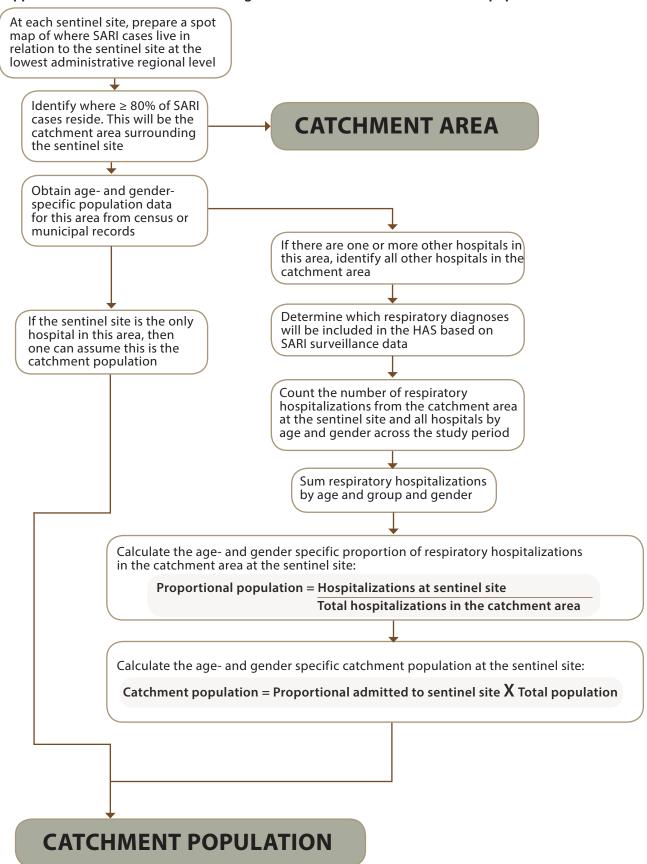
Appendix 1 Severe acute respiratory infection case definitions

Country or authority	Age group	Definition
Bangladesh (19)	<5 years	Severe pneumonia defined as cough or difficulty breathing, and at least one danger sign (i.e. chest indrawing, stridor while calm, history of convulsions, inability to drink, lethargy or unconsciousness, or intractable vomiting).
Bangladesh (19)	≥5 years	Admitted patients with subjective fever within the past 21 days and cough or sore throat.
Cambodia (20)	All	A respiratory infection with measured or history of fever and cough and difficulty breathing with onset within the past 10 days that requires hospitalization.
Kenya <i>(21)</i>	<5 years	Cough or difficulty breathing and any of the following symptoms or signs: unable to drink or breastfeed, vomits everything, convulsions, lethargic or unconscious, stridor when calm, lower chest indrawing or oxygen saturation <90%.
South Africa (3)	2 days to 3 months	Physician-diagnosed sepsis or acute lower respiratory tract infection.
South Africa (3)	3 months to <5 years	Physician-diagnosed acute lower respiratory tract infection including, for example, bronchitis, bronchiolitis, pneumonia and pleural effusion.
South Africa (3)	≥5 years	Sudden onset of fever or reported fever, cough or sore throat, and shortness of breath or difficulty breathing.
United States (22)	Adults	Pneumonia (not SARI): Presence of new infiltrate on chest X-ray and either an ICD-9-CM discharge diagnosis code for pneumonia (480–487.0) or diagnosis of pneumonia recorded on discharge summary.
WHO	All	A respiratory infection with measured or history of fever and cough with onset within the past 10 days that requires hospitalization.

CM, clinical modification; ICD, International statistical classification of diseases and related health problem; SARI, severe acute respiratory infection; WHO, World Health Organization

APPENDICES

Appendix 2 Flowchart for determining the catchment area and catchment population



APPENDICES

Appendix 3 Example of a data entry form for sensitivity analysis of application of case definitionRefer to the section titled Sensitivity Analysis Steps on page 10.

Но	Hospital name:	ne:							Data	a Collecti	Data Collection Date:			
Ward:	rd:								Data	Data Collector:	or:			
#	Week	Sex	Age (years)	Age (months)	District	Admin date*	Admin diagnosis⁺	Onset date	Fever	Fever meas.	Temp	Cough	# Sx days **	SARI
									_					
-	-						L	H -		i (

APPENDICES

Appendix 4 Example of official letter to participating hospitals

For private clinics

Re: Understanding influenza in Country B

D D	
Dear Drs.	
Deal Dis.	

The ministry of health is currently conducting a review to understand influenza in Country B. Influenza-associated illness is known to contribute substantially to morbidity and mortality globally. The ministry of health has already begun the process of evaluating the burden of influenza. However, further exploration is required to understand severe acute respiratory infections (SARI) cases seeking medical attention at private health facilities.

To complete this project, data collection is required. Data will be collected exclusively through medical chart review of admission logbooks and individual patient charts. No patients or other persons will be interviewed, and no personal identifying information will be recorded.

This review will be led by the Country B ministry of health with support from provincial health departments, the World Health Organization and the United States Centers for Disease Control and Prevention.

The steps for data collection that will be undertaken by the ministry of health from private admitting clinics are as follows:

- 1. Identify diagnoses associated with SARI (e.g. pneumonia, bronchitis, etc.).
- 2. Count all admissions with a defined respiratory diagnosis at the private clinic for x years.

We look forward to your cooperation with this review, which will inform policies for improved influenza programmes and outcomes.

APPENDICES

Appendix 5 Example of a hospital admission survey data collection form Refer to the section on Data Collection Steps on page 21.

	Data Collector Phone:	Residence Admin Sym diagnoses On diagnoses (DD/N					
Hospital District: Logbook Number:	Jone:	Admin Symptom Onset date (DD/MM/YY)					
Hospital Name: Logbook Date Range:	Data Collection Date:	Admission Discharge diagnoses (DD/MM/YY)					
		Outcome Referral					

^a Refer to list of relevant administrative units; ^b Refer to list of relevant respiratory diagnoses

APPENDICES

catchment population (females) for sentinel site **Estimated** $(c \times d)$ Proportion of female population accessing sentinel site for selected respiratory diagnoses out of all hospitals in catchment area € Census population of females in catchment area Estimated catchment population (males) for sentinel site $(a \times b)$ Proportion of male population accessing sentinel site for selected respiratory diagnoses out of all hospitals in catchment area 9 Census population of males in catchment area **a** 5 to <15 years 2 to <5 years 1 to <2 years AGE GROUP <6 months <65 years to <1 year ≥65 years 6 months 15 to <50 years 50 to Total

Appendix 6 Denominator population estimate using data from hospital admission surveys and census population estimates

A DDENIDICEC

						,	APPENDIO	.E5					
≥65 years													
50 to <65	years												
15 to <50	years												
5 to <15	years	00I								ROUP			
2 to <5 years		REPEAT EACH ROW FOR EACH MONTH OF TIME PERIOD								ACROSS MONTHS FOR EACH YEAR AND AGE GROUP			
1 to <2 years		FOR EACH MON								ITHS FOR EACH \			
6 months	to <1 year	PEAT EACH ROW											
<6 months		~ -								SUM ESTIMATES (E)			
AGE GROUP			Number of hospitalized ARI cases positive for influenza	Number of hospitalized ARI cases in whom clinical specimens were collected for laboratory confirmation of influenza	Proportion of hospitalized ARI cases positive for influenza (a)/(b)	Total number of hospitalized ARI cases identified	Proportion of hospitalized ARI cases underreported estimated during sensitivity analysis	Adjusted number of total hospitalized ARI cases (d) \times (1/(e))	Estimated influenza-associated ARI hospitalizations (f)*(c)		Annual estimated influenza- associated ARI hospitalizations	Estimated catchment population for the sentinel site	Annual incidence rate of influenza-associated hospitalized ARI at sentinel site (per 100 000 population) (h)/(i) × 100 000
AGI			(a)	(q)	(Ο)	(þ)	(e)	Œ	(g)		(h)	<u>(i)</u>	Ð

ARI, acute respiratory infection

Appendix 7 Influenza-associated incidence rate estimate

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Appendices

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A SUPPLEMENT

TO THE WHO PUBLICATION

"A manual for estimating disease burden associated with seasonal influenza"

Using a hospital admission survey to determine rates of influenza-associated severe acute respiratory infections

