



**Centers for Disease Control and Prevention
Case Studies in Applied Epidemiology**

**Influenza Surveillance Systems
(*International Setting*)**

Facilitator's Guide: January, 2009

After completing this case study, the participant should be able to:

- Define the surveillance objectives, methods of hospital selection, and key data collection priorities for sentinel surveillance for seasonal influenza and severe respiratory diseases
- List appropriate surveillance strategies and trigger criteria needed for the early detection of influenza A(H5N1) in hospitals and communities
- List appropriate surveillance strategies and trigger criteria needed for a broader pandemic early warning system
- Describe how a sentinel site surveillance system for influenza provides an important support function for a pandemic early warning system
- Identify five ways to enhance human avian and pandemic influenza surveillance activities in areas where there are known influenza A(H5N1) outbreaks in poultry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service



PART I. Routine Surveillance for Respiratory Disease and Seasonal Influenza

You have been asked to travel to the Republic of Pegu as an international consultant on Influenza. Your terms of reference for this trip are to work with the local Ministry of Health and other international partners to provide technical assistance on the development of a comprehensive National Influenza Surveillance System.

Republic of Pegu



Pegu is a “developing” country in Southeast Asia that contains 21 provinces and a population of approximately 50 million people. Its capital is Anawrahta.

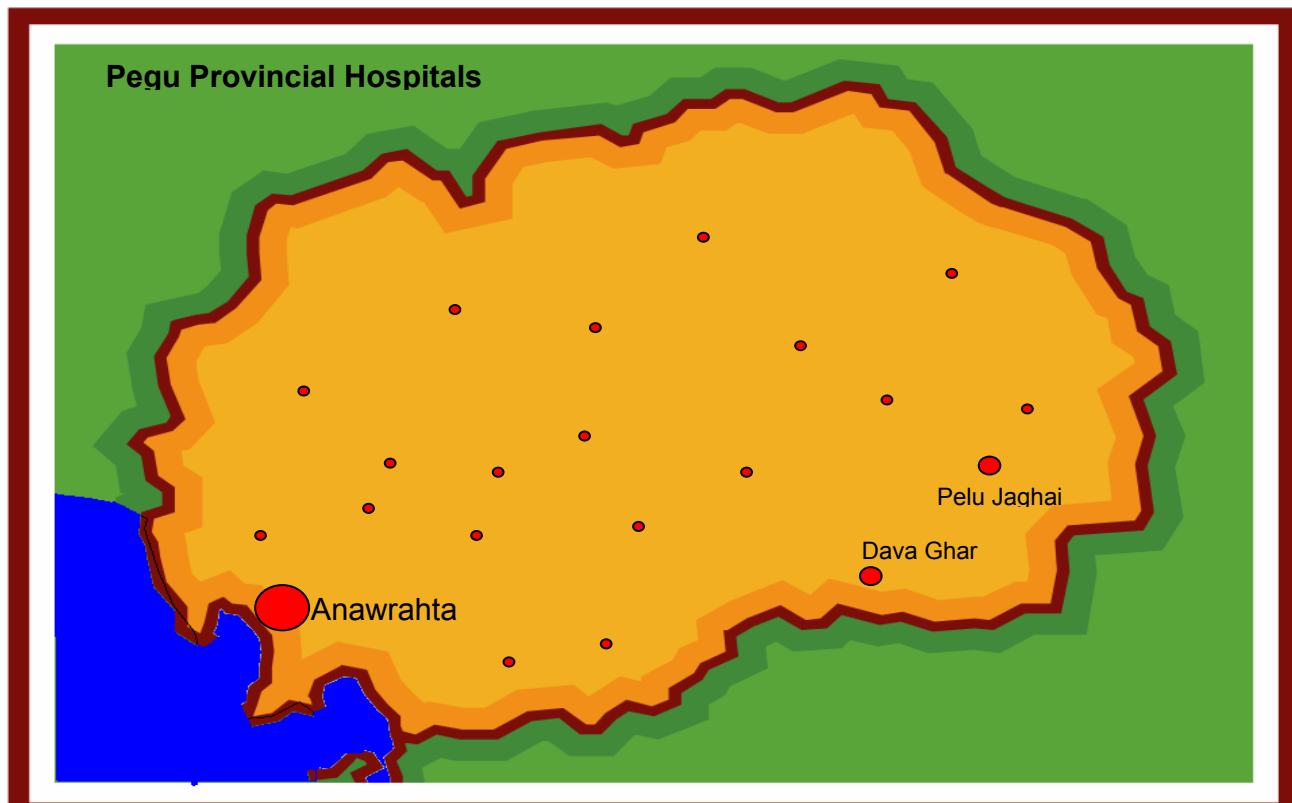
Geography: There is a monsoon climate. Pegu is bordered by five other countries, and faces the ocean on its southwestern border. Migrants regularly cross these borders and have prompted attempts at coordinated infectious disease surveillance activities among these countries. Approximately 75% of the population live in rural areas and do not have access to highways. Road conditions become poor or impassible during the monsoon season. In a recent health survey, 30% of rural respondents indicated that they would not take sick family members to local hospitals but instead would go to their village healer.

Health care: The Pegu Ministry of Health is the focal point for planning, organization, financing, regulation and provision of health care for the population. Hospitals within the country include teaching hospitals, specialist hospitals, provincial hospitals, district hospitals, and local health stations/traditional clinics. Every district has a 16-50 bed hospital, with a district medical officer who has both public health and curative responsibilities. There are 12 traditional medicine hospitals in the country as well.

There is an uneven geographical distribution of health care with poor quality of care and low service utilization in rural areas. Polio is on the verge of being eradicated, reflecting a well-established grassroots polio eradication infrastructure. This has produced a system of village health committees that provide informal communication mechanisms and some infrastructure for social mobilization.

Influenza laboratory testing capabilities: District hospitals and traditional hospitals have no laboratory capacity. The National laboratory is the only lab equipped to undertake PCR analyses although serologic diagnostic methods are undertaken at regional laboratories. While this laboratory uses the WHO influenza reagent kit, the closest WHO reference laboratory is in the neighboring country to the southeast.

Surveillance infrastructure: There is a national notifiable disease surveillance system in Pegu. Certain diseases such as diphtheria, cholera and yellow fever require immediate reporting while others are reported routinely (usually within 3 days), using a standard reporting form (that measures case demographics, condition being reported, hospitalization status, travel history and reporter information). Reporting is passive and is usually the responsibility of the health care provider who makes the diagnosis of a patient's illness.



Question 1:

What are the goals of routine (seasonal) influenza surveillance?

The goals of a routine seasonal or human influenza surveillance system should include:

- a) describing virus circulation and providing virus isolates for vaccine development,
- b) defining the epidemiology of influenza, patterns of viral circulation, clinical manifestations of influenza, and high risk groups for severe outcomes in order to make better recommendations for prevention of influenza infection—especially regarding the use of vaccines, and,
- c) providing a support mechanism for broader pandemic early warning and monitoring systems.

It is important to note that much of what is known about influenza is from data gathered in industrialized countries of the world. Very little is known about the occurrence and impact of influenza in the developing world and the tropics. Such a routine influenza surveillance system also has value for pandemic preparedness in that countries need data specific for their situation to plan appropriate interventions and to make accurate predictions and plans for outbreaks and pandemics. The establishment of a strong influenza surveillance system will support pandemic early warning activities through the enhancement of laboratory capacity for specimen testing, creation of a logistical network for specimen collection and transport and the training of a cadre of laboratorians who routinely work with influenza viruses, and can therefore accurately identify a novel virus. While a routine influenza surveillance system does not replace the need for the strengthening of a broader pandemic early warning network, these surveillance systems will help to strengthen the important relationships between trained epidemiologists and educated and aware health care workers. Finally, the only practically feasible formal surveillance for most countries during a pandemic will be to continue what is already done on a routine basis. A few well chosen and maintained surveillance sites will be sufficient for tracking the course of the pandemic, especially if combined with other data sources.

Question 2:

Would universal or sentinel surveillance best be used to achieve these goals?

Sentinel site surveillance for hospitalizations due to respiratory disease and possibly outpatient visits for influenza-like-illness probably makes the best sense in most situations. If sentinel sites are chosen well, a sample of cases can be tested for influenza to meet these surveillance objectives. For the goals of describing virus circulation and the epidemiology of influenza, obtaining a limited amount of high quality data from a few well-run sites is preferable to obtaining a lot of lower quality data from many sites.

After many hours of travel you land in Pegu. Your terms of reference are to evaluate the influenza and respiratory disease surveillance infrastructure and then work with the MOH staff to develop a protocol to implement a sustainable national influenza surveillance system. You start Monday morning with a visit to the office of the Pegu MOH Deputy Director. The Deputy Director says that he would like to improve the existing “pneumonia and influenza” surveillance system” in Pegu to help them better understand seasonal virus circulation, and epidemiologic risk factors for severe influenza. The surveillance officer joins you in the room and describes the current surveillance system that is in place.

- The system uses clinician initiated “pneumonia, ARI, and influenza surveillance” of hospitalized patients. There are no formal clinical case definitions as doctors may choose to select the hospitalized patients that they feel have signs and symptoms compatible with pneumonia/influenza and submit nasopharyngeal, oropharyngeal, and/or serum specimens to a regional laboratory for direct immunofluorescence or viral culture testing. When the regional laboratories undertake serologic testing for confirmation, convalescent sera are often obtained from cases. When there is a particularly severe or high profile case to be tested, the national laboratory will use PCR analyses for confirmation.
- Regional laboratories refrigerate specimens and test 90% of specimens within nine days of receiving them. The National Laboratory undertakes its confirmatory tests within 24-48 hours of receiving specimens.
- Isolates from all confirmed influenza A specimens at the regional level are sent to the national laboratory. However you cannot obtain a consistent answer regarding the number of these isolates which are shared with one of the four WHO collaborating centers.
- Routine surveillance reports are prepared monthly and are based on total counts of patients discharged with pneumonia, ARI or clinician defined influenza. These data are presented by age, gender and facility. The routine surveillance reports suggest that a very small percentage (1%) of these cases are diagnosed as having laboratory confirmed influenza, leading some MOH partners to suggest that influenza is not a very common disease in Pegu. However of specimens tested at the national laboratory, 3-4% were found to be influenza positive annually.
- A standard patient-level data form is completed for any case that is to be tested for influenza. There is fairly consistent and accurate data entry of case demographics and date of hospital admission into the surveillance database (data entry occurs at regional laboratories). However there is limited completeness of fields reflecting date of specimen collection, date of illness onset, presence of fever, and final laboratory results. Some of this lack of completeness is due to the incomplete and rapid filling of forms by clinicians submitting specimens, and some is apparently due to the lack of timely updating of the database with confirmatory results.

You spend the next 3 days visiting six different provincial hospitals, some of which are referral facilities for severe respiratory illnesses. While at the hospitals you notice several things:

- All 21 of the provincial hospitals have submitted pneumonia and influenza data into the system, but only four of the six hospitals that you visited (those in or near Anawrahta province) appear to be reporting data every month.
- It is unclear from hospital to hospital, and clinician to clinician, what clinical criteria are being used to define a discharge as “pneumonia” or “influenza”.
- Clinician interest in this surveillance system is minimal. While they understand the value of obtaining virus strains for global vaccine production, they are

uncertain about how the data they provide will be used to inform influenza control policies in Pegu.

- Confirmatory testing for influenza A and B (as well as subtypes H1, H3, and H5) is undertaken at the national laboratory by real time RT-PCR. This is not a WHO reference laboratory and you are unsure how this laboratory is integrated with the WHO/Flu-Net surveillance system.
- Your limited retrospective review of available records does not suggest any overt seasonality patterns. There is some evidence of a possible bi-phasic pattern that appears at two hospitals which seem to account for 70 percent of the reported pneumonia and influenza cases (with evidence of possible “peaks” in January and July).
- Local physicians and record keepers report rarely, if ever, receiving summaries of influenza circulation in their area.
- There is no system of immediate notification (within 24 hours) of specific cases that need to be prioritized and tested for the presence of Influenza A(H5N1) or other less common pathogens with pandemic potential.

This is all you have been able to learn about the existing surveillance system. The Deputy MOH asks you if the existing system will meet objectives for seasonal influenza surveillance?

Question 3:

Will this system meet all of the objectives for routine seasonal/human influenza surveillance that were discussed earlier? Why or why not?

Briefly remind the group of the objectives of routine influenza surveillance: a) describing virus circulation and providing virus isolates for vaccine development, b) defining the epidemiology of influenza, patterns of viral circulation, clinical manifestations of influenza, and high risk groups for severe outcomes, and c) providing a support mechanism for broader pandemic early warning and monitoring systems. Help them understand how the attributes below are important to meeting these objectives.

KEY POINTS: Discuss in context of surveillance system attributes.

Timeliness: The collection and reporting of surveillance data must be timely if it is to be useful to clinicians, public health authorities, and the community. Timeliness can be applied to data reporting, specimen shipment to the laboratory for testing, receipt of specimens by the laboratory, laboratory processing and testing of specimens, and reporting of laboratory results.

- It doesn't seem like a lot of metrics for timeliness have been defined in this system. However the lag of up to nine days for testing of refrigerated specimens at the regional laboratories may be a little long. This may have something to do with the low influenza confirmation rate being reported.

One method of quantifying timeliness is to calculate the percentage of times that a site achieves targets for specific time intervals, for example, the percentage of times that a site sends reports or specimens to the appropriate place within a specified time frame. A reasonable target might be that 80% of data reports sent within 48 hours of the data reporting deadline or that 80% of specimens shipped within 48 hours of specimen collection. Likewise, for the laboratory, the percentage of samples that are tested and have final results within a target time frame can be calculated. A similar quality metric that can be used is the calculation of the average time to accomplish surveillance activities. For example, a given site that is chronically late in sending data every month might have an average of 4.5 days between the deadline for receipt (the day of the week or month on which reports are due) and actual receipt of data per month over

time. For laboratory sample processing, the average number of days between receipt of specimens and the reporting of the results can be measured and followed similarly. Site time averages can be compared to identify sites that are underperforming and to target improvements. Either percentages of sites achieving timeliness targets or time lag averages can also be used as a quality metric to be followed over time.

Time intervals that are appropriate for quantification include:

- Data reporting from the sentinel site to the next administrative level
- Data reporting from that level to the national level
- Time interval between specimen collection and shipment to laboratory for testing
- Result reporting from laboratory to referring institution and physician
- Processing within the laboratory from receipt of specimen until result is available
- Time interval between shipment from the site and arrival in the laboratory
- Time interval between date of onset of fever and specimen collection

Acceptability and Representativeness: Continuous assessment of acceptability and representativeness should be included in regular surveillance system evaluations. Quantitative measures of acceptability can include sentinel site participation rate, interview completion and question refusal rates, completeness of report forms, facility reporting rate, and timeliness of data reporting.

- There is apparently very limited feedback of results to the reporting clinicians. Any feedback they would receive would not be likely to be timely enough to affect clinical decision-making. But even regular reports on strain circulation and reports on the start of influenza season in their region could be useful to them with regard to infection control planning and perhaps even empirical treatment decisions. Lack of feedback will limit acceptability to physicians and limit their desire to submit laboratory specimens into the system. It's clear that many already perceive that they are unsure how the data that they report will be used to inform national influenza control policies.

To assess representativeness, case characteristics can be compared to census data to ensure appropriate capture of a broad range of society. Furthermore, disease rates determined by special studies or other surveillance activities can be compared to sentinel surveillance data.

- Warning signs here are that a large percentage of cases are being accounted for by only a two provincial hospitals, although the original system wasn't overtly designed to be a sentinel system. There appears to be uneven reporting and it is also clear that many provincial hospitals are not regularly reporting data for their provinces into the system. You need to know more about the hospitals and their representativeness of the population at large.

Completeness

Indicators of completeness can be determined through analysis of reported data. Suitable completeness indicators may include the percentage of reports received from each site with complete data, percentage of total expected data reports that are received, and the percentage of total expected cases that have specimens submitted to the laboratory.

- Data reporting at the site level seems incomplete with an over-representation of some sites relative to others. Completeness of data entered into the surveillance database for cases tested in the laboratory also appears to be variable given a variety of reported empty fields such as date of illness onset and final confirmation results. There is a need for refresher training on form completion by clinicians, and a need to remind data entry staff to update the database more frequently with final laboratory results.

Data Validity/Data Quality: A lack of standardization in what is reported (e.g. no case definition) across hospitals limits any ability to determine a baseline of pneumonia or influenza cases by season, and severely limits the possibility of producing interpretable trends in respiratory disease in this population. This is a core component of data validity as without a standard case definition one cannot make

estimates of rates of illness, or assess the risk factors for pneumonia/influenza in the population. The apparently incomplete reporting by most of the facilities in the system also limits any ability to draw conclusions about laboratory confirmed influenza as a cause of hospitalized patients in the country.

- The combination of lack of a standard case definition and fairly long refrigeration times for specimens prior to laboratory testing with DFA may be issues of data quality that are influencing the low influenza positive rate being observed at regional laboratories in the system. Similarly, this limitation may also reduce the utility of the surveillance system to inform influenza control policy (a concern raised by the clinicians in Pegu).

Once a case definition is established, regular field evaluations and audits at a facility level must be a standard component of the surveillance system. This process can determine that cases are being counted appropriately, that reported cases meet the case definition, and that sampling procedures are being employed uniformly without evidence of bias. Data values recorded in the surveillance system can be compared to a gold-standard of chart-review values by a retrospective review of a sample of medical records. If a sampling procedure is employed for specimen collection, audits can ensure procedures are uniform without evidence of bias. Additionally, audits can determine whether clinical specimens are being taken, stored, processed, tested (if appropriate), shipped properly, and shipped in a timely fashion from all those who meet sampling criteria.

Flexibility: With appropriate laboratory facilities, this system may be flexible enough to also be used to examine the circulation and relative burden of other respiratory pathogens in hospitalized cases. However this can only happen if standard case definitions are implemented. Once the concept of case definitions is introduced in Pegu, this system could be expanded to include a wider range of hospitalized respiratory diseases under surveillance.

After sharing your perspectives on the different objectives for the national influenza surveillance system, and providing the MOH with a draft report of your initial surveillance evaluation, the Deputy MOH agrees with your arguments to build a sentinel site surveillance system for severe respiratory disease and seasonal influenza. Several key recommendations from your surveillance evaluation will be implemented in the new surveillance system:

- A standard case definition for “severe acute respiratory illness” will be developed
- Sentinel sites in the surveillance system will be formally identified
- Clinicians at sentinel sites will receive training on the future case definition, as well as on the importance of complete epidemiologic data capture for all cases tested
- Influenza isolates identified by the surveillance system will be routinely sent to the WHO collaborating centers, and entered into WHO/Flu-Net. Refresher trainings on the need for complete and timely data entry into the surveillance data base will also be undertaken.
- A plan for regular feedback of surveillance information to clinicians will be implemented. During periods of known epidemic influenza circulation this feedback will occur weekly.
- The surveillance system will add an immediate notification and response component for high priority cases and clusters so they can be quickly investigated at the request of local public health authorities.
- Performance indicators for objective monitoring and evaluation of sentinel sites will be developed. Site visits and data quality audits will be routinely undertaken.

- The national laboratory will increase the number of specimens tested annually by PCR methods. They will provide additional quality control and quality assurance on the methods of specimen collection, packaging, transport and testing that are being implemented at regional laboratories. They will provide random “blinded panels” of influenza specimens to the regional labs to assess the quality of their confirmatory methods, and will also test random samples of “influenza negative” specimens submitted by the regional laboratories.

The Pegu Ministry of Health now wants you to work with them to write a formal set of national surveillance guidelines that will be quickly written into law by the Government of Pegu. As a priority this should outline the approach to establish sentinel surveillance for a standard case definition of severe respiratory illness among hospitalized inpatients.

Question 4:

What criteria will you use to decide where sentinel hospitals should be located?

Ideally, selected sites would be representative of a wide cross-section of ethnic and socioeconomic groups of the country or region. In addition, because influenza virus activity varies with climate, it is important to include sites from different climatic regions. Placement of sites in areas where the population denominator can be estimated will facilitate burden of disease estimates. Ultimately, the choice of sentinel hospitals will often be based on practical issues of feasibility such as human resources, communication infrastructure, and the availability of specimen transport. There is no ideal number of surveillance sites, and the number chosen by a particular country will depend in part on resources available. There should be a focal point at each hospital that oversees collection and reporting of data and specimens.

Important characteristics of chosen sentinel sites

- Representative of a defined population
- Reasonable hospital logistics for case identification, specimen collection, and transport
- Politically acceptable
- Practically feasible

“An added benefit”: Surveillance sites can also be positioned to attempt to detect human cases of novel influenza virus infection (for example, near areas of intensive poultry husbandry). If the characteristics of the chosen sentinel sites listed above are also achieved then this may provide added support to any existing pandemic early warning systems.

Since there is no formal case definition for “pneumonia” in PEGU, you offer to help improve standardization of reporting by offering a CDC/WHO case definition for Severe Acute Respiratory Illness (SARI) for consideration:

| | |
|--|--|
| Severe Acute Respiratory Illness (SARI) >5 years | <p>ALL OF THE FOLLOWING</p> <ul style="list-style-type: none"> • Sudden onset of fever over 38°C, AND • Cough or sore throat, AND • Shortness of breath or difficulty breathing, AND • Requiring hospital admission |
| Severe Acute Respiratory Illness (SARI) ≤5 years | <p>EITHER</p> <p>IMCI Criteria for Pneumonia Any child 2 months to 5 years of age with cough or difficult breathing and:</p> <ul style="list-style-type: none"> • breathing faster than 50 breaths / minute (2 – 12 months) • breathing faster than 40 breaths / minute (1 – 5 years) • (Infants less than 2 months with fast breathing 60 breaths or more per minute are considered serious bacterial infection). <p>IMCI Criteria for Severe Pneumonia Any child 2 months to 5 years of age with cough or difficult and any of the following general danger signs:</p> <ul style="list-style-type: none"> • unable to drink or breastfeed • vomits everything • convulsions • lethargic or unconscious • or chest indrawing or stridor in a calm child. <p>AND Requiring hospital admission</p> |

Question 5:

What are the benefits and drawbacks of this case definition?

- **Benefits:** For seasonal influenza surveillance, even just testing a random sample of inpatient SARI cases during influenza season should give a sense of the strains that are circulating, the pathogens causing SARI, and the risk factors for severe illness. The use of a SARI case definition will provide some standardization of reporting across hospitals and regions. Surveillance for SARI can be used to understand the epidemiology and burden of other respiratory pathogens beyond influenza. It is a very important clinical entity in its own right and is the second leading cause of mortality in low income countries. It should be better understood so it can be better prevented. Finally, changes in the circulation of SARI could represent the emergence of a new respiratory pathogen in the population.
- **Drawbacks:** Reporting severe influenza in a standard way using a case definition is a major philosophical change for the clinicians of Pegu and will require training and explanation. The case definition appears sensitive. A single national laboratory would become overwhelmed if it received influenza testing requests for SARI cases from too many locations.

Question 6:

What kinds of data should be collected from the SARI cases from which specimens are being collected? Why do we want to collect this data?

Encourage students to think of these variables within the six broad categories of surveillance variables below. The data collected will be used to describe those persons most at risk for a serious respiratory illness. Minimum data elements collected from SARI cases should include: age, name, address, sex, vaccination status, co-morbid conditions including tobacco use, date of collection of epidemiologic data and specimen sampling, date of symptom onset, a unique identifier to link the case to a laboratory specimen, and a medical record number to allow for future data review. Collected data can be broadened to include clinical signs and symptoms, laboratory data, and therapies including antivirals. To provide a support function for pandemic early warning, additional variables on occupation, potential exposure to poultry, and other persons with severe respiratory illness might be added.

General Information

- Unique identification number*
- Medical record number*
- Name (of patient and parent's name, if a minor)*
- Date of Birth*
- Sex*
- Address*
- Date of onset of symptoms*
- Date of collection of epidemiologic data*
- Part of an outbreak investigation
- Inpatient or outpatient

Clinical Signs and Symptoms

- Fever >38*
- Cough*
- Sore throat*

Type of Specimen Collected and Date of Collection

- Throat swab specimen – date of collection*
- Nasal swab specimen – date of collection
- Other specimen (if collected) – date of collection

Possible H5N1/ Pandemic Pathogen Exposures

- Occupation of patient*
- Suspected H5N1 case (per WHO)

- SOB/Difficulty breathing*
- IMCI danger signs (per WHO protocols)*
- Diarrhea
- Other

- protocols)
 - Contact with sick or dead poultry or wild birds*
 - Contact with a friend or family who has severe respiratory illness
 - Travel in an area known to have endemic circulation of avian influenza H5N1
 - Eating raw or undercooked poultry products in an area of H5 N1 virus circulation

Pre-Existing Medical Conditions

- Liver disease*
- Kidney disease*
- AIDS, cancer, or other immune compromised state*
- Neuromuscular dysfunction*
- Diabetes*
- Heart disease*
- Lung disease*
- Smoking history*

Treatment History

- Vaccination against influenza within the past year*
- Currently taking antiviral medicine

Key Points:

*** Recommended essential data for Severe Acute Respiratory Illness surveillance.**

The importance of a lab-epi link must also be emphasized as critical. There must be a system in place where the same unique identifier is placed on both the laboratory specimen and epidemiologic data collection forms.

The Chief Surveillance Officer recognizes the value of this case definition to detect cases of severe influenza, pneumonia, and even to measure the contribution of influenza to exacerbations of illnesses such as chronic lung disease, heart disease and diabetes. She recognizes that standardization of reporting through the use of a case definition will help the Pegu MOH describe the epidemiology of severe seasonal influenza, and provide some isolates for identification of viruses. However, she raises the concern that if too many hospitals report SARI cases, the laboratory and response components of the surveillance system will become overwhelmed. She feels that randomly sampling SARI cases at multiple hospitals would provide good representation of the population, but also thinks that this would be complicated for hospital staff who are new to the concept of this kind of surveillance. Instead, she asks if Pegu might just sample *all* of the SARI cases from a *few* hospitals—this way surveillance staff wouldn't have to be taught the complexities of random sampling. You nod in agreement to her suggestion and agree that quality data can be obtained from a few well run sites. You both feel that practically speaking, small amounts of good data are better than large amounts of bad data. You will initially pilot the SARI surveillance in five geographically diverse hospitals. Two of these hospitals serve as regional reference centers for severe

respiratory illness, and three others are a bit smaller but have fairly well defined catchment areas of populations-served.

The next morning the Chief Surveillance Officer (CSO) greets you with an additional question. She says she would like the surveillance system to also capture some virus isolates and risk factor information from less severe, more common, influenza cases. She notes that certain influenza types and sub-types of influenza (for example influenza B and possibly influenza A (H1N1) may produce less severe disease than influenza A(H3N2). She thinks that only sampling hospitalized patients in the surveillance system could under-represent infections caused by influenza B, and possibly influenza A(H1N1) in the surveillance system.

Question 7:

How could the sentinel site system be expanded to include some less severe influenza cases?

The Chief Surveillance Officer has a good point! The highest priority should be to collect data on SARI cases because they contain the highest influenza-associated morbidity and mortality. However, if resources permit, data collection at sentinel sites could be expanded to include ambulatory patients with ILI. Surveillance for Influenza-Like-Illness (ILI) in outpatients would provide information about additional virus circulation and trends in less severe influenza-like-illness in Pegu.

- ILI is defined according to WHO criteria as:
 - Sudden onset of a fever over 38°C, AND
 - Cough or sore throat, AND
 - An absence of other diagnoses.

As you can see, the ILI case definition does not require hospitalization or difficulty breathing. If ILI surveillance were implemented in the outpatient clinics of the selected SARI sentinel site hospitals, one could then possibly compare the epidemiologic and demographic risk factors for mild and severe disease. Aggregate weekly counts of ILI outpatient visits and the proportion of weekly ILI cases testing positive for influenza have been shown to rise and fall with influenza virus circulation in a population. As the number of cases presenting to ambulatory care sites is likely to be very large, case counts would be aggregate, and only a small sample of cases would have clinical specimen and epidemiologic data collected. Weekly case counts should be categorized by age group according to well-studied and locally standard age range categories (6 months to 23 months, 2-4 years; 5 – 18 years; 19-49 years; 50-64 years; and ≥65 years). Cases chosen to have detailed epidemiologic data and clinical specimens collected should be selected in as unbiased a manner as possible. The selection protocol must take into account local health seeking behaviors such as differential use of evening and weekend clinics. Ideally, the weekly total number of patients seen by clinics by age group will also be collected to allow for proportion of ILI to be calculated. As with SARI Surveillance, ILI Surveillance should emphasize quality data from a few well-run sites, over broad system expansion.

Together you decide to also implement outpatient ILI surveillance at the five SARI sentinel site hospitals. You agree that systematically selecting the first two cases of ILI each day from the general adult and pediatric clinic for laboratory testing and epidemiologic questioning will be understandable to local staff. The sentinel site

hospitals will also provide weekly tallies of the total number of ILI cases presenting to the sentinel site facilities. You spend the next 3 days developing reporting forms and databases and training staff at the first proposed sentinel site. You are amazed at the speed and efficiency with which public health action can take place in the Republic of Pegu! It seems that the new SARI surveillance system will soon begin to operate. The CSO proudly provides the new draft guidelines at the morning briefing to the Deputy Minister of Health.

PART II. Influenza A(H5N1) and Pandemic Early Warning Surveillance

Republic of Pegu



Avian Influenza Update!

That evening at dinner the Deputy MOH indicates that over the last year there have been a series of reports from different media sources indicating mass deaths of flocks of chickens as well as geese and other waterfowl. These deaths have primarily occurred in the southeastern region of Pegu. The Ministry of Agriculture (MOA) recently sent investigators into this region to follow-up on a particularly large outbreak and has reported test results from three samples collected from dead chickens sent to the national laboratory in Anawrahta to be “weakly positive” for avian influenza A(H5N1). There is no systematic surveillance for avian Influenza A(H5N1) in poultry, wild bird or other animal populations. He is feeling pressure that high level political officials are demanding to hear from about his current plans for “detecting bird flu”, and he now needs you to develop surveillance guidelines for Pegu’s pandemic early warning system. He asks you based on your site visits, “if a human case H5N1 was admitted to a surveillance hospital or to another hospital in Pegu, do you think it would be immediately identified and reported?”

Question 8:

Are you confident that a hospitalized human case of influenza A(H5N1) would be recognized and responded to? Why or why not?

No

- There is not yet any system of immediate notification (within 24 hours) of specific SARI or severe respiratory illness cases that need to be prioritized and tested for the presence of influenza A(H5N1).

The incubation period for avian influenza usually ranges from 2-7 days, but treatment appears to be most effective when it occurs during the first 48 hours of exposure. Cases may also be infectious up to 24 hours prior to symptom onset so there is an urgent need to quickly identify close contacts of any suspected or confirmed cases.

Question 9:

How might surveillance for seasonal influenza support efforts to recognize an emerging pandemic or to detect human cases of influenza A (H5N1)?

The routine surveillance system should also provide a support function to pandemic early warning systems. The recently adopted International Health Regulations (2005) call for strengthened surveillance for all events which may constitute a Public Health Emergency of International Concern, including human cases of novel influenza virus infection. The establishment of a strong influenza sentinel surveillance system will support pandemic early warning activities through:

- the enhancement of laboratory capacity for specimen testing,
- creation of a logistical network for specimen collection and transport,
- the training of a cadre of laboratorians who routinely work with influenza viruses, and can therefore accurately identify a novel virus.
- These surveillance systems will also strengthen the important relationships between trained epidemiologists and educated and aware health care workers.

A severe pandemic will also place significant strains on health care infrastructure, limiting countries' capacity to collect and report data. As a result, monitoring the course of the pandemic will need to make use of existing sources of information that are being reported in the inter-pandemic phase as part of routine influenza surveillance, and so is a continuation of current surveillance activities. During a pandemic, data from the routine sentinel site surveillance system will help describe the:

- changing geographic location of the virus,
- the trend in cases, and,
- the severity of the pandemic.

As more countries institute routine SARI surveillance at sentinel sites, the data set that may be used to monitor a future pandemic will become more complete and standardized, and thus more useful. The only practically feasible formal surveillance for most countries during a pandemic will be sentinel-based and a few well chosen and maintained sentinel sites will be sufficient for tracking the course of the pandemic, especially if combined with other data sources.

You suggest that in order to ensure that any human case of influenza A (H5N1) is rapidly detected, clinicians who work in the sentinel site hospitals, *and also those working at non sentinel-site hospitals*, need to be trained in additional influenza A(H5N1) screening criteria. You add that because the clinical presentation of influenza A(H5N1) is similar to severe pneumonia caused by many other pathogens, these screening criteria would have to include epidemiologic risk factors that will help doctors elevate their index of suspicion that some cases of SARI may be more likely than others

to be due to infection with influenza A(H5N1). You add that these screening criteria have been called “triggers” (or “signal events”) in other countries’ pandemic early warning systems. The CSO replies that the use of epidemiologic criteria would be a useful way to prioritize certain cases of SARI for immediate alert, investigation and laboratory testing for influenza A(H5N1), seasonal strains, and possibly other pathogens as well. As you work on the pandemic early warning portion of the surveillance guidelines that morning, you provide the CSO with examples of trigger criteria for influenza A(H5N1) that were used in a neighboring country.

Question 10:

Suggest some epidemiologic “trigger criteria” that could be used to prioritize SARI cases for immediate reporting and laboratory testing for Influenza A(H5N1)?

Cases of severe acute respiratory infection (SARI) with a possible link to avian influenza:

- Any SARI case meeting WHO suspect, probable or confirmed case influenza (H5N1) definition.
- Close contact with a WHO suspect, probable or confirmed case
- SARI cases with an occupational exposure such as workers in poultry industry, poultry culling, etc.
- SARI cases who have consumed raw or undercooked poultry or wild bird products
- SARI cases who have handled samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting

The CSO agrees with these criteria but asks the question “what if the next pandemic isn’t caused by influenza A(H5N1), but some other respiratory pathogen that isn’t associated with poultry or wild bird exposure”? She adds that “we should learn our lesson from SARS and design a system that can also detect a respiratory pathogen that is spreading between humans and causing severe disease”.

Question 11:

Suggest some epidemiologic “trigger criteria” that might raise the index of suspicion that respiratory pathogen with pandemic potential is circulating in the population?

Indeed, the CSO makes another good point! As our experiences with SARS suggested, and because very few of the initial cases (and even less of the later cases) in an incipient influenza A (H5N1) pandemic are likely to have any reported exposure to sick or dying birds, health care workers also need to also be sensitized to immediately report clusters of any severe respiratory disease that could indicate the circulation of a new respiratory pathogen in their locality. These criteria should be used by persons working within the proposed sentinel surveillance system and could be disseminated to persons working external to the proposed sentinel system as well.

Cases of severe acute respiratory infection (SARI) representing a possible emerging pandemic:

- Clusters of 2 or more SARI cases occurring within 7-10 days of each other:
 - in a family

- in persons with a social connection
- in persons sharing an occupational connection
- Any SARI case in Health Care Workers who care for patients with pneumonia
- Any unexplained death due to SARI in persons aged 5-40
- Changes in the epidemiology of SARI such as a shift in the age group affected or changes in mortality rates
- An increase in the numbers of SARI cases occurring in a facility compared to an established baseline

Key Points: Surveillance for CLUSTERS of SARI is also a critical component of detecting a new respiratory pathogen with pandemic potential. Even if the next pandemic were to be caused by avian influenza A (H5N1) it is quite possible that most cases would not have epidemiologic links to sick or dying poultry.

Summary of Influenza A(H5N1) and Pandemic Early Warning Trigger Criteria:

Cases of severe acute respiratory infection (SARI) with a possible link to avian influenza A (H5N1):

- Any SARI case meeting WHO suspect, probable or confirmed case influenza (H5N1) definition.
- Close contact with a WHO suspect, probable or confirmed case
- SARI cases with an occupational exposure such as workers in poultry industry, poultry culling, etc.
- SARI cases who have consumed raw or undercooked poultry or wild bird products
- SARI cases who have handled samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting

Severe acute respiratory infection (SARI) patterns of occurrence possibly representing an emerging pandemic without obvious link to avian influenza:

- Clusters of 2 or more SARI cases occurring within 7-10 days of each other:
 - in a family
 - in persons with a social connection
 - in persons sharing an occupational connection
- Any SARI case in Health Care Workers who care for patients with pneumonia
- Any unexplained death due to SARI in persons aged 5-40
- Changes in the epidemiology of SARI such as a shift in the age group affected or changes in mortality rates
- An increase in the numbers of SARI cases occurring in a facility compared to an established baseline

Note: There must be a free and easy mechanism (e.g. toll free hotlines, disseminated cell phones etc...) for clinicians to report trigger cases/clusters. There must also not be any perceived penalty for reporting these trigger cases/clusters, regardless of their final diagnosis.

Together you decide that there will be a national program to educate clinicians about these “trigger criteria”. *It is important to note that clinicians who work at hospitals that are included within sentinel surveillance system as well as those who work at hospitals that are not in the sentinel surveillance system will receive sensitization training on these trigger criteria.* Cases that meet these criteria will require immediate notification to

the Provincial Medical Officer (who will investigate, and if necessary, request deployment of a regional Rapid Response Team). Oropharyngeal and nasopharyngeal swabs will also be collected and tested with a full panel of influenza diagnostics at the national laboratory. The regional Rapid Response Teams will make use of specimen collection and transport infrastructure located in the sentinel site hospitals in order to assure timely transport and testing of specimens. Clinicians in Pegu will also receive training on the mechanism for reporting cases meeting these trigger criteria. This reporting system will make use of a toll-free telephone number for reporting cases to the office of the Provincial Medical Officer.

You recognize that specimens from these “trigger cases” will initially be tested for influenza in the laboratory. However you also feel that the surveillance system could facilitate timely diagnostic testing of other respiratory pathogens of pandemic potential if the initial laboratory diagnostics for influenza A, B, A/H1, A/H3, and A/H5 are negative. The CSO makes a plan to develop a more detailed laboratory testing algorithm for this surveillance system following meetings with the director of the national laboratory.

Finally, you add to the guidelines that the WHO case definitions must still be used for standard international reporting purposes (under the International Health Regulations, 2005, all persons meeting the probable or confirmed WHO case criteria must be immediately reported to WHO).

The next morning you are taken on a tour of the Pegu National Laboratory. While at the laboratory you learn that the poultry specimens that tested positive for H5 by PCR were all from a southeastern province named Pelu Jaghai. Specimens were also sent to a nearby WHO reference laboratory. However you recall that Pelu Jaghai is a very rural area, and most of the population in that region does not regularly go to hospitals for urgent health needs. The CSO worries that a person sick with influenza A(H5N1) infection might not go to the hospital in Pelu Jaghai, and additional community-level surveillance is needed.

Question 12:

How could influenza A(H5N1) and pandemic early warning surveillance be expanded beyond the surveillance hospitals in Pegu?

- Given that there are 12 traditional medicine hospitals in Pegu, these probably should be included in education and awareness training to report trigger criteria. This implementation of enhanced passive surveillance might also consider outreach to diagnostic laboratorians, coroners, local veterinarians, and drug dispensers. And it may also include others with potential awareness of individuals with severe or atypical respiratory infections such as traditional healers, religious leaders, or unlicensed medical practitioners. An efficient reporting system will make use of existing public health infrastructure such as village volunteers who have relationships with surrounding families and are aware when anyone in this area becomes ill. Thus, education on the recognition and reporting of trigger cases/clusters should target any important gatekeepers to health care in the country.

- Rumor surveillance is a passive process, where rumors are identified from media reports, professional groups, the public, and persons in the WHO network (which is made up of WHO headquarters, country offices, and WHO Collaborating Centers). In an enhanced system, rumor surveillance is intensified by actively seeking out rumors and undertaking more rigorous follow up. This surveillance includes analyzing more media sources and regularly requesting information from the WHO network about outbreak events. The importance of rumor surveillance is likely to increase as the international community considers the revised draft of the International Health Regulations (IHR). Article 8 of the IHR Working Paper states, "WHO, in consultation with the health administration of the State concerned, shall verify rumors of public health risks which may involve or result in international spread of disease." An important part of rumor surveillance is the timely dissemination of accurate information to reduce misunderstanding and unwarranted concern, especially for rumors reported in the media. One example was the need to address the international concern that arose about the rumor that pigs were infected with avian influenza. If the rumor had not been reported to be incorrect publicly after the verification process, health authorities may have misdirected limited surveillance resources.
- Messages can also be targeted to the general population via various media including print, radio and television. These can improve awareness of severe respiratory infections that also meet trigger criteria. These public service messages should address general disease information including risk factors for infection, methods to reduce individual risk, trigger events that should be reported to public or animal health authorities, and a suggested mechanism for reporting.

The MOH indicates that they would like to use some available World Bank Funds to have one team Rapid Response Team trained in each province by the end of the year, with the provincial AFP/Polio surveillance officer also becoming the principle surveillance officer for influenza A(H5N1). He will be known as the provincial "bird flu person" and T-shirts will be printed.

You spend the next few days formally revising the surveillance guidelines with your MOH partners. You also provide several short trainings to the "bird flu persons" on the detection and reporting of trigger cases and clusters, appropriate infection control practices, data analysis and outbreak investigation.

As your time in Pegu draws to its close, you pack your bags for the airport feeling like you accomplished a great deal during your short visit. You feel that the foundation has been put in place for a routine seasonal influenza sentinel surveillance system that includes case definitions and specimen collection protocols for SARI and ILI. The MOH has committed to sending isolates from confirmed influenza A positive cases to the WHO collaborating centers. You also feel that plans are well underway to implement the key components of a pandemic early warning system. Your colleagues have formally defined trigger criteria for laboratory specimen collection and public health investigation. The ongoing education and awareness trainings of hospital-based clinicians will help assure that trigger cases will be reported by clinicians in hospitals internal and external to the sentinel system. The training of additional health care "gatekeepers" and key members of the community using village health volunteers will further enhance the sensitivity of the pandemic early warning system. The establishment of the proposed system will have to occur in stages, and likely require several more visits in the future, but you are off to a good start.

However the next morning, the Deputy Director of the MOH calls you and tells you that Pelu Jaghai is reportedly experiencing yet another large poultry die-off in farms and backyard populations. Specimens have been collected by the Ministry of Agriculture and sent to the National Laboratory for testing. The MOH would like his district staff to establish active surveillance for human cases of influenza A(H5N1) in the affected region. He asks you for advice.

Question 13:

What types of surveillance enhancements for human disease might you recommend for the affected province?

- Door-to-door surveys for ill people and chickens
- SARI surveillance among health care workers at local health care facilities
- Additional active case finding among the occupationally exposed, including those personnel involved in the veterinary response to the outbreak
- Sensitization of community to report illness (including risk reduction messages)
- Temporarily expanding/enhancing SARI surveillance to local hospitals, traditional healers and dispensaries.
- Recruiting private practices, NGO, religious institutions, and schools into the surveillance system for H5N1 and pandemic trigger criteria
- Rapid “just in time” refresher training on reporting procedures. The reporting mechanism (e.g. toll free number) must be clear!
- Active daily networking with village health monitors
- Confirmation of the availability of telephone reporting hotlines

Key Points: The active nature of surveillance in this context should be emphasized. Consider what must be done to make surveillance more active in both the hospital and community setting. This would include an active search in poultry workers and door-to-door surveys in the surrounding community. In much of the world, most poultry husbandry is done in backyards and may not be known to the authorities. Poultry workers and the community need to be made aware of the importance of seeking treatment if they become ill. Instruct workers to be vigilant for the development of fever and respiratory symptoms for 1 week after last exposure to avian influenza-infected or exposed birds or to potentially avian influenza-contaminated environmental surfaces. Health care facilities should be aware that this education activity is occurring and know whom to notify if they detect a possible case. Facilities should implement screening / triage / reporting procedures for patients presenting with influenza-like illness. Consider adding non-public facilities delivering healthcare to the reporting network including private practices, NGO's, and religious institutions. Expand SARI and/or trigger surveillance to local hospitals, traditional healers and dispensaries and train all in the reporting network on procedures (forms, time for reporting, where, etc...). Village health monitors and leaders can be important sources of information for outside investigators. If the technology is available, telephone hotlines can be useful for rapid reporting of suspect events.

That evening you additionally learn of two possible human cases in neighboring Dava Ghar province. Surprisingly, no poultry outbreaks have ever been reported in that province! Despite being homesick you are convinced to extend your stay and participate in the outbreak investigation. With your heart beating rapidly you travel with the District Epidemiologist and two local officials to Dava Ghar Province.

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