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ABSTRACT

AN EPIDEMIOLOGICAL REVIEW OF THE SEVERE ACUTE RESPIRATORY SYNDROME AND HANTAVIRUS PULMONARY SYNDROME, A COMPARABLE DISEASE

By

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The global epidemic severity of SARS contributed to a need for implementation of public health control and prevention mechanisms in 2003. Though these measures were ultimately successful in bringing the epidemic to a halt, a re-emergence could bring new and possibly greater challenges.

Outbreak investigations of emerging diseases from the past may be an important resource for understanding newly emerging diseases of the future, such as SARS. This epidemiological review examines a parallel comparison of SARS and HPS in order to formulate important conclusions for applying the previous experience of HPS public health responses to future SARS outbreaks. Suggested recommendations include integration of modern technology, strict biosafety guidelines, prioritizing education to health professionals, implementing strict travel guidelines, risk reduction, education of quarantine laws, creating guidelines for virus eradication, implementing occupational guidelines, and initiating public health education.

These future recommendations suggested for SARS, formulated from the HPS parallel comparison, may be a means to produce more beneficial outbreak outcomes if SARS recurs in the future. Furthermore, though every communicable disease is unique, this comparative approach may be useful in tailoring responses to other such emerging diseases in the future.

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LIST OF SYMBOLS OR ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CDC	Center for Disease Control
CFR	Case Fatality Rate
CSTE	Council of State and Territorial Epidemiologists
D.P.I.	Days Post Inoculation
ENSO	El Nino-Southern Oscillation
HFH	Hanoi French Hospital
HPS	Hantavirus Pulmonary Syndrome
IHS	Indian Health Service
MOH	Ministry of Health
OMI	Office of Medical Investigations
PAHO	Pan American Health Organization
PT-PCR	Reverse Transcription Polymerase Chain Reaction
R_0	Basic Reproductive Rate
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	SARS-associated Coronavirus
SARS RUI	SARS report under investigation
SNV	Sin Nombre Virus
TTSH	Tan Tock Seng Hospital
VSV	Vesicular Stomatitis Virus
WHO	World Health Organization

INTRODUCTION

The Severe Acute Respiratory Syndrome (SARS) is the first severe and highly transmissible new pandemic disease to emerge in the 21st century. SARS is a viral lower respiratory illness characterized clinically by high fever, headache, body aches, malaise, and myalgia [1]. The newly emerging disease originated in November 2002 in the Guangdong Province of China. By the end of August, SARS had spread to Hong Kong and 32 other countries or regions, infecting around 8,459 known patients with more than 800 deaths [2]. The overall economic cost from the SARS outbreak was estimated at $30 to $140 billion [3]. The global epidemic severity of SARS contributed to a need for implementation of public health control and prevention mechanisms. Outbreak investigations of emerging diseases from the past may be an important resource for understanding those newly emerging diseases of the future, such as SARS.

Hantavirus Pulmonary Syndrome (HPS) was a previously unknown disease until 1993. The newly emerging disease was identified among residents of the southwestern Unites States in "The Four Corners" region including Arizona, New Mexico, Colorado, and Utah. HPS is an acute zoonotic viral disease characterized clinically by fever, body aches, myalgias, nausea, vomiting, and gastrointestinal complaints [4]. These initial symptoms are often followed by rapid onset of respiratory distress and hypotension. From 1993 to 2004 there have been about 1910 cases of HPS reported in the United States, Canada, South and Central America. The case-fatality rate is approximately 37% [5], which represents a significant public health concern.

By providing an epidemiological overview of both SARS and HPS, the parallel nature of the disease relationship can be formulated with a sufficient emphasis on the

human to reservoir contact for each disease. From this information, important conclusions may be used for applying HPS outbreak investigations, outbreak control measures, and public health awareness to the current newly emerging disease SARS outbreak situation. With the knowledge developed from the previous emergence of HPS in 1993, there may be important recommendations to consider for public health initiatives and prevention of the newly emerging disease of 2003, SARS, along with other not yet newly emerging diseases.

Chapter 1

SEVERE ACUTE RESPIRATORY SYNDROME (SARS) DESCRIPTIVE EPIDEMIOLOGY

1.1 TIME PERIOD OF INTEREST

The earliest known cases of SARS originated in the Guangdong Province of Southern China in November of 2002, when cases of severe pneumonia of unknown etiology were reported [1]. The first official report of an outbreak of atypical pneumonia in China was received by the World Health Organization on February 11, 2003. At this point in the disease emergence, there were 305 affected individuals resulting in five deaths [1]. The epidemic spread was later linked to a SARS infected 65-year-old physician from the Guangdong Province of China who had accommodations for the night of February 21 on the 9th floor of a Hong Kong hotel. The physician had been ill since February 15, admitted to a hospital on February 22, and died on March 3, 2003 [6]. Unfortunately, the illness was spread to at least seventeen other hotel guests. Ten of the SARS patients were in the hotel the same day as the index case and 2 stayed in the hotel the same time that three other symptomatic patients were guests at the hotel. Environmental sampling was completed on the carpet outside room 911, the index case's room, and the elevator area. The results showed a possible "hot zone" (possible fomites or respiratory secretions) which were PCR positive for 3 months after the stay of the index case in the hotel. Interestingly, the index case did not have unusually high viral loads when tested on days 9 and 11 of illness. This may be important as to why those on the airplane were not significant in the outbreak of SARS.

This specific hotel location and time marks the beginning of the international spread of SARS, which allowed the newly emerging disease to later reach global

epidemic levels. Those guests who became infected carried the virus to hospitals and homes in Hong Kong, Singapore, Vietnam, while travelers extended the transmission to Canada and the United States, producing the SARS epidemic of 2003. The World Health Organization issued a historic global alert on SARS on March 12, 2003 [7]. Global alerts are used as a global radio-communication network during times of international threat. The SARS global alert included non-specific recommendations such as recent SARS statistics, case definition and name, case management guidelines through isolation, infection control recommendations, and general guidance to travelers. Table one represents a time line of the important events in the SARS outbreak and control. The chronology of events emphasizes the efficient actions and outbreak investigation conclusions determined in a relatively minimal time span.

The worldwide epidemic curve produced from the outbreak is an important reference for understanding the epidemiological time elements. Figure 1 represents the distribution of probable SARS cases by week of onset covering the entire time interval of the outbreak from November 2002 to June 2003. It's important to note that the graph does not include 2,521 cases of SARS from Beijing, China in which the onset was not currently available. Figure 2, on the other hand, represents an updated epidemic distribution of SARS probable cases by date of report for the main time period of interest in which the outbreak was at the highest levels, from mid-March until the end of May. This graph does not include 1,190 cases of SARS from November 2002 to the beginning of April.

The most important characteristic of the distribution of onset dates is the clustering of SARS cases around a specific time period, indicating a disease epidemic.

The graphics clearly show a change in the number of cases of SARS over time. From January to February 2003 there was a slight increase in probable SARS cases with a following decline in early March. However, the number of simultaneous cases was significantly higher from mid March to mid May than the previous two months. Also, a key peak in SARS cases appeared in mid April. After this time, there was a steady decline till June. The epidemic curve pattern is characteristic of a propagated epidemic since there is a series of progressively taller peaks. This type of outbreak scenario is indicative of a person-to-person spread outbreak. The specific SARS transmission patterns will be discussed in detail in Chapter 2.

Any tendency toward seasonality of SARS is still undescribed. In December 2003, the first suspected case of SARS since June 2003 was reported [8]. Two more cases were later reported in late December and January. A few months later, on April 23, 2004 the Chinese Ministry of Health (MOH) reported four patients with possible SARS to the World Health Organization (WHO). Two of the cases were from Beijing and two were from the Anhui Province, located in east-central China [9]. Only a few days later, five more SARS cases were reported. Of the nine China SARS cases reported in 2004, four were classified by Chinese health authorities as "confirmed" and five were listed as "suspected" [10]. It's important to note that two of the nine patients worked at the National Institute of Virology Laboratory of China's CDC in Beijing. The laboratory is known for conducting research on SARS-CoV.

The number of newly reported cases is insufficient to accurately determine any seasonal variation. As we learn and understand more about SARS, a more accurate

understanding of patterns for season may be established if the disease is recurrent in future years.

1.2 GEOGRAPHIC DISTINCTIONS

SARS is the first severe and highly transmissible new pandemic disease to emerge in the 21st century. The disease is identified as pandemic since it has occurred in a geographically widespread location. Figure 3 portrays the number of cumulative probable SARS cases reported worldwide for various geographic regions from the beginning of SARS emergence until June 16, 2003. The three areas experiencing the highest level of SARS cases were China, Singapore, and Canada. Since SARS originated in China, this would explain the higher number of cases in these regions compared to other parts of the world. All the cases outside of China resulted from an index case that had traveled to China, hence creating the international spread of SARS.

The SARS outbreaks occurring before the World Health Organization's global alert on March 15, 2003 included the following regions: China, Hong Kong, Viet Nam, Singapore, and Canada. The only region to experience SARS at an outbreak level after the March 15 global alert was Taiwan. This distinction is important and clarifies that the control and prevention strategies implemented in concordance with the global alert were substantial in decreasing the outbreak potential and levels of SARS. It becomes important to understand the geographic regions where most of the cases of SARS cases came from and discuss the epidemiological patterns in these areas and details of the emergence of SARS in these areas.

A. China

The People's Republic of China experienced the greatest number of SARS cases in the world and is the region where the emergence of SARS has been located. Figure 4 represents the epidemic curve for Chinese SARS probable cases by date of report from February to July of 2003. Throughout the graphic distribution there are a few distinct peaks in the number of cases. This pattern is indicative of multiple cluster outbreaks of SARS cases during the specified date of report. All the areas in China can be classified into four regions according to the epidemic conditions during this time period including:

1. Local epidemic: Guangdong Province
2. Imported cases leading to a local epidemic: Beijing, Tianjin, Shanxi Province, Hebei Province, Inner Mongolia Autonomous Region
3. Imported cases NOT leading to a local epidemic: Shanghai, Shandong Province, Hunan Province, Liaoning Province, and Ningxia Autonomous Region
4. No cases reported: Hainan Province, Yunnan Province, Guizhou Province, Qinghai Province, Tibet Autonomous Region, Xinjiang Autonomous Region, Heilongjang Province [11]

In January 2003, a clustered outbreak of unknown atypical pneumonia was reported to the Health Bureau of the Guangdong Province in China [1]. By completing a retrospective study of the atypical pneumonia cases identified, studies linked the first cases of SARS occurrence to November 2002. It wasn't until February 2003 that the World Health Organization received a report from the Chinese Ministry of Health of an outbreak of an acute respiratory syndrome resulting in 305 cases and 5 deaths in the

Guangdong Province [12]. The first distinct peak on Figure 4 represents the reporting of these cases. The overall pattern of China's epidemic curve is indicative of a multiple clustered pattern with a person-to-person transmission distinction. Figure 5 portrays the number of SARS probable cases per specific region in China and other key regions of the world. From this figure, it is clear that the various regions of China contributed to the largest number of probable SARS cases. For a visualization of the exact regions in China that were affected see Figure 6. The map shows the country of China divided up into the various Provinces and the key regions within these areas. The geographic areas affected by SARS in China are greatly dispersed over the country.

China-Hong Kong

Hong Kong, China represented an important location of multiple clusters contributing to the outbreak. Hong Kong is located in the southeastern portion of China next to the Guangdong Province (see Figure 6). The two important "superspreading events" that have been identified in Hong Kong resulted in over 1000 SARS cases [1]. "Superspreading" refers to one person infecting many other people. The epidemic curve of SARS cases for Hong Kong by date of onset is represented in Figure 7. Again, a pattern of person-to-person transmission can be detected with a majority of the SARS cases occurring around the end of March.

Case 1

The first important superspreading event was referred to as the Metropole Hotel outbreak [1]. This specific SARS cluster is significant as we consider the severe potential of the international spread of an infectious disease such as SARS. As mentioned previously, the epidemic spread of SARS was linked to a SARS

infected 65-year-old physician who had accommodations for the night of February 21 on the 9th floor of a Hong Kong hotel [6]. The illness was spread to at least seventeen other hotel guests, marking the beginning of the international spread of SARS, which allowed the newly emerging disease to later reach global epidemic levels. The index cases from Toronto, Hong Kong, Singapore, and Hanoi outbreaks were all associated with the Metropole hotel, as were cases identified in the United States and Ireland [1].

Case 2

The second superspreading event was referred to as the Amoy Gardens outbreak, representing a cluster of SARS cases. The index patient in this outbreak was a 33-year-old man from Shenzhen who had visited his brother in the Amoy Gardens, Kowloon Bay, Hong Kong [1]. This individual was being treated for chronic renal disease at the Prince of Wales Hospital in Hong Kong. The index case developed SARS symptoms on March 14, 2003. On March 14 and 19, he had visited his brother, who owned a flat on Block E of Amoy Gardens. At this time the patient had diarrhea and used the toilet regularly during the visit. From this initial event, the SARS case's brother, sister-in-law, and two nurses at the Prince of Wales hospital developed SARS. Also, person-to-person spread contributed to the disease development in other blocks within the Amoy Gardens complex, creating a cluster of SARS cases within this specific location. Aerosolization of fecal waste contamination of the SARS agent has been proposed to contribute to this cluster of SARS cases [2], although new reports are questioning this hypothesis. These specific modes of transmission will be

discussed in more detail in the Chapter 2. From these two important events in Hong Kong, multiple SARS clusters were generated and the international spread of SARS was initiated.

China-Beijing

Beijing, China reported the highest number of SARS probable cases during the outbreak of 2003 (see Figure 5). The SARS outbreak was first reported in Beijing in April 2003 after previous outbreaks were detected in other regions of China. Beijing's outbreak involved multiple imported cases in contrast to other outbreak regions such as Canada that resulted from a single imported case of SARS.

Case 1

The earliest cases of SARS in Beijing occurred from individuals who had traveled to the Guangdong Province and Hong Kong. The first index case of SARS recognized occurred in a 27-year-old businesswoman who developed symptoms on February 22, 2003 while traveling in Guangdong [13]. She first went to a hospital in the Shanxi Province for treatment. After returning to Beijing, she was hospitalized in a military hospital and later transferred to an infectious disease health care facility. The patient transferred SARS to 10 healthcare workers and 8 family members and friends.

Case 2

The second index case was a 72-year-old man who visited Hong Kong's Prince of Wales Hospital after developing symptoms on March 14. The patient was treated in two Beijing hospitals after flying back from Hong Kong. He later died on March 20. After thorough contact tracing investigations, there were at

least 59 cases of SARS in Beijing traced back to this one patient including family members and health care workers from both facilities [13]. Figure 8 represents the epidemic curve produced from the SARS cases in Beijing by date of hospitalization. A clear pattern of person-to-person transmission is indicated by the shape of the epidemic curve. Multiple clusters of SARS were recognized in Beijing particularly in hospital facilities. These exact transmission patterns and characteristics will be discussed in Chapter 2.

China-Taiwan

Taiwan has extensive business relations with Hong Kong and the mainland of China where the first SARS cases were reported. This distinction is highly related with the spread of SARS to Taiwan. The first known case of SARS in Taiwan was identified on March 14 in an individual who had traveled to the Guangdong Province in China [14]. Figure 9 represents the epidemic curve for SARS probable cases in Taiwan by date of onset. The distribution shows the greatest number of SARS cases occurring between mid-April to the end of May. For the specific geographic distribution of SARS cases in Taiwan see Figure 10. The majority of cases appeared in the Northern region of Taiwan and in the Southwestern region.

The epidemic in Taiwan had two distinct phases, before and after April 20, 2003. From March 7 to April 19, 78% of the probable SARS cases were travel related, 6% were hospital-acquired, and 16% occurred in households and among social contacts of SARS cases. Interestingly, these proportions of SARS cases changed significantly from April 20 to May 16. During the second phase in Taiwan, 89% of SARS cases were hospital-

acquired, 9% travel related, and 2% acquired from the community [1]. These statistics represent an important epidemiological change in transmission of SARS in Taiwan.

B. Canada

Canada's SARS outbreak resulted from a single imported case resulting in two distinct epidemiological clusters. Figure 11 represents the epidemic curve of probable SARS cases produced in Canada in which the two phases of the outbreak are clearly distinguishable by the two clustered SARS distributions.

Case 1

The initial transmission of SARS into Canada began with an index case that had traveled to China and spent some time in the Metropole Hotel in Hong Kong during February 2003. As noted previously, this specific location has been linked to the source of the initial international spread of SARS. A family contact of the individual that traveled to China became ill with symptoms related to SARS and was treated at a hospital in the Greater Toronto Area (GTA). This individual transmitted SARS to other patients and staff at the hospital. The first phase of SARS cases as seen in Figure 11 occurred from late February to mid April creating a cluster of SARS cases in about 100 healthcare workers [1, 15].

Case 2

From Figure 11 the second cluster phase of SARS in Canada distinctly occurred between mid-May and the beginning of June. The first case of SARS linked to the second phase of SARS in the Ontario outbreak was a 96-year-old man with a fractured pelvis admitted to an orthopedic hospital ward in the index hospital on March 22, 2003 [15]. Onset of symptoms occurred on April 2 with

the development of respiratory symptoms, fever, diarrhea, and evidence of atypical pneumonia. From the hospital admission of this SARS case, other patients close to the SARS patient, visitors, and health care workers who developed SARS were all later linked to the initial hospital case. Of the SARS cases reported in Canada to the Toronto Public Health Department, 39% occurred among healthcare workers, 38% resulted from direct exposure to SARS during hospitalization, and 23% occurred among those visiting the hospital [1]. Also, 90% of the SARS cases reported from the second outbreak phase of SARS in Canada resulted from direct exposure in the index hospital [1]. It becomes important to note the epidemiological clustering of SARS in the hospital setting and the transmission of SARS into Canada from one distinct international traveling incident.

C. Singapore

The experience of SARS in Singapore was analogous to that in Hong Kong, Vietnam, and Canada in which the first cases of SARS were associated with a large number of health-care associated infections. Figure 12 shows the epidemic curve of probable SARS cases in Singapore by date of onset. Person-to-person transmission is assumed based upon the distribution of cases with two clearly distinct peaks in the number of cases reported.

On March 6, 2003 the Singapore Ministry of Health (MOH) was notified of three individuals who traveled to Hong Kong during late February and were later admitted to the hospital with pneumonia [16] before the WHO issued the first global alert. The index case had stayed at the Metrople hotel on February 20 and 21 along with the index SARS

case that transmitted the virus to other hotel guests allowing for the international spread of SARS. During this early phase of the outbreak in Singapore, the original imported case (described as case 1 below) and a nurse contact was associated with large clusters of SARS in Singapore.

One important epidemiological component of the SARS outbreak in Singapore was that five people with probable SARS accounted for various super spreading events, defined as infecting 10 or more people with SARS. Those people resulting as secondary transmission cases included health-care workers, family and social contacts, or visitors to the health-care facilities where the SARS patients were hospitalized. These five specific probable SARS cases accounted for 103 of the 206 cases reported in Singapore [1]. Each of these five important cases is discussed below.

Case 1

The recognized index case was a 22-year-old who had visited Hong Kong for a shopping trip and had stayed at the Metrople Hotel in Hong Kong. On February 25, the visitor developed a fever and dry cough and was later admitted to the Tan Tock Seng Hospital (TTSH) on March 1 [16] for atypical pneumonia. On March 4, the patient was transferred to the intensive-care unit for a decrease in blood oxygen saturation. For the first six days of admission, the patient was cared for in Ward 5A of the hospital which was lacking infection control measures. The patient was then later transferred to Ward 8A in isolation. This specific patient was directly linked to three people with suspected SARS and probable SARS infection in 21 other people including nine health-care workers and 12 family members and visitors [16]. Of those with secondary infections from case

one, the patient's mother, father, and one visitor died from the infection. From the index case described over 120 cases were linked to the development of SARS, mainly as a result of the other four cases with SARS reported as super spreading events.

Case 2

A 27-year-old nurse who attended case one on TTSH Ward 5A, became ill on March 7 and was admitted to Ward 8A on March 10 with a fever and sore throat. The patient experienced vomiting, but diarrhea was not present. The nurse was put into isolation on March 13. This specific patient was linked to infecting 23 people with probable SARS including 11 health-care workers and 12 family members and visitors along with 4 people with suspected SARS. [16]

Case 3

A 53-year-old individual with diabetes and ischemic heart disease was admitted to the TTSH Ward on March 10 for sepsis and diarrhea. The patient was placed in the same room as case 2. On March 12, the patient developed a fever requiring mechanical ventilation and transferred to the coronary care unit for severe congestive heart failure. The patient was later isolated on March 20 and died on March 29 [16]. This SARS patient was directly linked to 23 people with probable SARS including 18 health-care workers and five family members and visitors along with 18 people with suspected SARS.

Case 4

From March 5 through March 20, a 60-year-old individual was admitted to the TTSH Ward 5A for chronic kidney disease and diabetes. The patient was

later readmitted on March 24 to Singapore General Hospital for gastrointestinal bleeding. The patient developed high fever, found to be infected with *Escherichia coli* bacterium and given an antibiotic for treatment. On April 4, the patient was isolated as a suspected SARS case after a chest radiograph showed signs of pneumonia [16]. This specific patient was linked to 62 probable or suspected SARS cases including 25 health-care workers, 20 other patients, and 17 family and social contacts.

Case 5

A 64-year-old vegetable hawker visited case four in the Singapore General Hospital on March 31. The individual had a medical history of ischemic heart disease and left ventricular failure and developed onset of illness including myalgia, cough, and fever on April 5. On April 8, the patient was admitted to the National University Hospital through the emergency department and was intubated for increased respiratory distress. The patient was transferred to TTSH on April 9 to be isolated after the patient's history of visitation to case four was established. The patient later died on April 12. [16] This patient was directly linked to SARS infection in 15 other people including five health-care workers, two hospital patients, two family members, one visitor, two taxi drivers who transported the patient, two hawkers from the same wholesale market, and a visitor to the emergency department.

Unfortunately, it is not understood specifically whether Singapore's key epidemiological super spreading events are due to unique conditions suitable for virus transmission or too some specific characteristic of the index case one described. More

research is necessary to understand the epidemiological distinctive SARS transmission characteristics that took place in Singapore during the outbreak time period.

D. Viet Nam

Case 1

The SARS index case in Viet Nam was a business man who stayed in the Metropole Hotel in Hong Kong between February 21 through February 23, traveling back to Viet Nam on February 23 [1]. After the patient was admitted to the Hanoi French Hospital (HFH), an outbreak of SARS occurred among staff, other patients, and visitors. The epidemic curve for SARS probable cases by date of onset in Viet Nam can be seen in Figure 13. A surge of SARS cases occurred at the beginning of March as seen on the epidemic curve and decreased thereafter. On March 11, the HFH closed the hospital to all new admissions and discharged all patients without SARS.

Case 2

Two specific community clusters were identified in Viet Nam. A doctor working at the HFH transmitted SARS to three family contacts. The second cluster resulted from a man who had visited his daughter at the HFH hospital. He later transmitted SARS to five close contacts in the town of Hanoi [1]. The total time span of the outbreak in Viet Nam lasted 43 days from the index case arrival at HFH to onset of symptoms of the last SARS case patient.

E. United States

The epidemiology of SARS in the United States showed different characteristics than other countries in being limited to mostly travel related cases with limited spread to

close contacts and health-care workers [17-19]. Therefore, local transmission of SARS was limited in this region compared to the other geographic areas. As a result, the epidemic curve produced from the United States experience of SARS looks dramatically different than the other regions discussed previously. Figure 14 shows the probable case of SARS by date of onset in the United States. The graph does not imply a person-to-person spread of the disease, but instead with the slight increase in cases in mid-March and then a fairly continuous pattern of cases thereafter, the graph is more indicative of a common and continuing exposure to the etiologic agent.

From the epidemiological studies completed in the United States, about 97% of probable SARS cases were due to a travel exposure [19]. A distribution of the number of probable SARS cases and those traveling to various SARS affected regions is seen on Figure 15. The graphic shows the greatest number of SARS probable cases in those who traveled to mainland China and the Hong Kong Special Administrative Region in China. This is understandable considering that the outbreak of SARS originated in China.

As addressed previously, the local transmission of SARS in the United States was limited to health care workers and close contacts of suspected SARS patients who had traveled outside the United States. Two local transmissions of SARS were observed during the outbreak and are important to summarize. The first local transmission pair resulted from a 40-year-old United States resident who had traveled to mainland China and Hanoi during February 23 through March 9 [17]. On March 10, the individual experienced symptoms including fever, cough, and shortness of breath. The patient was hospitalized from March 15-16 after a chest radiograph showed pneumonia. On March 16, the patient's child began experiencing fever and a cough and was later hospitalized

for observation and evaluation showing no evidence of pneumonia, however, meeting criteria as a documented SARS case. The described transmission is representative of the only close contact transmission of SARS documented in the United States.

The second local transmission pair involved a 39-year-old man who traveled to Hong Kong from March 1 through March 6 with his wife staying in Hotel M, the initial source of the international spread of SARS. On March 13, the man experienced fever and respiratory symptoms and was later hospitalized with pneumonia [17]. Later, on March 19, the wife became ill with similar symptoms and was hospitalized with evidence of pneumonia. From an epidemiological perspective, the difference in secondary transmission in the United States was distinctly different from the other geographic regions discussed, and various levels of surveillance and early detection procedures may help explain this difference in transmission.

1.3 CASE DEFINITION

During the SARS outbreak of 2003, the CDC and Council of State and Territorial Epidemiologists (CSTE) developed specific surveillance procedures for identifying SARS cases. The case definition changed throughout the epidemic time frame as a more thorough understanding of the clinical, laboratory, and transmission characteristics of SARS developed. On March 15, a preliminary case definition was issued for suspected cases of SARS as follows [20]:

Suspected Case

Respiratory illness of unknown etiology with onset since February 1, 2003, and the following criteria:

- Documented temperature >100.4° F (>38.0°C)

- One or more symptoms of respiratory illness (i.e. cough, shortness of breath, difficulty breathing, or radiographic findings of pneumonia or acute respiratory distress syndrome)
- Close contact within 10 days of onset of symptoms with a person under investigation for or suspected of having SARS or travel within 10 days of onset of symptoms to an area with documented transmission of SARS as defined by the WHO.

When the following case definition was determined, there were only approximately 264 cases of SARS that had been reported from 11 countries. The case definition is limited to a small amount of clinical and epidemiological criteria. As mentioned, the case definition changed considerably as more knowledge developed about SARS. The case definition for SARS was updated on December 2003 by the CDC and CSTE. The revised case definition is as follows [21]:

Clinical Criteria

Early Illness

- Presence of two or more of the following features: fever (might be subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, or rhinorrhea

Mild-to-moderate respiratory illness

- Temperature of >100° F (>38° C) and
- One or more clinical findings of lower respiratory illness (eg. Cough, shortness of breath, or difficulty breathing)

Severe respiratory illness

- Meets clinical criteria of mild-to-moderate respiratory illness and

- One or more of the following findings:
    - Radiographic evidence of pneumonia, or
    - Acute respiratory distress syndrome, or
    - Autopsy findings consistent with pneumonia or acute respiratory distress syndrome without an identifiable cause

Epidemiological Criteria

Possible exposure to SARS-associated coronavirus (SARS-CoV)

One or more of the following exposures in the 10 days before onset of symptoms:

- Travel to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV or
- Close contact with a person with mild-to-moderate or sever respiratory illness and history of travel in the 10 days before onset of symptoms to a foreign or domestic location with documented or suspected recent transmission of SARS-CoV

Likely exposure to SARS-CoV

One or more of the following exposures in the 10 days before onset of symptoms:

- Close contact with a person confirmed SARS-CoV disease or
- Close contact with a person with mild-to-moderate or sever respiratory illness for whom a chain of transmission can be linked to a confirmed case of SARS-CoV disease in the 10 days before onset of symptoms

Laboratory Criteria

Tests to detect SARS-CoV are being refined and their performance characteristics assessed; therefore, criteria for laboratory diagnosis of SARS-CoV are changing. The following are general criteria for laboratory confirmation of SARS-CoV:

- Detection of serum anti-body to SARS-CoV by a test validated by CDC (e.g. enzyme immunoassay) or
- Isolation of cell culture of SARS-CoV from a clinical specimen or
- Detection of SARS-CoV RNA by reverse transcription polymerase chain reaction test validated by CDC and with subsequent confirmation in a reference laboratory

Exclusion Criteria

A case may be excluded as a SARS report under investigation (SARS RUI), including as a CDC-defined probable SARS-CoV case, if any of the following apply:

- An alternative diagnosis can explain the illness fully or
- Antibody to SARS-CoV is undetectable in a serum specimen obtained >28 days after onset of illness or
- The case was reported on the basis of contact with a person who excluded subsequently as a case of SARS-CoV disease, then the reported case also is excluded, provided other epidemiologic or laboratory criteria are not present.

Case Classification

SARS RUI

Reports in persons from areas where SARS is not known to be active

- SARS RUI-1: Cases compatible with SARS in groups likely to be first affected by SARS-CoV if SARS-CoV is introduced from a person without clear epidemiologic links to known cases of SARS-CoV disease or places with known ongoing transmission of SARS-CoV.

Reports in persons from areas where SARS activity is occurring

- SARS RUI-2: Cases meeting the clinical criteria for mild-to-moderate illness and the epidemiologic criteria for possible exposure (Spring 2003 CDC definition for suspect case)
- SARS RUI-3: Cases meeting the clinical criteria for severe illness and the epidemiologic criteria for possible exposure (Spring 2003 CDC definition for probable cases)
- SARS RUI-4: Cases meeting the clinical criteria for early or mild-to-moderate illness and the epidemiologic criteria for likely exposure to SARS-CoV.

SARS-CoV disease

- Probable case of SARS-CoV disease: meets the clinical criteria for severe respiratory illness and the epidemiologic criteria for likely exposure to SARS-CoV
- Confirmed case of SARS-CoV disease: clinically compatible disease (i.e. early, mild-to-moderate, or severe) that is laboratory confirmed

As more information was learned about SARS, the case definition clearly developed to be more specific and distinct to include all those individuals that may be a potential SARS case. The detailed case definition listed above is credited to the CDC and CSTE.

1.4 INCUBATION PERIOD

The incubation period represents the time interval between the exposure to an infectious agent and the onset of the first signs or symptoms of the disease [22]. The estimates of the incubation period for SARS began to converge as the outbreak progressed. Table 3 represents an overview of the incubation period for the countries that were affected most by SARS. The range for the onset of symptoms after exposure is 1-

14 days according to the table. The minimum incubation period of 1 day was reported from China and Singapore and the maximum of 14 days was reported from China. However, the majority of SARS cases had an incubation period ranging from 2-7 days with a median incubation period of 4-5 days and a mean incubation period of 4-6 days [1, 6, 23]. One of the key reasons SARS spread so quickly was the short incubation period.

Currently, the mean incubation period for SARS is estimated to be 6.4 days [1, 6, 7], with a mean time from onset of clinical symptoms to hospital admission between 3-5 days. The disease usually begins with a fever greater than 100.4°, often followed by chills, myalgia, dry cough, headache, and dizziness [7, 23]. Less common initial symptoms may include sore throat, sputum production, coryza, nausea or vomiting, and diarrhea [7]. After 2-7 days, the SARS patient may develop a dry cough that may progress to an insufficient amount of oxygen getting into the blood. As a result, about 10-20% of SARS cases will likely require mechanical ventilation.

A substantial amount of discussion has been on-going related to the range of the incubation period and the effect of outliers at the higher end of the incubation period. Outliers beyond a 10 day incubation period are limited and have not been investigated thoroughly. However, other mammalian coronavirus infections have shown a long right-hand tail for incubation periods, therefore this is feasible. Also, it is possible that some SARS patients have multiple incubation periods due to multiple contact dates with SARS patients [24]. As a result, a detailed investigation of the outliers is needed before public health policy is changed to lengthen the incubation period to more than 10 days. If the incubation were increased to include a wider range of days, this would have a tremendous effect on public health practices and control techniques

The clinical course of the SARS appears to produce a bi- or tri-phasic pattern. The three phases include the following [7]:

Phase One

- Period of viral replication associated with an increase in viral load
- Clinical symptoms include fever, myalgia, and other systematic symptoms showing improvement in about 2 days

Phase Two

- Immunopathological imbalance
- Clinically described as recurrence of fever, oxygen desaturation, and clinical and radiologic progression of acute pneumonia
- Decrease in the viral load
- Almost 80% of SARS patients have abnormal chest radiographs that show airspace consolidation
- Majority of patients respond to treatment, but about 20% may progress to phase three

Phase Three

- Acute respiratory distress (ARDS) with likely need for mechanical ventilation

1.5 PERSONAL CHARACTERISTICS

A. Age

Patients who developed SARS ranged from 0 to 97 years of age. However, the majority of SARS patients were young and middle-aged adults. The age group 20 to 60 years accounted for approximately 85% of all SARS cases [11, 25]. Among this group, about 30% were in their twenties, representing the age group with the highest incidence

rate. The incidence rate for the 10 to 15 year old age group was lower than adults, and those under 9 years old had the lowest age group incidence of SARS [11, 25]. For example, in Beijing the incidence rate for the age group 20 to 29 was 30.85 per 100,000 population compared to the age group 0 to 14 which had an incidence of 2.54 per 100,000 population [25]. This SARS case age distribution may be indicative of the fact that the majority of health care workers fall within this specific age group. The other SARS affected countries follow similar patterns related to the age distribution.

Table 2 summarizes the median age range of SARS cases by country from November 2002 through August 2003. The median was likely used instead of the mean age, because there may have been outlying ages that would not reflect the true age groups at the highest risk of SARS. The table indicates that those countries with the highest cases of SARS were the countries highlighted in the geographic distribution section of the paper, including China, Hong Kong, Taiwan, Canada, Singapore, United States, and Viet Nam. All of these countries show a median age of 35 to 49, which represents the portion of the group with the most SARS cases reported.

SARS is a condition with substantial morbidity and mortality. The case-fatality ratio of SARS is estimated to range from 0% to 50% depending upon the age group [1]. The overall case-fatality rate (CFR) is approximately 11 to 15% [1, 26]. The case-fatality rate of SARS by age group is as follows [12]:

- $\leq$ 24 years old = Less than 1%
- 25-44 years old = 6%
- 45-64 years old = 15%
- $\geq$ 65 years old = Greater than 50%

These age groups CFR's represent an overall estimate for all regions affected with SARS. However, Table 2 shows the case fatality rates for each area with SARS cases reported. It is important to note the number of cases reported in specific areas to determine the CFR. The areas with the highest rates include Taiwan, Hong Kong, Canada, Singapore, Thailand, South Africa (note only one case of SARS reported), and Malaysia (note only five SARS cases reported). The areas with the highest rates are the key geographic locations discussed previously for the important outbreak regions and high risk areas.

B. Gender

Of the SARS cases reported throughout the outbreak of the newly emerging disease, approximately 53% were female [3]. The incidence rates of SARS in males and females were not statistically significant [7]. However, the greater percentage of females with SARS may be attributed to the fact that more females tend to be involved with direct health-care positions compared to males, and healthcare workers is a group at high risk of developing SARS. These figures will be presented under the other risk factors section below. One interesting aspect of gender shown in studies is that males are more likely than females to die from SARS [3]. These results showed statistical significance. Further research is needed to understand the mechanism for these findings.

C. Residence Location

SARS has been shown to spread more prominently under residence conditions of high density, greater population fluidity, poor sanitary conditions, or bad health habits [11]. Therefore, it can be understood why the outbreak showed high numbers in big areas such as Hong Kong and Toronto. There areas represent locations that have high

population concentration, high traffic patterns, and sufficient medical resources. All of these factors are more likely to sustain a SARS outbreak scenario.

D. Other Risk Factors

An essential SARS high risk group to mention is health-care workers, which were considered the primary risk group in the second generation of SARS transmission [12]. Health-care workers (particularly those involved with procedures that generated aerosols) accounted for approximately 20% of the SARS cases reported during the outbreak [1, 3, 26]. When discussing the important elements of modes of transmission for SARS, the health-care worker group will be addressed more specifically. Other at risk groups for SARS included those family members of the health-care workers and index cases and their other contacts.

Other high risk groups include those with co-morbid chronic conditions such as hypertension, diabetes, cardiac disease, emphysema, and neoplasm's [3, 11, 27]. Also, those groups of people whom were involved in the care and slaughter of wildlife for human consumption in the wet markets of Southern China are also at higher risk for SARS. This specific group and will be discussed in more detail in Chapter 2 when discussing modes of transmission.

A key epidemiological component to SARS risk was directly related to those whom had traveled to the original SARS infected areas in China. As mentioned previously, the initial international spread was associated with this specific geographic location. Any individual who had traveled to mainland China, had visited the Amoy Gardens, Prince of Wales Hospital or other hospitals or clinics were at greater risk of

transmitting SARS [28]. This component is essential for understanding the transmission of SARS globally.

Chapter 2

SEVERE ACUTE RESPIRATORY SYNDROME (SARS) ANALYTIC EPIDEMIOLOGY

2.1 EPIDEMIOLOGICAL AGENT

"The terror of the unknown is seldom better displayed than by the response of a population to the appearance of an epidemic, particularly when the epidemic strikes without apparent cause [29]". This 1977 quote by Edward Kass described the feelings related to the newly emerging Legionnaire's Disease and can be applied to the public response to the appearance of SARS and understanding the possible cause of the newly emerging disease.

The SARS outbreak of 2003 involved a microbial agent now known as SARS-associated coronavirus (SARS-CoV), a novel coronavirus that was not previously recognized as part of the coronavirus family [1, 30, 31]. The agent was initially identified as a coronavirus by thin-section electron microscopic examination of a virus isolate. The virions identified from SARS were spherical, 78 nm in mean diameter, and were composed of a helical nucleopcapsid with an envelope and surface projections [32] (See Figure 16). This structure noted is representative of the coronavirus family *Coronaviridae*, consisting of an enveloped, single-stranded RNA virus group causing disease in humans and animals [6]. However, in comparison with other human and animal coronaviruses, SARS-CoV was shown to be distinct and warrants classification of a new group of *Coronaviridae.*

In humans, coronaviruses are responsible for approximately 20% of common colds in the wintertime [31]. However, up until the SARS outbreak, the coronaviruses had never been strongly associated with any serious human illness. The virus family has

always been interesting scientifically, but a relatively unimportant medical virus family to the human population. On the other hand, coronavirus infection of farm animals is common and often substantial, justifying routine vaccination administration.

By experimental infection of cynomolgus macaques (monkeys) with the SARS-CoV, proof was provided that the virus was the aetiological agent of SARS [30, 33] by fulfillment of Koch's postulates. Based upon Koch's Postulates (modified for viral disease), in order for a virus to be established as the cause of a disease, six criteria are required including [30]:

1. Isolation of the virus from a diseased host
2. Cultivation in host cells
3. Proof of filterability
4. Production of comparable disease in the original host species or a related one
5. Re-isolation of the virus
6. Detection of specific immune response to the virus

The first three criteria above have been fulfilled from several studies [30, 33] and provide convincing procedures to support that SARS-CoV is linked to SARS. The other three criteria were tested after more knowledge of SARS was acquired. The procedure used involved inoculation of two macaques with vero-cell cultured SARS-CoV isolated from a fatal SARS patient. The macaques were monitored for clinical signs, virus excretion, and antibody response. Six days after inoculation the animals were killed to complete histopathological examinations.

Several laboratory tests were used to detect the SARS-CoV. A reverse transcription polymerase chain reaction (PT-PCR) test can detect SARS-CoV in clinical

specimens, including blood, stool, and nasal secretions [23]. PT-PCR is a laboratory method for detecting the genetic material of an infectious disease agent and has become a necessary procedure for the detection of infectious diseases. Serologic testing can also be used to detect SARS-CoV antibodies produced after infection from human serum. A final test involves viral culturing by using a small sample of tissue or fluid. The specimen is placed in a container along with other cells in order for the virus to grow. After the virus grows, any changes in the cells can be recognized under a microscope [23]. The results produced from the study for Koch's Postulates are as follows [30]:

Clinical Signs

- 2 macaques were lethargic 3 days post-inoculation (d.p.i.) with temporary skin rash
- 1 macaque had respiratory distress 4 d.p.i
- At gross necropsy, 1 macaque had severe pulmonary consolidation
    - SARS-CoV was detected in the lung tissue by RT-PCR and virus isolation
- 2 macaque had interstitial pneumonia
- 1 macaque had gross lesions with diffuse alveolar damage (See Figure 17b)
- Occasional multinucleated cells were present in the lumen of bronchioles and alveoli (See Figure 17c)
    - Lesions were indistinguishable from those in biopsied lung tissue of SARS patients

Virus Excretion

- Macaques excreted virus from nose and throat 2 to 6 d.p.i.
- Isolated virus was identical to that inoculated in the macaques (See Figure 17a)

- Virus isolated from feces of 1 macaque

Immune Response

- Seroconversion to SARS-CoV, determined by using infected Vero cells in 2 macaques at 16 d.p.i.

From the data obtained from the animal experimentation with macaques, Koch's Postulates were fulfilled, supporting SARS-CoV as the primary aetiological agent of SARS. From this information obtained, scientists concluded that SARS-CoV is a necessary cause for SARS in humans, but more research is needed to understand if microbial or other possible cofactors enhance the severity or transmissibility of SARS.

Due to the identification of the coronavirus as the etiologic agent of SARS, research on the coronavirus family *Coronaviridae* has shown to be stimulating both research and public interest. There are various characteristics of SARS-CoV worth mentioning in comparison to previous known coronaviruses. The morphological features of SARS-CoV isolates were similar to other members of the coronavirus family [32]. For example, multinucleated cells were present, virions maintained an envelope structure by budding into the cisternae forming spherical particles, virus particles were observed in membrane bound vesicles, tubuloreticular structures formed along the cell membrane, and induction of fibrosis was noted [31, 32]

A notable similarity of SARS-CoV to previous coronaviruses is the genetic characteristics. The emerging genetics of SARS-CoV may be attributed to two important factors. First, as an RNA virus SARS-CoV is likely to undergo mutation at a very high frequency. The SARS-CoV genome can be expected to accumulate an average of 3 mutations per round of RNA replication [31]. In comparison, measles virus has been

estimated to have a genomic mutation rate of 1.43 mutations per round of replication and vesicular stomatitis virus (VSV), a non-segmented RNA virus, has been estimated ranging from 2.75 to 4.28 mutations per round of replication [10]. At this point in time, the main RNA species from the various SARS patients appear to be homogenous differing by no more than ten amino acids in the entire genome. Further analysis is needed to confirm the overall patterns of viral spread of SARS-CoV, but the genetic characteristics implies that the SARS-CoV has likely been circulating for awhile in China [34].

Using the viral sequences derived from the clinical specimens collected in Hong Kong from the 139 SARS patients, an estimate of the last common ancestor of the SARS-CoV was determined. The mutation rate was assumed to be uniform while linear regression analysis was completed. The divergence was based on the genetic distance between the isolates and the root of the phylogram and was plotted as a function of sampling time (See Figure 18). The last appearance of the common ancestor of SARS-CoV was estimated to be on December 12, 2002 indicating a divergence value of zero [35]. Therefore, the first deviation of the ancestral virus may have occurred in late 2002, which is closely represents the timing of the first reports of SARS in China. Additional samples may be useful for repeating this specific analysis, but the analysis is interesting for providing information on the evolution of SARS-CoV into the China population.

The second genetic distinction is that coronaviruses have a tendency to evolve through RNA recombination, occurring at a high frequency [7]. The theory is that recombination will not only introduce genetic alterations, but also balance the harmful effects of mutations by removing undesirable traits. In natural infections, both mutation

and recombination have contributed to the evolution of coronaviruses and likely to the emergence of SARS-CoV.

In contrast to other coronaviruses, disease due to SARS-CoV has both a higher mortality rate and contagiousness than other known human and animal coronaviruses [7]. Another important difference is that SARS-CoV likely consists of unusual envelope structures since SARS cases often show GI symptoms, and the virus is detected in the stool [7]. Presumably due to the structure of SARS-CoV envelope, the virus has been shown to survive in diarrheal stool for as long as four days and on a dry surface for 24 hours, indicating the survival potential of the virus outside the host.

2.2 MODE OF COMMUNICATION

The mode of communication for an infectious disease is the phenomenon in the environment that brings the host and the agent together. The various possible modes of communication include:

- Vector- A live organism that serves to communicate disease (i.e. mosquitoes and arthropods)
- Vehicle- An inanimate object which serves to communicate disease (i.e. glass of water containing microbes, or a dirty rag, etc.)
- Reservoir- A location that serves as a continuing source of infection (i.e. water tower, soil for tetanus, etc.)

In epidemiology, it is sometimes more important to have knowledge of the modes of communication for an infectious disease than to identify the etiologic agent.

SARS-CoV is understood to almost certainly involve an animal reservoir, which is one of the most important types of reservoirs for human disease [5, 36]. About 75% of

human emerging infectious diseases have a zoonotic (animal species) origin [37]. There are several important factors that may contribute to emerging zoonotic diseases including [38]:

- Transportation of human and animals into new places
- Increased contact between animals and humans
- Changes in the environment and husbandry practices
- A larger immunocompromised population
- Increased recognition of diseases as a zoonotic origin
- Discovery of new organism not previously recognized

For SARS, an animal origin was considered the most probable explanation in the outbreak for the following reasons [37]:

- The novel nature of the SARS-CoV
- The clustered Guangdong outbreak pattern in China
- The occupational and spatial association with early cases
- The range of wild-caught mammals, birds, and reptiles in Chinese markets
- The use of wild animals for food and medicine and China offers an effective bridge to humans
- 75% of human emerging infectious disease are zoonotic

The SARS-CoV has been isolated from various animals in China, providing evidence that an animal reservoir does indeed exist for SARS-CoV, but to date the research findings are insufficient to permit the identification of the natural reservoir of the disease or the species that may be responsible for the cross-species transmission to humans. A cross-species transmission of such a virulent and transmissible virus like

SARS is likely a rare event; however its frequency can not currently be predicted [36]. Research shows that when SARS was first detected it infected only about 3% of the people it came in contact with. However, within a few months, the virus had evolved into a huge risk to the human population; causing illness in about 70% of the population it encountered [39]. The entire evolutionary process of SARS from animals to a virulent human virus took a little under three months, effectively reinventing and altering itself as a very potent human virus.

Figure 19 provides a logical mechanism for the process involved for cross-species transmission. The original coronaviruses found in animals are coated with proteins specific for attaching to the tissues of an animal cell. Through mutation, the viral surface receptors likely changed shape to be compatible with the human cell tissues. After introduction into the human population, scientists believed the virus to fine-tune itself for enhancing its access to the new human host cell. Influenza has shown to resemble the proposed mechanistic theory making the virus mutation of SARS theory plausible. A team of virologists in China from several universities reported, after analysis of SARS-CoV samples taken from China in the early, middle, and late stages of the outbreak, that the surface spike proteins may optimize their adherence to host cells under selective pressure. This had the effect of "learning" to spread from person to person, then adapting to the most effective virulent version of the surface protein structure [39]. These specific properties are important for understanding the virulence and future potential of the SARS-CoV.

The SARS outbreak investigation of the potential animal reservoir of the SARS-CoV was focused around wild mammals served as exotic food in China. This specific

group of animals was targeted after the SARS-CoV was isolated from Himalayan palm civets found in a live animal market in Guangdong, China [40]. The hypothesis was further supported when some of the SARS patients in the Guangdong Province reported a history of occupational exposure to live, caged animals that were used as "game food", a culinary delicacy in southern China [6].

As mentioned, researchers focused their investigations on the wild animal market in China as the potential animal reservoir after the SARS-CoV was isolated from the Himalayan palm civets (See Figure 20) found in a live animal market. Evidence of the virus infection was also found in other animals, including the raccoon-dog (See Figure 20), and in humans working in the market.

The focus on humans was centered among wild animal traders after studies showed a higher seroprevalence of SARS-CoV from these traders compared to other workers in other parts of the market or unrelated controls [6]. Of the 508 animal traders whose blood was sampled during the outbreak, 13% tested positive for the IgG antibody to SARS-CoV. The control groups had 1.2% to 2.9% testing positive for these antibodies [41, 42]. Also, from the first market in Guangdong Province in which SARS-CoV was isolated from civet cats, serologic surveillance showed that 40% of the animal traders and 20% of the animal slaughterers had antibodies to SARS-CoV, but none of them had shown any SARS symptoms in the previous six months before the study was completed [43]. This finding led to the idea that the SAR-CoV or a similar virus may have been prevalent in the human population of Southern China before the SARS outbreak.

Isolation of the virus from the animals in wild animal markets was another support for the potential source of the outbreak, which initiated the focus of investigation

on these specific areas. When the full genome of two Himalayan palm civets and five human viruses were compared, the animal virus isolates contained a 29-nucleotide sequence which was not found in most human isolates (See Figure 21). After completion of a full-length genome sequence, results showed that there was 99.8% homology between the human and animal SARS-CoV, indicating that the human and animal SARS-CoV are closely related [40, 44]. However, phylogenetic analysis of the S gene of both the human and animal SARS-CoV showed that the animal viruses are separate from the human virus cluster (See Figure 22). The animal viruses SZ3 and SZ16 differed by 18 nucleotides, whereas the human viruses differed by only 14 nucleotides. These results show that the animal virus SZ13 (raccoon-dog) and the SZ16 virus (palm civet) were almost genetically identical [40, 44].

In an effort to decrease the spread of SARS to the human population by cutting off the source, Chinese officials ordered a sweep through farms and food markets to locate and kill all animals that may harbor the SARS virus, including palm civets and raccoon dogs. The decision to slaughter an estimated 10,000 civets and a much smaller number of other animals came on the same day that China confirmed the first SARS case of the 2003-2004 winter [45]. Some of the techniques involved to kill the animals included disinfectant spraying and clubbing. The problem with this decision was that we still are not sure whether the civet cats are the natural reservoir of the virus or if they are simply an intermediary carrier [46].

Interestingly, studies have shown that other wild animals were also found to be carriers of the virus, including foxes and domestic cats [47]. Still other studies have shown that ferrets and domestic cats are also susceptible to SARS-CoV infection and are

capable of effectively transmitting the virus to other uninfected animals that are in their living quarters [48]. Non-inoculated cats were housed with previously inoculated cats and ferrets and later became infected with the SARS-CoV, as confirmed by an increase in viral titers 2 days post inoculation. This is an interesting concept for epidemiological transmission purposes, because the virus is not only capable of a human-to-human threat, but also animal-to-animal. These results suggest the virus is more promiscuous than previous considered.

The above findings could be beneficial for the use of animal models in experimenting with the SARS-CoV and testing for antiviral drugs and possible vaccines for SARS if needed. These findings also help to extend the range of animal species that are carriers and harbor the SARS-CoV. The study results suggest that transmission of the virus from civets to humans is less efficient than from other animals [47]. From this, can we say that a large number of animals were slaughtered unjustifiably by Chinese authorities? Unfortunately, until scientists come closer to the origin and natural reservoir of the SARS-CoV it is difficult to answer this question.

The findings regarding the animal reservoir thus far suggest that Chinese markets provide a network for the animal SARS-CoV to alter and transmit to new hosts, including humans. One thing is not clear, however: It may be possible that one or more of these animals are the natural reservoir of SARS-CoV in the wild. It is also possible that these animals investigated including civets, raccoon dogs, and others were infected by another unknown animal source, representing the "true" reservoir of SARS-CoV. More investigation and research is needed for assessment of the animal reservoir(s) responsible

for SARS before any more extreme measures, such as mass culling of animals, is initiated.

2.3 TRANSMISSION

The predominant mode of transmission of SARS-CoV appears to be through direct or indirect contact of mucous membranes (eyes, nose, or mouth) with infectious respiratory droplets or fomites through close person-to-person contact [1, 2, 6, 23, 49]. The virus laden droplets of SARS-CoV travel only a few meters rather than by lighter airborne particles. Influenza and measles are two other examples of diseases that are transmitted through the air; however, they travel in the lighter particles through a method called aerosol [1]. Other diseases that spread via airborne droplets include tuberculosis, a mycobacterial disease causing disability and death in many regions of the world, and pertussis, an acute bacterial disease involving the respiratory tract [4]. If an individual coughs while infected with the flu they are likely to infect the entire room, whereas the transmission of a disease like SARS appears to require closer contact and also may be reduced by frequent hand washing.

This mode of transmission discussed is consistent with the observation that most patients can be linked to persons with SARS or places where SARS transmission is documented or suspected, such as health care settings and households. For example, in Toronto and Singapore over 94% of the case patients documented contact with a SARS patient or with a hospital ward where a SARS patient was located [49]. It is important to understand what close contact represents for the transmission of SARS. Close contact could occur between people who live in the same household or if someone is providing care for a SARS patient. Close contact examples include kissing or hugging, sharing

eating or drinking utensils, close conversation (within 3 feet), physical examination, and any other direct physical contact between two people [23]. Close contact does not include activities such as walking beside a person or being in the same room.

The transmission of SARS is reflected in and measured by the pathogen's basic reproductive rate (R_o). R_o represents the average number of secondary infections arising from one infected individual in a completely susceptible population in the absence of specific control measures [50-52]. The successful emergence of a pathogen requires that R_o exceed 1.0 in the new host (See Figure 25). If the R_o of a potential pathogen is greater than one, this scenario is capable of the occurrence of an epidemic; furthermore, if the population is large enough and dispersed then the infection may become endemic. By contrast, if R_o is less than 1.0 the infection will go nowhere. If R_o is equal to 1.0 the infection will be transmitted from one person to another and likely will eventually die off by chance with no real epidemic potential. There are various mechanisms that can increase R_o for a specific pathogen including [51, 52]:

- Ecological Changes
    - Changes in the host density
    - Changes in human behavior
    - Population size effect- each additional host infected before the infection dies out provides another opportunity for a mutation that might push R_o over the epidemic threshold
- Genetic Changes
    - Neutral drift
    - Co-evolution of the pathogen and its reservoir host

- Adaptive evolution of the pathogen during chains of transmission in humans

A R_0 of almost 3 is consistent with a disease spread by direct contact or larger virus-laden droplets and is not highly infectious in comparison to a disease such as influenza and measles that have a R_0 of 10 and 15 respectively in a typical community [1, 3, 50]. A number of researchers have estimated R_0 for SARS-CoV by fitting models to the initial growth of epidemics in a number of countries [1]. Their observations show that SARS-CoV is less transmissible than initially thought, with an estimate of R_0 in the range of 2-4. For public health purposes, SARS is less transmissible than most other respiratory infections, which makes it more susceptible to control measures.

As mentioned, healthcare settings have played an essential role in the epidemiology of SARS. One of the most important means for the spread of SARS-CoV has been between humans in hospitals. Those working within these facilities were some of the earliest and most severely affected groups from almost all the SARS outbreaks reported across the globe. For example, in the Toronto and Singapore outbreaks, 43% and 41% respectively of the SARS cases were healthcare workers. SARS-CoV has been estimated to have a R_0 of 4 in the hospital setting [49]. Once the patients have been recognized as having SARS and are isolated, the R_0 drops to less than 1.0, a value as mentioned that is not capable of sustaining an outbreak. Outside the hospital setting and other situations, the R_0 of SARS-CoV has shown to be consistently less than one, as demonstrated by the failure of the virus to establish and maintain itself in the community [49].

Nosocomial transmission of SARS from critically ill patients to health care workers has been prominent throughout the outbreak and a worrisome epidemiological characteristic. Studies have shown the use of aerosol-generating procedures (such as endotracheal intubation, bronchoscopy, and treatment with aerosolized medication) may amplify the transmission of SARS-CoV [6]. Those physicians and nurses who performed endotracheal intubation were at a significantly greater risk of developing SARS (RR=13.29, p=.003) than compared to their respective reference controls [53]. In these hospital settings, if a cluster is recognized early and the source of the SARS transmission is identified and isolated, the outbreak will likely be contained. Such measures would include closing the hospital ward or clinical area, isolating all SARS patients and contacts within the ward, and quarantining health care workers and visitors who had visited the ward. If the outbreak is detected later (beyond 1-2 incubation periods in which secondary cases have occurred among staff and inpatients and other wards); however, the most prudent course of control is to close the hospital and place all healthcare workers on work quarantine immediately [54].

In the SARS epidemiological investigation, there are two key but unusual events in the transmission patterns of SARS. These events involved the Hotel M in the Guangdong Province and the Amoy Garden cluster, both of which were discussed in detail in Chapter 1. The original index case of SARS in Hotel M was the sentinel event in the evolution of the SARS outbreak, apparently initiating the global spread of SARS (See Figure 23). From this single event, superspreading of SARS occurred with successive generations of horizontal spread of SARS, resulting in cases that were mainly on the same floor of the hotel as the index case. Figure 24 shows the generational

transmission of SARS starting with the index case as the first source of the infection. This patient then transmitted the virus to the second generation including close direct contact with health care workers and others (family, friends, others). The third generation then represents the family members of the healthcare workers or other direct contacts. Finally, the fourth generation would consist of infection in other contacts in the community. Figure 27 gives a schematic of how the spread of SARS appeared in Beijing. These superspreading events could have proven to be more severe if there had been a greater number of any generation of cases of SARS, having the potential to produce a flame of infection throughout society. Fortunately, the control procedures once administered were successful in eliminating the completion of the four generations of transmission.

When looking at the infectious period of SARS, the transmission efficiency appeared to be the greatest from severely ill patients or those patients with rapid clinical deterioration, usually during the second week of illness. Singapore data has shown that very few secondary generation cases result when symptomatic cases are isolated within 5 days of illness onset (See Figure 26). Laboratory data completed on SARS cases correlated closely with this idea that the infectivity of the SARS-CoV is linked to the incubation period and time of isolation. From this knowledge, control measures and procedures for isolation of SARS cases can be initiated to help eliminate and control the generational spread of SARS, particularly to potential secondary cases. Interestingly, the United States showed a lack of transmission of the SARS-CoV to potential secondary contacts [55, 56]. The findings support the idea that under certain circumstances, SARS-CoV is not easily transmitted. These findings may be explained by the idea that

transmission appears to be more likely when the patient is shedding higher amounts of virus, generally coinciding with their hospitalization. As a result, the degree of exposure to close contacts was decreased since the time of higher infectiousness occurred in the hospital setting [55]. This epidemiological distinction is still worth mentioning and more studies may be needed to thoroughly understand this specific aspect of the transmissibility mechanism of SARS-CoV.

The second unusual transmission event involved residents in the Amoy Gardens, a private housing estate in East Kowloon, Hong Kong. When the outbreak ended in April a total of 321 residents from 15 blocks had been affected [6, 57]. The initial exposure was traced to a 33-year-old patient of the Prince of Wales Hospital who had chronic renal disease. He lived in Shenzhen and visited his brother in unit 7 on a mid-level floor of Block E of Amoy Gardens. Studies have shown that residents of Block E had a SARS attack rate of 38.9%, compared to those in other blocks of the Amoy Gardens (19.6%) and community controls (18.3%) [58]. These results show the area of significance for the central location of the outbreak.

In this outbreak, other modes of transmission may have played a key role in the spread of the infection. Given the point-source nature and the temporal and spatial progression of the community outbreak in the Amoy Gardens, it is unlikely to have been caused distinctly only by transmission through respiratory droplets and contacts. Several hypotheses have been proposed to explain the initial outbreak [58]:

1. Contaminated sewage droplets were sucked back into the bathrooms by powerful bathroom fans through dried-up floor drains, then escaped through windows and rose as a plume in a narrow light well

2. Passive carriage by pests
3. Faecal-oral contact through contaminated surfaces

The problem is that none of these hypotheses necessarily explains three important attributes of the Amoy Garden outbreak: dose, timing, and spatial distribution. In order for the index patient to have infected those in the Amoy Gardens the individual would have had to excrete a large amount of the virus into the environment to serve as a static common source of the epidemic. Also, those floors above Block E in which the index case visited were affected more than those floors below Block E. The introduction of an infected vector would be sufficient to distribute the infectious material. Infected vectors can produce live virus for days, providing the large dose required for the outbreak. Therefore, researchers had concluded in August 2003 that the most likely vector at the Amoy Gardens was a roof rat. There is various circumstantial evidence for the existence of a rat vector including [57]:

- Virologists suspect the SARS-CoV originated from animals and jumped species to infect humans. The virus can infect and survive in animals as well as humans.
- Viral remnants were detected in four of eight samples of rat dropping found in the Amoy Gardens and in the throat or rectal swabs of five housecats, one dog, and at least one rat from the estate.
- The location of Amoy Gardens is in one of the most densely populated areas in Hong Kong, known for poor hygiene and rat infestation.

- Rats are mobile, territorial, and can reach high floors through external pipes. The sewage and water pipes are located close to the bathroom windows allowing easy access of rats into households.
- Viral footprints were found around toilet bowls, kitchen sinks, and on kitchen floors in several households in Block E. These are common points of use for humans in the household and represent an opportunity for exposure.
- The presenting symptoms and clinical course of SARS patients from the Amoy Gardens was significantly different from other SARS patients. These patients from the Amoy Gardens outbreak had more diarrhea, higher percentage of admission to intensive care units, and a higher mortality. The characteristics mentioned above are all indicative of a different route of infection, mutation of the virus, or both.
- The diversity of the SARS-CoV as an RNA virus to reshuffle genes may have produced a virus that was transmissible to rats and humans.

The rat vector hypothesis for the cause of the Amoy Garden outbreak has recently been brought under speculation in April 2004 [59] along with the need to consider all possible modes of communication for the spread of SARS. Some of the criticisms are as follows:

- No sign of active disease was found after autopsies were completed on four rats in the Amoy Gardens. However, "Rats may also be able to transmit SARS without having overt disease [57]."

- To begin an outbreak infecting such a large number of people, a lot of rats would have to be infected in a short period of time, and infectiousness of rats would have to be short-lived for the outbreak to die out [57].
- The role of rats in the Amoy Gardens could have involved mechanical transmission instead of urine/fecal contamination. For example, a rat may have crawled or swam out of a SARS-CoV previously contaminated toilet and then tried to exit the toilet facility by means of the ventilation fan opening or by means of the ventilation shaft [59].

From this information, it becomes important for SARS investigators to explore all possible SARS reservoirs and transmission mechanisms. Due to the various epidemiological properties and the past recombination events of the SARS-CoV lineage, the virus proves to have the potential for a rapid unpredictable change. In other words, what we understand about the transmission of SARS currently may change with later knowledge and investigation of the transmission and properties of the SARS-CoV.

Chapter 3

HANTAVIRUS PULMONARY SYNDROME (HPS) DESCRIPTIVE EPIDEMIOLOGY

3.1 TIME PERIOD OF INTEREST

In May 1993, an outbreak of an unexplained pulmonary illness occurred in the Southwestern region of the United States known as "The Four Corners", which included Arizona, New Mexico, Colorado, and Utah [60]. The initial suspicion of the disease can be traced to a young, physically fit Navajo man who suffered shortness of breath, was rushed to a New Mexico hospital and died shortly thereafter. Through the observations of an Indian Health Service (IHS) clinician reviewing the results of the case, it was discovered that the young man's fiancée had died a few days earlier after showing similar symptoms of disease. This key piece of case information was important in the discovery of the newly emerging disease, Hantavirus Pulmonary Syndrome (HPS). Dr. James Cheek of the IHS responds, "I think if it hadn't been for the initial pair of people that became sick within a week of one another, we never would have discovered the illness at all [60]."

The clinician later contacted other practicing physicians and the Office of Medical Investigations (OMI) of the state of New Mexico. An investigation combining the entire Four Corners regions was initiated at this time for detection of patients with similar case histories. Within only a few hours, through collaboration of physicians and the OMI, five, young, healthy people had been determined to have died after acute respiratory failure [60, 61]. Laboratory tests proved to be unsuccessful in implicating any known disease as the cause of any of the deaths.

On May 27, 1993 the IHS and the New Mexico Department of Health requested the assistance from the CDC, of which four epidemiologists later traveled to the area to join and assist the outbreak investigations [61]. During the next few weeks, additional cases of the disease were reported from the Four Corners Area. Investigation of the initial patients indicated the disease affected healthy young adults and first manifested as fever and muscle aches. Hospitalization occurred shortly after and was prompted by sudden onset of pulmonary edema rapidly progressing to respiratory failure and in many cases death.

Physicians and scientific experts worked intensely to narrow down the possible cause for the disease. Laboratory studies by the State Health Departments and the University of New Mexico eliminated the most likely etiologic agents, *Yersinia pestis* (cause of pneumonic plague), *Legionella, Mycoplasma,* and influenza virus [61]. The diversity of symptoms and clinical findings steered researchers away from toxic agents such as herbicides or a new type of influenza, and moved toward a possible virus etiological cause. On June 4, 1993 serologic tests conducted by the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, and CDC showed the pulmonary syndrome to be caused by a new hantavirus initially called both the Muerto Canyon Virus and the Four Corners virus. However, these names were not acceptable to the Native American communities of the area and the virus was eventually called Sin Nombre (unnamed) Virus (SNV) (Discussed in Chapter 4) [60, 62] and the disease was later referred to as Hantavirus Pulmonary Syndrome (HPS)

During the high profile investigation of HPS, new understanding and emphasis was focused upon the possibility of new and emerging infectious diseases. However, HPS later turned out to be a newly identified disease, but not a "new" disease. By examination of samples of tissues belonging to people who had died of unexplained adult respiratory distress syndrome in these areas, the disease origin was traced back several years. In fact, the earliest case of a serologically confirmed SNV infection was in a 38-year-old Utah man who developed an HPS-compatible illness in July 1959. The case patient was shown later to have IgG antibodies in September 1994 [60, 63].

Through March 3, 2004, a total of 363 cases of HPS have been reported in the United States and a total of about 1910 cases reported in the United States, Canada, and South America combined [60]. The case count began when the disease was first recognized in 1993. These cases have occurred in a sporadic pattern since the 1993 outbreak in the Four Corners region and about 37% have resulted in death [64].

The epidemic curve produced from HPS in the United States from 1993 to 2004 is shown in Figure 28. The pattern from the curve is indicative of a point source epidemic with a peak in the number of cases and a gradual decline, in contrast to a person-to-person spread or continuous common source outbreak scenario. A point source is often associated with an animal reservoir for transmission of the virus to humans, as was found for HPS being related to rodents (discussed in Chapter 4). The graph also shows seasonal variation in the HPS cases particularly in the spring and summer time frame.

An interesting weather phenomenon has been suggested as the cause of the outbreak of HPS in the southwestern United States in 1993. This weather pattern known as "El Nino", also called El Nino-Southern Oscillation (ENSO), is a cycling recurring

disruption of the oceanic/atmospheric system in the tropical Pacific [65]. The El Nino phenomenon has consequently affected weather around the world, including an increase in rainfall across the southern regions of the United States and in Central and South America. Evidence suggests that a dramatic increase in rodent populations (known carriers of HPS causing virus) occurred in the Southwestern United States during 1991-1993 [65]. The increased rainfall may have produced conditions more suitable for the rodent populations such as a greater food supply, more cover and shelter. A population density increase in rodents would allow them to encounter each other and potentially transmit the hantavirus. A dense rodent population would produce scenarios for more rodents to come in contact with virus infected rodents, hence the possibility of transmitting the virus. Also, when the rodent density is higher, there is a greater chance for encounters between rodents and humans. This pattern of spread in the mouse population was essentially recorded through a population survey of the mouse population in this specific area prior to the HPS outbreak in the Four Corners region of the United States and may have been the factor essential to the outbreak of HPS in this region. The sporadic nature of cases of HPS may signify an important temporal characteristic that the infection may disappear from a population of the mouse vector if environmental conditions and seasons are adequate, only to reoccur sporadically when the conditions and season change [66]. A more logical explanation is that the disease "remains endemic within the rodent population with human disease cases occurring sporadically from unusual contacts. Outbreaks may then result from unusual population surges due to climatic changes."

3.2 GEOGRAPHIC DISTINCTIONS

HPS was first noted in the United States, but since the emergence HPS has been documented in other regions as well including Argentina, Brazil, Canada, Paraguay, Uruguay, Chile, and Panama, making HPS a pan-hemispheric disease [60]. The disease has only been reported thus far in the Western Hemisphere. The distribution of cases in these regions can be seen on Figure 29. The figure shows the cumulative number of HPS cases reported from 1993 to 2004 in North and South America. Figure 30 presents a clearer graphic of the distribution of HPS cases per country. The countries with the largest number of cases reported between 1993-2004 are Argentina, Brazil, Bolivia, and the United States. A detailed description of the number of cases and deaths per country for each year is provided in Table 4. An overview of these countries will be provided for the epidemiological components of HPS in each of these areas.

A. North America

As of 2004, 450 cases of HPS have been reported in 31 U.S. states and 3 Canadian Provinces [67]. Three-quarters of the HPS cases have been from rural areas in the western half of the continent on either side of the Rocky Mountains [64, 68]. No cases have currently been reported in Mexico; however four cases reported in the United States have occurred in areas near the border of Mexico. Studies have shown at least four distinct hantaviruses to be associated with HPS in North America [68]. These specific viruses will be discussed in Chapter 4.

North America-United States

As mentioned previously, the initial recognition of HPS in the spring of 1993 stemmed from an epidemic of approximately 27 cases of unknown respiratory disease in

the southwestern United States. Since that time period, retrospective analysis of HPS has determined that cases occurred as far back as 1959. The majority of cases since the initial outbreak in 1993 have occurred sporadically at a rate of 20 to 40 cases per year [422] throughout the United States, which suggests an uncommon yet epidemic pattern of occurrence. A distribution of HPS cases reported per state in the United States is presented in Figure 32. From this figure, a majority of the cases of HPS occurred in the southwestern region of the United States. In the United States, HPS cases have been documented in all months of the year, bur are less frequent during the winter months of December, January, and February [68]. The United States case-fatality rate of HPS was 44% at the start of the outbreak. However, this number has steadily declined since the time of the initial outbreak in 1993. Those cases with an onset of illness after January 1, 2004 had a case fatality rate of approximately 35% [68]. The decrease in mortality can be attributed to improved clinical management rather than changes in the virus or pharmacological therapies.

North America-Canada

For surveillance purposes, Canada has adopted the HPS case definition of the U.S. CDC (see below). As of 2004, there have been 88 cases of HPS reported [68]. A majority of the cases occurred in three western provinces including: British Columbia, Alberta, and Saskatchewan. These areas account for 25% of Canada's population. Through retrospective studies, the earliest known cases of HPS in Canada occurred in Alberta in 1989. Since 1994 when HPS was recognized in Canada, an average of about 5 cases of HPS per year has been reported. However, a significant increase in the number of cases was reported for 2002 (44 cases) and 2003 (14 cases). More than 45% of the

HPS cases have occurred during the months of April, May, and June [68]. Studies have shown that landscape composition in Canada is a more important predictor of rodent seroprevalence than other factors such as season, viral strain, climate, buildings, or association with humans [68].

B. Central America

Central America-Panama

No cases of HPS were reported in the Central American region or the Caribbean from 1993 through 1998. However, in 1999 cases of HPS occurred in this region and to date there have been 35 HPS cases reported [67]. It is difficult to determine what may have led to the occurrence of cases during this time period, but the cases may be linked to changes in the environment and an introduction of various host species for HPS.

C. South America

In South America, the presence of hantavirus infections (not HPS associated) has been known since the 1980's. Studies have shown that nearly 56% of captured rats were seropositive for antibodies reactive to Hantaan virus antigen during that decade [68]. Following the outbreak of HPS in the United States in 1993, HPS was diagnosed in three people in Brazil. By the third quarter of 1998, 239 cases of HPS were reported from five countries in South America. Cases have occurred in an endemic fashion as seen in the North America. However, several clusters have accounted for more than 25% of all the cases of HPS on the continent [68]. These clusters have mostly occurred from September to January in a variety of habitat regions. A few of the highly HPS affected countries are highlighted below.

South America-Argentina

As of 2004, 592 cases of HPS have been reported in Argentina [67]. They were predominantly in the Salta and Jujuy provinces in the northwest, Santa Fe and Buenos Aires provinces in the central part of the country, and Rio Negro, Chubut, and Neuquen in the south [68]. The prevalence of hantavirus antibodies in the general population in these areas was about 6.5% [69]. The overall case fatality rate in this region is approximately 44%.

After the 1993 outbreak in the United States, acute, prospective, and retrospective surveillance procedures were completed of patients presenting with fever and unexplained respiratory distress syndrome between 1987 and 1995. In central Argentina, HPS was detected in patients during surveillance of leptospirosis and Argentine hemorrhagic fever in which laboratory tests for these agents produced negative results. In northern Argentina, local physicians in the Salta province had reported case clusters of acute respiratory distress syndrome of unexplained etiology since the 1980's [68]. Due to serologic testing of cases, results supported hantavirus as the etiologic agent of the disease. In southern Argentina, a cluster of three family members with HPS were identified in the Province of Rio Negro in March 1995. Another cluster of cases occurred between September and December 1996 in the same region, affecting about 18 people. Four of the 18 cases were physicians who lived in the area. Epidemiological, molecular, and ecological data have established person-to-person transmission, primarily after a physician living in the non-endemic region became infected after having contact with a HPS patient [68]. The mode of transmission will be discussed more thoroughly in Chapter 4.

South America-Brazil

From 1993 to 2004, Brazil has reported 321 cases of HPS [429]. In December 1993, three brothers from Juquitiba in the Sao Paulo area were diagnosed with HPS, of which two later died from the illness. The brothers lived together in a rural area that showed evidence of rodent infestation. 6.1% of the case contacts tested positive for antibodies reactive to hantavirus antigen, with no symptoms of disease for HPS [68].

South America-Chile

HPS was not recognized in Chile until 1995 when a patient from Cochamo, Los Lagos was diagnosed with the illness. As of 2003, 331 cases of HPS have been reported in the country [67]. The majority of cases occurred in the Southern regions and between October and December. The overall case fatality rate was approximately 61% [68], which is higher than reported for other regions of the Americas.

Chile had three family clusters which occurred in the Aysen Region. In one cluster, family members became ill within one to five days of each other. In another family cluster, illness occurred in a sequential manner, with a period of 16 to 41 days between the index case and the onset of illness of the last family member. The third family cluster included a husband working in a rural area and his wife who stayed at home in the urban area of Coyhaique. The husband developed symptoms suggesting HPS 12 days after returning to his urban home, was hospitalized, and died. The wife became ill 22 days after the initial onset of her husband's symptoms. No known rodent exposure was determined [68].

South America-Paraguay

As of 2004, 99 cases of HPS have been reported in Paraquay [429]. An outbreak of HPS occurred in an agricultural community in the western Chaco region, affecting about 17 people in the spring and summer of 1995 through 1996. The case fatality rate during the initial outbreak period was 12% [68]. This may have been underestimated, however, since autopsies were completed only infrequently in this region. The human seroprevalence in asymptomatic groups was 7% and 21% in community residents [68]. These findings may be indicative of a mild illness in these regions with higher rates of sub-clinical infection than documented elsewhere.

3.3 CASE DEFINITION

HPS, commonly referred to as hantavirus disease, is a febrile illness characterized by bilateral interstitial pulmonary infiltrates and respiratory compromise usually requiring supplemental oxygen and clinically resembling acute respiratory disease syndrome (ARDS). Typical disease onset consists of fever, myalgia, headache, and gastrointestinal symptoms. The surveillance case definition in 1993 during the initial outbreak was as follows [60]:

- A confirmed case is defined as unexplained adult respiratory distress or acute bilateral pulmonary interstitial infiltrates and/or prodromal symptoms in a person with onset during 1993 having laboratory evidence of recent hantavirus infection.

As more epidemiological and clinical knowledge developed about the newly emerging disease the case definition for HPS became more thorough and was revised as follows [63]:

Clinical Case Definition

- A febrile illness (T> 38.3 °C [101 °F] oral) requiring supplemental oxygen, *plus*
- Bilaterial diffuse infiltrates (may resemble adult respiratory distress syndrome [ARDS]), *plus*
- Develops within 72 hours of hospitalization in a previously healthy person, OR
- Unexplained illness resulting in death *plus* an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death

Laboratory Criteria for Diagnosis

- Presence of hantavirus-specific IgG antibodies to a 4-fold or greater increase in IgG antibody titers OR
- Positive reverse transcriptase-polymerase chain (RT-PCR) results for hantavirus RNA OR
- Positive immunohistochemical results for hantavirus antigens

Case Classification

- *Suspected:* Presentation compatible with the clinical case definition
- *Confirmed:* A suspected case that is laboratory confirmed

HPS is divided into four phases: febrile, cardiopulmonary, diuretic, and convalescent phases [422]. The febrile phase typically lasts 3 to 5 days (range 1-12 days) and is indistinguishable from many other viral diseases. This stage's symptoms include fever, myalgia, chills, asthenia, dizziness, headache, anorexia, nausea, abdominal pain, and diarrhea. Signs of upper respiratory tract infection such as sore throat, rhinorrhea, sinusitis, and ear pain are usually absent in HPS.

The second phase of cardiopulmonary begins with onset of hypotension and pulmonary edema with rapid progression over a 4-24 hour time period. Pulmonary edema is indicated by a respiratory rate of about 24/min or by a chest x-ray [68]. At this phase of the disease, hypoxia is apparent with an oxygen saturation of hemoglobin less than 95% at sea level and less than 90% at 2000 m or more above sea level.

The third phase is initiated with the occurrence of spontaneous diuresis. This stage is characterized by a rapid clearance of the pulmonary edema fluid, resolution of fever, and shock. The convalescence phase extends over the next two week to two months.

3.4 INCUBATION PERIOD

The incubation period of HPS is not completely defined since few cases have had clearly defined exposures in time and place. Currently the incubation period for HPS is thought to be approximately two weeks with a possible range of a few days to six week [4] The incubation period of other hantavirus disease is typically one to four weeks [68]. However, in the United States, it has often become difficult to determine when and where the case-patient contracted the virus.

In an effort to determine the incubation period of HPS-causing viruses in the United States, eleven HPS cases from the national HPS case registry were identified with well-defined exposures. Review of these eleven cases suggests the incubation period to be 9 to 33 days, with a median of 14-17 days [70]. Figure 31 shows an overview of the exposure periods for these eleven case patients. There are still some gray areas for the incubation period. About half of the study population used did not note exposure to rodents or rodent-infested areas. Also, in those patients who did report an exposure to

rodents that had carried hantavirus, many had multiple or continuous exposure, especially those living in rural areas. Other limitations for accessing the incubation period of HPS include limited recall, a high case-fatality ratio of about 37%, and continuous exposure to rodents. By reviewing histories of case patients, estimates of the incubation period for HPS can be suggested. It becomes essential in investigating HPS cases to have an understanding of the incubation period for public health and clinical outcomes.

3.5 PERSONAL CHARACTERISTICS

A. Age

The age distribution of cases is fairly consistent among the regions affected with HPS. The overall mean age is around 37 years of age. A summary for some of the regions' mean ages are summarized below [68, 71]:

- United States: Mean age 37 (range 10-75)
- Canada: Mean age 39.5 (range 15-62)
- Argentina: Mean age 34.7 (range 4-71)
- Chile: Mean age 29.7 (range 2-60)

In the United States, HPS is rare in young children under 18 years of age. Roughly, 5.2% of the HPS cases are from this age group [68]. However, in Argentina and Chile a larger proportion of pediatric HPS cases have been reported. For example, in Chile, approximately 21.4% of the cases occur in those less than 17 years of age [68].

B. Gender/Race

All regions affected by HPS show male dominance in the number of cases reported. This may be representative of the other risk factor behaviors associated with HPS, which are more commonly utilized by males (see other risk factors). Some region

gender percentages with HPS include: United States (61%), Canada (68%), and Chile (75%) [68, 71]. The majority of case patients are also white in all areas affected by HPS. For example, in the United States 77% are white, 20% American Indian, 1% are Black Asian [71].

C. Other Risk Factors

As mentioned previously, about 75% of HPS cases have been residents in rural areas [64]. The most effective way to decrease the risk of HPS is to limit exposure to rodents and their excreta [72]. HPS cases have been associated with a variety of activities including [68, 69]:

- Inhabiting dwellings with indoor rodent populations
- Occupying previously vacant cabins or other dwellings
- Cleaning barns and other outbuildings
- Disturbing rodent infested areas
- Residing or visiting in areas in which the rodent population has shown a marked increase in density
- Trapping or handling live or dead rodents or their excreta
- Planting or harvesting field crops
- Disturbing rodent-infested areas while hiking or camping

These factors are highly associated with HPS infection. Another risk factor that has been documented but infrequent is occupational exposure. Among those cases that occurred in the United States due to occupational circumstances, those patients included grain farmers, an extension livestock specialist, field biologists, and agricultural, mill, construction, utility, and feedlot workers [63]. Interestingly, travel to HPS infected areas

is not considered a risk factor. To date, no restriction on travel to HPS infected areas have been initiated [63, 72].

Chapter 4

HANTAVIRUS PULMONARY SYNDROME (HPS) ANALYTIC EPIDEMIOLOGY

4.1 EPIDEMIOLOGICAL AGENT

Within three weeks of the previously unrecognized respiratory disease in the United States in 1993, the first evidence of the etiologic cause of the illness was determined. Antibodies cross-reactive with recognized hantaviruses were identified in sera from patients meeting a provisional case definition, and the pattern of reactivity was suggestive of a pathological agent that was not previously recognized [61, 73]. The investigations led to the identification of the Sin Nombre virus (SNV) (originally referred to as Four Corners or Muerto Canyon Virus), a novel hantavirus, as the causative agent of the outbreak of HPS in the United States [74].

Since the 1930's, epidemic and sporadic hantavirus-associated disease has been described throughout Eurasia, particularly in Scandinavia and northeastern Asia [75]. Hantaviral disease first became a U.S. public concern in the 1950's [61, 75]. During this time period, thousands of United Nations military personnel were infected with hantavirus during the Korean conflict. The illness was referred to as Korean hemorrhagic fever or hemorrhagic fever with renal syndrome (HFRS) [61]. The causative agent called Hantaan virus was not isolated until the late 1970's.

Hantaviruses are part of the viral family *Bunyavirida*, representing a group of zoonotic viruses that can be transmitted from animals to humans [63, 73, 75, 76] This particular family of viruses comprises roughly 14 viruses, including those causing HPS and HFRS as discussed above. Phylogenetic analysis of rodent-borne hantavirus genes

has revealed two main lineages. The HFRS-causing viruses are linked to an Old World lineage of viruses (See Table 5) including [77]:

- Hantaan: Asia, Far East Russia
- Dobrava: Balkans
- Seoul: Worldwide
- Puumala: Europe

All HPS-causing viruses share a common New World lineage of viruses (See Table 5) including [77]:

- Sin Nombre: West and Central , U.S. and Canada
- Monongahela: Eastern U.S. and Canada
- New York: Eastern U.S.
- Bayou: Southeastern U.S.
- Black Creek Canal: Florida
- Andes: Argentina and Chile
- Laguna Negra: Paraquay and Bolivia
- Bermejo: Northwestern Argentina
- Juquitiba: Brazil
- Choclo: Panama

A distribution of these various hantavirus strains is presented in Figure 33. The origin of HPS in the United States, as mentioned previously, was associated with the Sin Nombre strain of hantavirus. This particular strain is unique from other known hantaviruses in a few respects. First, the overall effects of the virus are more rapid and lethal, killing almost two-thirds of those infected in comparison to 5%-20% for the Hantaan strain. Also, the virus attacks and affects the lungs instead of the kidneys [78]. The distinctiveness of the clinical manifestations of the disease and the phylogenetic analyses completed support the idea that the virus is genetically distinct from previously described hantaviruses (See Figure 35).

Hantaviruses form a separate genus within the family *Bunyavirida.* They are primarily rodent borne and are not transmitted by an arthropod vector like the other four

genera (Bunyavirus, Phlebovirus, Nairovirus, Tospovirus) in this family of viruses [73, 75, 79, 80]. Hantaviruses are lipid-enveloped, spherical viruses about 80 to 110 nm in diameter [68, 77, 80]. Figure 34 shows a thin-section electron micrograph of Sin Nombre Virus isolate, the causative agent of HPS.

Interestingly, unlike human-cells, the genetic material of hantaviruses is not composed of double-stranded DNA. Instead, the viruses are composed of a single strand of RNA in three segments. The RNA genome tri-segments include a large (L) segment approximately 6500 nucleotides long, a middle (M) segment approximately 3600-3800 nucleotides long, and a small (S) segment approximately 1700-2100 nucleotides long. The L segment encodes a viral polymerase, the M segment encodes G1 and G2 envelope glycoproteins, and the S segment encodes the N nucleocapsid protein [68]. The viruses are surrounded by a lipid envelope adding fragile characteristics. Like other enveloped viruses, hantaviruses are readily inactivated by heat, detergents, organic solvents, and hypochlorite solutions [80]. The lipid envelope can be destroyed and the virus can be killed by fat solvents such as alcohol, disinfectants, and household bleach [76]. Depending on the environmental conditions, hantaviruses likely survive less than one week in indoor environments and for shorter periods when exposed to sunlight outdoors.

To date, there has been no evidence of genetic re-assortment of the newly identified strain with the Old World hantaviruses. All known SNV strains shared almost 90% nucleotide sequence homology and even higher amino acid sequence homologies [68]. From these findings, is it unlikely that genetic re-assortment with other viruses accounted for the newly recognized HPS-causing virus in the southwestern United States.

A more logical possibility is that HPS and HPS-causing viruses may have existed in the Western Hemisphere for many years despite only being detected in 1993.

4.2 MODE OF COMMUNICATION

Murid rodents (order *Rodentia,* family Muridae) are the natural hosts and reservoirs of hantaviruses. Fossil records have shown that these specific rodents have been present for the past 20 million years in North America and 3.5 million years in South America [68]. Each hantavirus appears to have a single predominant natural reservoir, showing exceptional concordance of the host and virus through phylogenetic interrelationships. Findings have shown that hantaviruses do not adapt readily to new hosts and are closely adapted to be successful in their specific host [79]. Some scientists hypothesize that the genus *Hantavirus* evolved in the Old World and that the viruses may have been carried by rodents across the Bering land bridge when migration occurred during the Oligocene period (33.7 to 23.8 million years ago) and into South America in the Pliocene period (5.3 to 1.8 million years ago) [79].

Rodents belonging to the murid subfamily *Sigmodontinae* have been implicated as the hosts of HPS-causing viruses. This subfamily contains around 430 species of mice and is widespread in North and South America. Each hantavirus is maintained in the environment by infecting a single rodent species [68, 73]. As a result, the range of the host species restricts the distribution of any particular virus.

Investigation of the 1993 outbreak of HPS in the southwestern United States identified the Sin Nombre virus (SNV) as the causative agent and the implication of the deer mouse as the principal reservoir (see Figure 36). The deer mouse is one of the most common small mammals in North America, occupying almost every dry land habitat and

widespread among rural areas [74, 81]. Figure 37 shows a distribution of the species within the United States, showing that a majority of the United States regions have deer mouse populations. The overall prevalence of these rodents will vary both geographically and temporally and approximately 10% of the deer mice test positive for evidence of SNV within the deer mouse population range [81]. More studies are necessary to determine if this proportion varies regionally.

There have been cases of HPS occurring outside the range of the deer mouse, implicating other rodents as host to hantaviruses with the potential for causing serious disease. For example, other hantaviruses associated with rodents known to cause HPS include the New York Virus, hosted by the white-footed mouse (See Figure 38). A single case in south Florida led to the isolation of Black Creek Canal virus, hosted by the cotton rat (See Figure 39). Three initial cases in Louisiana and east Texas implicated the Bayou virus, hosted by the rice rat (See Figure 40). Most of the land area in the United States lies within the range of one or more of the host species known to carry hantavirus.

HPS is more common in South America than in North America currently. Andes virus has been associated with HPS in Argentina and Chile. Other viruses linked to HPS in Argentina include Bermejo, Hu39694, Lechiguanas, Maciel, Oran, and Pergamino viruses. Bermejo and Laguna Negra virus causes HPS in Bolivia, and Laguna Negra virus is also linked to HPS in Paraguay. In 1999, an outbreak in Panama began the first cases of HPS in Central America implicating Choclo virus, hosted by the rodent *Oligoryzomys fulvescens.* Currently, since the rodents mentioned above are restricted to the Americas, HPS is restricted to the Americas geographically [81]. Table 5 provides a summary of the various types of viruses associated with HPS and their known reservoirs.

4.3 TRANSMISSION

Hantaviruses do not cause overt disease in their reservoir hosts and the rodents remain asymptomatic during their lifespan of carrying the virus [68, 81]. The infected rodents shed the virus in saliva, urine, and feces for many weeks, months, or for life, however the quantity of virus shed can be much greater approximately 3-8 weeks after infection. Field data suggests that transmission in the host population occurs horizontally with a higher frequency among male rodents. Transmission from rodent to rodent is most likely from weaning and through physical contact. Also, genomic sequencing has indicated that the virus likely has evolved concurrently with its rodent host over a long period of time [63]. Biting may be another important mode of transmission among rodents as demonstrated by the presence of infectious virus in saliva of infected rodents. Some evidence has shown the infectious virus in a number of other rodent species and their predators. This is indicative that other mammal species coming in contact with an infected rodent may become infected.

As mentioned previously, rodent infection is asymptomatic, whereas human infection is often associated with disease. The main route of transmission to humans is respiratory via small particle aerosols from rodent excreta, particularly freshly shed urine [63, 68, 81]. When fresh rodent urine, droppings, or nesting materials are stirred up, tiny droplets containing the virus get into the air. This process is known as "aerosolization" [82]. Figure 41 gives a representation of how the virus is transmitted. When humans breathe these particles of an infected rodent, this begins the possibility of becoming sick with HPS. High risk exposure has been associated with entering or cleaning rodent infested structures. Many hantavirus infections have occurred in persons of lower

socioeconomic status because poorer housing conditions and agricultural activities favor close contact between rodents and humans. However, other activities such as suburbanization, wilderness camping, and outdoor recreational facilities have spread HPS infection to persons of middle and upper incomes also. Other ways in which rodents transmit HPS to humans may include the following [60, 79, 81]:

- If an infected rodent bites a human, the virus may be spread to that person. This type of transmission is rare.
- Some researchers think that if humans touch something that has been contaminated with rodent urine, droppings, or saliva, and then touch their nose they may become infected with the virus.
- Researchers also think that if humans eat food contaminated by urine, droppings, or saliva from an infected rodent they may become sick.

Person-to-person transmission has not been associated with HPS cases in the United States. However, person-to-person transmission including nosocomial transmission of Andes virus was well documented in an outbreak in Southern Argentina in 1996 and suspected to have occurred to a lesser extend in an outbreak in Chile [63, 81]. Suggestion of person-to-person transmission began when there was an increase in the number of HPS cases from 1995 to the spring of 1996 in an area 150 km around the El Bolson area in Southern Argentina. During this time period, a few physicians who were in contact with El Bolson cases of HPS developed the disease during the same period. Epidemiological analysis suggested person-to-person transmission of the Andes hantavirus by either nosocomial or household contact.

For evaluation of person-to-person transmission in these designated regions, homologies of PCR-amplified viral sequences were analyzed from 26 Argentine and Chilean cases. All hantavirus variants studied were genetically similar, and 16 of the cases were linked epidemiologically as having close contact through the household, health caring, marital contact, and/or traveling together in a vehicle [83, 84]. Contact with rodents was not evident in this specific outbreak. The direct genetic evidence provided from these outbreaks strongly supports a person-to-person transmission pattern.

After the Argentinean and Chilean findings of the possibility of person-to-person transmission of HPS, the United States initiated epidemiological investigations through retrospective analysis of the United States HPS registry. During this time period, the registry had records for 160 HPS patients with clinical and laboratory evidence of HPS. Household or social contacts (n=320) of 40 of the HPS patients were tested for antibodies that react with SNV antigen. Of these household or social contacts, 310 had no serologic evidence of hantaviral infection, three had IgG that reacted with SNV antigen but no illness, one had SNV-IgG and was diagnosed with HPS retrospectively, and six had IgM that reacted with SNV antigen [85].

Clearly, these findings do not provide definitive evidence of interhuman or nosocomial spread of HPS. Person-to-person transmission can not be considered as proven, because the few case clusters that were observed may simply have originated from a common exposure to rodent-infested living conditions. Currently, it is not known whether the secondary transmission of HPS observed in Argentina and Chile is a feature unique to hantaviruses in Southern Argentina or a rare interaction between host and virus.

More studies are needed to understand the epidemiological components of transmission for hantaviruses.

Chapter 5

PARALLEL COMPARISON OF SARS AND HPS

In order to provide application of the previous knowledge obtained from HPS to the recent outbreak of SARS it is essential to address the important similarities and distinct differences between the two diseases with a thorough emphasis on the nature of disease to human reservoir contact. With these specific distinctions, an understanding of the degree of parallelism between SARS and HPS can be determined and important recommendations for public health practice can be addressed.

5.1 SIMILARITIES

One important aspect for choosing HPS as the parallel disease comparison to SARS is the fact that both diseases are recent newly emerging/identified diseases. HPS was first recognized in the southwestern United States in 1993. Through a high profile investigation of HPS, the disease was determined to be a newly identified disease, but not a new disease. The disease emergence was traced back several years, with the earliest HPS-comparable illness identified in July 1959. One decade after the recognition of HPS in the United States, the SARS outbreak of 2003 began with the earliest known case of disease originating in the Guangdong Province of China in November 2002. By comparing these two diseases that were identified within a short time frame, previous public health measures for HPS can likely be applied to the more current SARS outbreak situation.

Interestingly, both diseases are geographically diverse in the cases reported and are not localized in one specific area. HPS is now considered a pan-hemispheric disease with the disease only reported in the Western Hemisphere. SARS, on the other hand, is

considered the first new pandemic disease to emerge in 2003 in that it sustained a global spread. The geographic capabilities for both HPS and SARS are important to consider for future public health awareness and recommendations.

When addressing clinical criteria for HPS and SARS, there are three important parallel conclusions to discuss. First, the laboratory methods of both diseases are largely consistent since they are both viral diseases. Detection of serum antibodies (IgG) for both hantaviruses (HPS) and coronaviruses (SARS) is determined by enzyme immunoassay. Also, a RT-PCR test is the necessary procedure to detect a positive result for the specific viral RNA for each virus. Second, the clinical presentation for both HPS and SARS are remarkably similar. Both diseases present with a high fever defined as a body temperature of greater than 101°F for HPS and 100° F for SARS. Also, both diseases resemble ARDS from chest radiographs and the autopsy findings in both cases are likely to be consistent with pneumonia and noncardiogenic pulmonary edema. Third, the clinical courses of the diseases are multi-phasic. HPS has four phases and SARS has three stages as addressed in previous chapters. The parallel stage descriptions for the diseases are as follows:

- Stage one- symptoms including fever, myalgia, and other systemic symptoms
- Stage two- rapid progression of pulmonary edema and oxygen desaturation

Without the current tests for detecting specific viral antibodies in patients, the clinical aspects of HPS and SARS could be indistinguishable in specific areas, from each other or from other infectious diseases. Fortunately, science has allowed for lab testing within the hospital setting along with the clinical presentation of the disease to ensure optimal diagnosis of disease.

HPS and SARS exhibit important epidemiological similarities including characteristics of the incubation period and age distribution. SARS and HPS research studies have both addressed the possibility that patients may appear to have unclear incubation periods due to multiple exposures. As a result, the incubation period for HPS is not completely defined since few cases have had clearly defined exposures, and the SARS incubation period deserves more studies devoted to investigating the outlier values obtained.

The age distribution for both HPS and SARS is also an interesting component of the parallel comparison. Both diseases exhibit an age distribution with the majority of cases occurring in young to middle-aged adults. HPS showed an average mean age of approximately 37 years of age, while the majority of SARS cases were in the age range of 20-60. Surprisingly, both diseases rarely occurred in children under age 18. These age distributions are likely directly correlated to other risk factors that contribute to cases of disease. For example, for HPS those individuals with occupational exposures through farming, biology, construction, utility service, and other related positions are at a higher risk of developing HPS since these positions are prone to rat exposure. On the other hand, a high occupational risk factor group for SARS includes health-care workers. For both HPS and SARS, the age distribution may be explained since a majority of those working in these occupations are likely younger and middle-aged adults.

The etiological agents for HPS and SARS show unique similarities. First, both viruses determined to be the causative agent for the diseases were novel and not previously recognized as part of their specific virus family. Phylogenetic analyses have shown that both causative viruses were genetically distinct from previous types of the

virus described. As a result, the virus linked to HPS was labeled as SNV, a new group in the family of *Bunyavirida*, and the virus linked to SARS labeled as SARS-CoV was classified as a new group in the family of *Coronaviridae*. Another important possibility inferred from the genetic analysis of each virus genome is that both causative agents likely were already circulating within the human population in which the virus was first recognized. These populations include the United States for HPS and mainland China for SARS.

The structure and virus characteristics for both HPS and SARS are parallel in that both HPS-causing hantaviruses and SARS-CoV are lipid-enveloped spherical viruses containing a single strand of RNA. Hantaviruses are larger with a diameter of about 80 to 110 nm compared to approximately 78 nm in diameter for SARS-CoV. The main difference in the structures is the surface projections of the lipid envelope for SARS-CoV.

Two significant parallel considerations include the animal reservoir and mode of transmission for each disease. An important epidemiological component is that HPS and SARS are both zoonotic diseases, meaning they have an animal reservoir to harbor the causative agent of the disease. As a result, known contact with animals is a risk factor for infection with both HPS and SARS. The disease to human reservoir contact will be discussed in more detail in section 5.3. When accessing the modes of transmission of HPS and SARS, both diseases are linked by respiratory means as a source of disease. HPS's main route of transmission to humans is respiratory from small particle aerosols from rodent excreta. Similarly, SARS predominant transmission is through respiratory droplets through close person-to-person contact. Also, the mode of transmission in a

southern Argentina HPS outbreak has been suspected to have a person-to-person transmission pattern. This would directly parallel the mode of transmission for SARS, which is primarily known to be through person-to-person contact.

5.2 DIFFERENCES

For a thorough assessment of HPS and SARS, the contrasting characteristics are important to determine to clarify the limitations of using HPS as a parallel disease for SARS public health understanding. One very important distinction between the two diseases is the epidemic curve produced from each outbreak situation. HPS's curve has a pattern representing a point source epidemic with a peak in number of cases and a gradual decline (See Figure 31). This type of scenario is often associated with an animal reservoir for transmission from animals-to-humans. In contrast, the SARS epidemic curve signifies a propagated epidemic indicative of a person-to-person mode of transmission (See Figure 1).

Since HPS has been present a longer time than SARS the seasonality is understood, with the majority of cases occurring during the spring and summer months. These seasons are more prone to exposure to rodents with activities such as cleaning, handling, and hiking around rodent-infested areas. However, the seasonality of SARS is still undescribed. More knowledge and time is necessary to describe the pattern of SARS cases related to various seasons.

As mentioned as a similarity, HPS and SARS are both geographically diverse diseases. However, a key difference in the geographics involves the disease origin and the potential for diverse spread of disease. HPS was first recognized in the United States while SARS was first recognized in China. Interestingly, HPS appears not to present

such a global threat as SARS as a human disease. HPS has currently only been identified in the Western Hemisphere, whereas SARS was quickly an international problem. A likely explanation for this key difference is the mode of transmission necessary for the spread of disease. Specific rodents in other regions may not harbor the virus necessary to produce HPS. Therefore, unless the rodent was introduced to these geographic locations it is unlikely the disease will be present in these areas since HPS has shown to involve no or limited person-to-person spread. As a result, there currently has been no restriction on travel to HPS infected areas. However, a person-to-person spread disease is problematic primarily due to the international relations and travel the population is accustomed to. Therefore, the SARS outbreak situation forced a recommended travel restriction to China since SARS was a problem in these areas. For public health purposes, these restrictions are likely correlated to fewer cases of SARS in other regions of the world.

Within the specific regions affected by these diseases, the residence location reporting the majority of cases is completely different. Approximately 75% of HPS cases have been reported from rural areas, whereas SARS has spread more prominently under conditions of high density and greater population fluidity indicative of urban regions. These differences are likely associated to where the interspecies transition likely occurred when the disease originated.

HPS and SARS are quite contrasting with regards to the actual incubation period range and the CFR. The incubation period for HPS ranges from 9-33 days with a median of 14-17 days. SARS, on the other hand, has a much shorter incubation period of about 4-5 days with a mean incubation period of 4-6 days. The short incubation period of SARS may have been a key factor in the quick spread of SARS globally. Interestingly,

HPS has a much higher CFR of about 37%, while SARS is approximately 11% to 15%. From this information, it is clear that HPS is generally more severe than SARS; however both viruses are more severe than any previous virus in their designated family.

The epidemiological agent and reservoir of disease show some differences between HPS and SARS. First, the causative agent of HPS is a hantavirus, whereas SARS causative agent is a coronavirus. Historically, hantaviruses have been documented as causing human disease, whereas coronaviruses have never been associated with human disease until the SARS outbreak. Second, the principal reservoir of HPS is known to be rodents, unlike SARS whose reservoir(s) is still under speculation. Third, HPS is transmitted to humans via small aerosols primarily from rodent excreta. Only one outbreak in Southern Argentina has reported the possibility of human-to-human transmission. In contrast, SARS is predominately transmitted person-to-person through direct or indirect contact of mucous membranes with infectious respiratory droplets or fomites. Also, documentation of nosocomial transmission in HPS is rare despite a large number of cases observed and treated within the hospital setting. In contrast, one of the most important epidemiological attributes of SARS involved nosocomial transmission. Finally, from a clinical standpoint, asymptomatic infection is rare for HPS, whereas asymptomatic infection for SARS is very common. For SARS prevention, this distinction could be quite detrimental in containing and controlling the virus. As a result, more drastic measures may need to be considered if someone has been exposed to a SARS case, but is not showing symptoms. This idea will be discussed in more detail in Chapter 6. All of these specific distinctions between HPS and SARS are important

contrasting factors to consider when addressing a parallel comparison of diseases for public health practice.

5.3 DISEASE TO HUMAN RESERVOIR CONTACT

As mentioned previously, the mode of communication for an infectious disease is the phenomenon in the environment that brings the host and the agent together. The various modes of communication include vectors, vehicles, and reservoirs. HPS is *clearly* understood to involve rodents as the principle reservoir for disease, whereas SARS-CoV is *almost certainly* understood to involve an animal reservoir. Animals are one of the most important types of reservoirs for human disease as mentioned in previous chapters. About 75% of human emerging infectious diseases have a zoonotic (animal species) origin. As addressed previously, there are several important factors that may contribute to emerging zoonotic diseases including:

- Transportation of human and animals into new places
- Increased contact between animals and humans
- Changes in the environment and husbandry practices
- A larger immunocompromised population
- Increased recognition of diseases as a zoonotic origin
- Discovery of new organism not previously recognized

Technology has been a key component for helping to eradicate disease, but it can also contribute to exacerbating disease. Historically, there are numerous examples that support this philosophy including the following:

- Modern farming practices, such as feeding livestock remains of other animals, aided to help spread Creutzfeldt-Jakob disease through England.

- Suburban development destroyed predator populations, creating habitats for tick-carrying mice, which are highly efficient spreaders of Lyme disease.
- Medical technologies like transfusions and transplants increase the risk of spreading bloodborne disease such as Hepatitis C.
- HIV likely passed from chimpanzees to African hunters, spreading beyond these isolated regions when cities began to develop around Africa.
- Live-poultry markets like China's serve as breeding grounds for viruses that can spread to humans like influenza.

Is there an explanation as to the why an animal virus may cross the interspecies barrier and develop into a problematic human disease? As mentioned previously, RNA viruses characteristically have high mutation rates and evolve through RNA recombination. This fact alone may contribute significantly to the evolution of a hantavirus and coronavirus into the human population. Another logical reason is that the specific animal virus genes mutate to allow the surface proteins receptors to change shape and be compatible with human surface proteins. The final result may produce a more virulent strain of the virus, one that may be asymptomatic in the animal reservoir but fatal to humans. Hantaviruses do not cause overt disease in their reservoir hosts and the rodents remain asymptomatic during their lifespan of carrying the virus. However, the natural reservoir of SARS-CoV has not been identified and the animal that may be responsible for the cross-species transmission to humans is not known. Once more knowledge is obtained about SARS and its natural reservoir; more risk factors for prevention can be initiated. Also, the more research completed on specific viral characteristics necessary for crossing the interspecies barrier from animals to humans, the

better understanding of various risk factors for disease and prevention measures for both HPS and SARS.

Chapter 6

PUBLIC HEALTH OUTBREAK MEASURES

Determining public health strategies to control disease outbreaks is an essential component of epidemiology. Human experience with SARS is new, but is likely to recur, and the strategies used in the first outbreak were not optimal. An overview of the more extensive experience with HPS may help to develop and implement sufficient public health responses to any future SARS outbreaks.

6.1 OUTBREAK INVESTIGATIONS

Laboratory Handling

As mentioned in Chapter 3, the first suspicion of HPS was traced to the observations of an IHS clinician in the southwestern portion of the United States. After record of 4 cases of similar unknown respiratory illness, extensive investigations began involving CDC epidemiologists and local healthcare professionals. During the process of sending samples to the CDC laboratories for investigation, biosafety became an important consideration. A biosafety level refers to a specific combination of work practices, safety equipment, and facilities which are designed to minimize the exposure of workers and the environment to infectious agents [86]. The biosafety levels are as follows [87]:

- Level 1 (no or very low individual or community risk) -- This level applies to microorganisms that do not ordinarily cause human disease.
- Level 2 (moderate individual risk, low community risk) -- This level is appropriate for pathogens that can cause human or animal disease, but is unlikely to be a serious hazard to laboratory workers, the community, livestock, or the environment. If laboratory exposure occurred, serious infection may result, but

effective treatment and preventive measures are available and the risk of infection spread is limited.

- Level 3 (high individual risk, low community risk) -- This level applies to pathogens that usually cause serious human or animal diseases, but do not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.
- Level 4 (high individual and community risk) -- This level applies to pathogens that usually cause serious human or animal diseases and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are NOT usually available.

By June 4 2003, the serologic tests that were conducted by the CDC provided the first lead to the disease etiology, showing antibodies cross-reactive with recognized hantaviruses. The serum used was obtained from a patient meeting the initial case definition [61]. In only a few months, the hantaviral etiology of HPS was identified, illustrating the potential of the modern molecular biology and epidemiology when applied within a multidisciplinary approach to a new disease.

Laboratory transmission of hantaviruses from rodents to humans via the aerosol route is well documented [88]. Viral antigens have been detected in necropsy specimens, including tracheal aspirates, bronchial washings, blood, and plasma. Therefore, exposure to fresh necropsy material, rodent excreta, and animal bedding are associated with HPS risk. Other routes of laboratory infection include ingestion, contact of infectious materials with mucous membranes or broken skin, and animal bites [88]. Biosafety level 2 facilities are recommended for laboratory handling of sera from persons potentially

infected with hantavirus. Any potentially infected tissue is to be handled in level 2 facilities in accordance with level 3 practices. Any large-scale growth of the virus should be performed in a biosafety level 4 laboratories. For experimental purposes, infected rodent species known not to excrete the virus can be housed in animal biosafety 2 facilities. Because of the virulent nature of the HPS agent and since animal to human transmission can occur, persons working with the natural host species should take special precautions [88]. These recommended guidelines are based on the current knowledge of HPS. Revisions may be necessary in the future as epidemiologists learn and understand more specific components of risk reduction for HPS.

As mentioned in Chapter 1, SARS emerged in the southern province of Guangdong in November 2002, but the worldwide epidemic was triggered in late February 2003 when an ill physician infected several other guests at a hotel in Hong Kong. The WHO implemented biosafety level 2 and level 3 guidelines for the handling of SARS clinical specimens and materials derived from laboratory investigations [89]. As with the initial HPS outbreak, modern technology in the epidemiological investigation of SARS became an essential component in rapidly identifying the etiological agent in less than two weeks and the implementation of control measures that contained the outbreak within about four months.

Biosafety levels of prevention reinforced for SARS were similar to HPS. Activities such as routine diagnostic testing of serum and blood samples, examination of cultures, and packaging of specimens for transport are a few examples of SARS investigations in biosafety level 2 facilities. Activities that are performed in biosafety level 3 facilities include viral cell culturing of SARS-CoV, any manipulations involving

growth or concentration of SARS-CoV, inoculation of animals for potential recovery of SARS-CoV samples, and any protocol involving animal inoculation for confirmation and/or characterization of putative SARS agents [89].

The important distinction in laboratory handling between HPS and SARS is in the level of public health concern if an incident occurred. Effective HPS laboratory handling benefits the individual by decreasing risk to a pathogen that has a high mortality rate. In comparison, since SARS is transmitted person-to-person, laboratory handling is extremely important for the individual, colleagues, and personal contacts. A laboratory incident case of HPS would not be as problematic to public health as a laboratory incident case of SARS, thus producing more stringent guidelines. However, both infectious diseases should be handled with caution and under the strict guidelines of biosafety implemented by the WHO and CDC.

Professional Education

During the time period of the initial recognition of HPS in 1993, the CDC focused educational efforts on educating medical and public health professionals. Since the disease was newly recognized, physicians, nurses, and epidemiologists needed information about the disease; therefore, the first educational material was targeted to this specific group of people. Some of the educational programs initiated included [68]:

- Comprehensive educational/informational videos established
- Educational activities including training courses for state public health laboratories on diagnostic testing and an audio conference for health care workers, epidemiologists, and pathologists
- Internet site development

- HPS educational material provided by request for healthcare facilities
- Developed and promoted a HPS video in English and Spanish
- Initiated a telephone hot line to answer general public questions about HPS

In the case of SARS, which was not publicly announced by the Chinese government until April 20, 2003 [90], the education of healthcare workers seemed substantially delayed. Transmission of SARS in the healthcare setting was a major epidemiological component in the spread of SARS during the 2003 global outbreak, unlike HPS which has shown rare nosocomial transmission. Despite this fact, it is important with any newly emerging/recognized disease to prioritize education to healthcare workers for thorough control and prevention. This specific aspect of public health would strongly shadow the education of HPS; however, since SARS represents person-to-person transmission there would be some clear additional considerations.

SARS education in China did not officially begin until April 18,2003 [90], five months after the emergence of the new disease. This distinction may be attributed to the fact that a substantial proportion of SARS cases resulted from delays in clinical recognition and isolation of patients [91]. Once the education of healthcare workers was prioritized, training began through in-person course instruction, videotapes, and printed materials on the management of patients with SARS, infection control, and the use of personal protective equipment. These specific educational strategies used for SARS are comparable to HPS and should be a "gold standard" for any new disease outbreak investigation.

SARS presented more complications in training than HPS since the mode of transmission primarily involved person-to-person. Therefore, additional education was necessary for those healthcare workers involved with the SARS outbreak. For example, the following are additional educational and preventive measures for healthcare workers treating SARS patients [90, 91]:

- Early detection and isolation of SARS cases through clinical and epidemiological characteristics. This would include a thorough history of the patient by healthcare workers to distinguish a SARS case from other respiratory illnesses. Rapid decision making is essential to eliminate spread.
- Educate healthcare workers on the risk of exposure to SARS-CoV and the importance of reporting personal illness or exposure to eliminate spread of disease to patients and other healthcare workers.
- Personal protective equipment required 2 or 3 sets of gowns, gloves, and masks, in which the outer layer was to be removed and disposed after contact with each SARS patient. Goggles were also required.
- Education on basic infection control practices in the healthcare facility.
- Patient education on proper hygiene/cough etiquette practices to help decrease the transmission of respiratory droplets.
- Isolation of possible SARS cases in the healthcare setting on a designated ward
    - Capacity of rooms and units sufficient to house SARS patients
- Education on cleaning and disinfecting environmental surfaces within healthcare settings.

- Education on proper use of ventilators, nebulizers, endotracheal intubation, and other droplet and aerosol generating devices and procedures to eliminate rate of transmission of SARS in the hospital setting.
- Education on special handling of medical waste, textiles, or eating utensils has not been recommended since the SARS-CoV has not currently been implicated as spreading by these means.

The use of personal protective equipment (PPE) is an important aspect of SARS control and prevention, which deserves special attention. From a hospital perspective, it becomes important to classify respiratory diseases (i.e. airborne, contact, droplet, etc.) in order to determine the type of PPE necessary to protect healthcare workers and patient contacts. Looking at the use of PPE from the hospital perspective is very practical since SARS was important within the healthcare setting.

A case-control study on 458 staff (127 SARS cases and 331 controls) was completed to evaluate the effectiveness of respiratory and standard precautions in a multi-centre study in Hong Kong, China. The findings showed those with an intervention of only a N95 mask (represents government efficiency rating blocking about 95% of particles 0.3 microns in size or larger) 85.8% of cases were infected compared to 99.4% of controls. In comparison, those with an intervention of an N95 mask, gloves, gown, and hand washing showed 40% of cases infected and 81% of controls. These findings showed that the risk of infections was associated with the length of stay of patients with SARS and that infection control, including PPE use, must be used **rigorously** to prevent transmission of SARS-CoV. Therefore, the use of PPE becomes an important aspect for

SARS and more research should be completed to understand the best techniques necessary for prevention within the hospital setting.

The basic educational strategies initiated for HPS and SARS for healthcare workers is comparable; however, any disease like SARS that involves person-to-person transmission naturally requires more thorough standards for educating the healthcare professionals that will come in contact with these patients. These educational strategies are important for prevention of disease not only for the healthcare worker and hospital patients, but also for the surrounding community.

Surveillance

Surveillance is a crucial public health component that aids with understanding the trends in incidence and distribution of disease, helping to initiate proper planning of prevention strategies. During the outbreak of HPS in 1993, there was no computerized surveillance system in existence for reporting cases since the disease was previously unrecognized. As a result, the CDC initiated a toll-free telephone hotline number for the public. The purpose of the hotline was to serve as a passive system for reporting suspected cases of HPS and to provide updated information about HPS [92]. The national surveillance technique through this passive phone based system was successful in quickly identifying the widespread sporadic geographic distribution of the newly identified HPS throughout the United States. This system emphasized the need for physicians and other health care workers to include HPS in the differential diagnosis of unexplained ARDS.

The reports received through the surveillance system helped to identify one third of all confirmed cases of HPS detected in the United States through December 31, 2003

[92]. About 7.5% of suspected HPS cases reported through the system tested positive for Hantavirus infection [92]. The system also helped identify the earliest confirmed cases of HPS and allowed for the identification of cases of HPS due to variant Hantavirus species. The surveillance system proved to be quite beneficial; however, a few limitations were present. For example, the surveillance system may have underestimated the true number of HPS cases, the system may experience a dependence on news media and overall public interest, and indirect costs incurred were difficult to estimate [92]. Despite these limitations, the surveillance system technique may be a useful tool for future outbreak situations.

In the case of SARS, understanding the geographic diversity of cases becomes essential in surveillance reporting strategies. Like HPS, a SARS informational 24-hour hotline was provided [90]. At its peak, the hotline received 11,000 calls per day from individuals interested in obtaining SARS information. Since SARS presented such a serious global threat in 2003, it would have been interesting to see a surveillance geared telephone hotline specifically initiated for detection of SARS cases. Anyone having symptoms and epidemiological characteristics as mentioned nationally by the CDC could have access to call the hotline and report necessary information. At the end of the outbreak, a comparison of SARS cases reported through the telephone surveillance system and through general surveillance techniques could have been utilized. This information would be useful for public health to determine the efficiency of reporting SARS cases through a telephone system. Unfortunately, the previous limitations involved with the HPS telephone system would likely still exist for SARS case reporting.

The main limitations for a telephone based case reporting system for SARS would be the quantity of calls since more people overall were affected by SARS than HPS. SARS also presented more of a global threat than HPS; therefore a number of people may have been frantic and more likely to falsely report illness and epidemiological characteristics. Another problem remains in that SARS is very commonly asymptomatic, unlike HPS in which asymptomatic infection is rare. For control and prevention of SARS, this distinction warrants consideration since an individual could still transmit disease if harboring the virus. Recommendations could be initiated for those calling with likely illness of SARS, but not for those who weren't even aware they carried the virus. Despite these limitations, a telephone-based SARS reporting and informational hotline may be beneficial for future SARS situations.

Travel

Another important distinction between HPS and SARS is the impact on travel. Since HPS has been shown to involve no or limited person-to-person spread, there currently has been no restriction on travel to HPS areas. SARS, on the other hand, creates serious problems for travel and the risk of spread from person-to-person forced a recommended travel restriction to China during the outbreak. Therefore, the public health approach for SARS travel surveillance is distinct from HPS. For transit surveillance, fever checks were instituted at the Beijing airport, major train stations, and 71 roads connecting Beijing to other areas [90]. Infrared thermometers were used to screen passengers followed by axillary thermometers on those found to be febrile on screening. Of the approximately 14 million people screened at these sites, 12 probable cases of SARS were identified [90]. If control measures had not been implemented

SARS would have spread rapidly through international travel, whereas HPS would not likely spread by similar means since the mode of transmission is from rodents to humans.

6.2 OUTBREAK CONTROL

Risk Reduction

Eradication of the reservoir hosts of hantaviruses is neither feasible nor desirable because of the wide distribution of sigmodontine rodents in the Americas and their overall importance in the function of natural ecosystems. Potentially the most effective approach for disease control and prevention is risk reduction through environmental modification and hygiene practices that deter rodents from colonizing the home and work environment, along with safe clean up of rodent waste and nesting materials [81].

Initiating rodent control in and around the home environment is the primary strategy in preventing HPS. CDC has issued recommendations for rodent-proofing urban and suburban dwellings and reducing rodent populations through habitat modification and sanitation. These specific recommendations are as follows [68, 69, 81, 93]:

Eliminate rodents and reduce the availability of food sources and nesting sites used by rodents inside the home.

- Keep food (including pet food) and water covered and stored in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Store garbage inside homes in rodent-proof metal or thick plastic containers with tight-fitting lids.
- Wash dishes and cooking utensils immediately after use and remove all spilled food.
- Dispose of trash and clutter.

- Use spring-loaded rodent traps in the home continuously.
- As an adjunct to traps, use rodenticide with bait under a plywood or plastic shelter (covered bait station) on an ongoing basis inside the house.

Prevent rodents from entering the home. Specific measures should be adapted to local circumstances.

- Use steel wool or cement to seal, screen, or otherwise cover all openings into the home that have a diameter ≥ ¼ inch.
- Place metal roof flashing as a rodent barrier around the base of wooden, earthen, or adobe dwellings up to a height of 12 inches and buried in the soil to a depth of 6 inches.
- Place 3 inches of gravel under the base of homes or under mobile homes to discourage rodent burrowing.

Reduce rodent shelter and food sources within 100 feet of the home.

- Use raised cement foundations in new construction sheds, barns, outbuildings, or woodpiles.
- When possible, place woodpiles 100 feet or more from the house, and elevate wood at least 12 inches off the ground.
- Store grains and animal feed in rodent-proof containers.
- Near buildings, remove food sources that might attract rodents, or store food and water in rodent-proof containers.
- Store hay and pallets, and use traps or rodenticide continuously to keep hay free of rodents.
- Do not leave pet food in feeding dishes.

- Dispose of garbage and trash in rodent-proof containers that are elevated at least 12 inches off the ground.
- Haul away trash, abandoned vehicles, discarded tires, and other items that may serve as rodent nesting sites.
- Cut grass, brush, and dense shrubbery within 100 feet of the home.
- Place spring-loaded rodent traps at likely spots for rodent shelter within 100 feet around the home, and use continuously.
- Use an EPA-registered rodenticide approved for outside use in covered bait stations at places likely to shelter rodents within 100 feed of the home.

In the case of SARS, the natural reservoir(s) of SARS-CoV or the species responsible for the cross-species transmission to humans is currently not known. As mentioned in Chapter 2, investigations of SARS focused around wild animals served as exotic food in China implicating civet cats and raccoon dogs as SARS-CoV carriers. However, other animals also were shown to harbor the virus. One of the key epidemiological components of SARS still lacking is the possible "true" reservoir of the virus. After the first cases in 2004, China slaughtered a number of civet cats and raccoon dogs with hopes of eliminating the source of exposure. However, until a clear understanding of the reservoir is known, no extreme public health measures as mentioned should be an option. Therefore, HPS's primary prevention of risk reduction through environmental modification and hygiene practices that deter the reservoir from human contact may not be suitable for a SARS unless the rodent reservoir hypothesis shows further support. Focus for SARS control and prevention should include SARS transmission in localized areas such as hospitals or households of SARS patients and

preventing global transmission through travel. Again, since SARS is a person-to-person spread disease stronger public health measures are essential for controlling potential outbreaks.

Quarantine and Isolation

Two important outbreak control measure essential for the control of the SARS outbreak in 2003 involved isolation and quarantine of patients and contacts. The goal of this public health measure was to separate those patients with the disease or those at increased risk from those at lower risk [90]. Isolation is a commonly used practice in modern public health and involves the separation of ill persons with a communicable disease from those who are healthy. Quarantine is the separation or restriction of persons who are not ill but who are believed to have been exposed to a communicable disease [90]. Quarantine was developed in the 14th century but has been used rarely on a large scale in the past century [94]. Quarantine does restrict some personal liberties, but essentially is a collective action implemented in outbreak situations for the common good. It is important that federal, state, and local officials work closely in coordinating quarantine actions at all levels of government. Also, it is essential for the government to ensure that the public understands that quarantine may be a necessary public health measure to prevent an infectious disease such as SARS, particularly when neither vaccine nor antibiotics are available for treatment. The use of quarantine in the SARS outbreak likely was an essential control measure in preventing additional cases. Unlike HPS, SARS presented a high enough level of severity to justify initiating quarantine in some areas. Currently, quarantine wouldn't be considered or necessary for HPS since

transmission is from a rodent principal reservoir and is only minimally documented to spread from person-to-person.

Cleanliness Procedures

Areas with any evidence of rodent activity (i.e. dead rodents, rodent excreta) should be thoroughly cleaned to help reduce the possibility of exposure to hantavirus-infected materials. Clean-up procedures should be initiated to help limit the potential for aerosolization of dirt or dust from all potentially contaminated surfaces and household materials and goods. Precautions are also necessary in affected HPS areas for cleaning homes and buildings with rodent infestations. Anyone conducting these specific activities should contact a local, state, or federal public health agency for specific guidance. Any individual who is involved in the clean up process should have a thorough orientation from a knowledgeable public health official about hantavirus transmission and safety requirements. The following recommendations are below [68, 69, 81, 93]:

- Persons involved in the clean-up should wear rubber or plastic gloves.
- Spray dead rodents, rodent nests, droppings, or foods or other items that have been tainted by rodents with a general-purpose household disinfectant. Soak the material thoroughly, and place in a plastic bag. When clean-up is complete, seal the bag, then place it into a second plastic bag and seal. Dispose of the bagged material by burying in a 2 to 3 food deep hole or by burning.
- After the above items have been removed, mop floors with a solution of water, detergent, and disinfectant. Spray dirt floors with a disinfectant solution. A second mopping or spraying of floors with a general purpose household disinfectant is optional.

- Disinfect countertops, cabinets, drawers, and other durable surfaces by washing them with a solution of detergent, water, and disinfectant, followed by an optional wiping down with a general purpose household disinfectant.
- Rugs and upholstered furniture should be steamed cleaned or shampooed. If rodents have nested inside furniture and the nests are not accessible for decontamination, the furniture should be removed and burned.
- Launder potentially contaminated bedding and clothing with hot water and detergent. Machine wash dry laundry on a high setting or hang it to air dry in the sun.

SARS-CoV, like HPS-causing viruses, can be inactivated by various chemicals. Therefore, similar practices could be used for SARS control and prevention in potentially contaminated areas such as healthcare facilities, apartment complexes implicated in SARS clusters, and SARS patient households. The SARS-CoV is completely inactivated by ≤5 minutes of exposure to 75% ethanol, 2% phenol, hypochlorite (500 ppm available chorine), and household detergent [95]. Since the major mode of transmission of SARS-CoV is exposure to droplets of respiratory secretions and possible contamination of inanimate materials or objects by respiratory secretions or body fluids (i.e. saliva, tears, urine, and feces), it is important to consider implementing specific disinfecting procedures for future outbreaks.

Occupational Exposure

Persons who frequently handle or are exposed to wild rodents are likely at a higher risk of HPS than the general public since they have a higher frequency of exposure. For example, persons include, but are not limited to, mammalogists, pest-

control workers, some farm and domestic workers, and building and fire inspectors [69]. As a result, enhanced precautions as follows are warranted to protect these people against HPS [68, 69, 81, 91]:

- A baseline serum sample, preferable drawn at the time of employment, should be available for all persons whose occupations involve frequent rodent contact. The serum sample should be stored at -20° C.
- Workers in potentially high-risk setting should be informed about the symptoms of the disease and be given detailed guidance on prevention measures.
- Workers who develop a febrile or respiratory illness within 45 days of the last potential exposure should immediately seek medical attention along with a blood sample being drawn.
- Workers should wear half-face air-purifying respirators when removing rodents from traps or handling rodents in infected areas.
- Workers should wear rubber or plastic gloves when handling rodents or handling traps containing rodents. Gloves should be washed and disinfected before removing them.
- Traps contaminated by rodent urine or feces or in which a rodent was captured should be disinfected with a commercial disinfectant or bleach solution.
- Persons removing organs or obtaining blood from rodents in affected areas should contact the Special Pathogens Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention for detailed safety precautions.

Currently, insufficient information is available to allow general recommendations regarding risks or precautions for persons in the affected areas who work in occupations with unpredictable or incidental contact with rodents or their habitats. For example, telephone installers, maintenance workers, plumbers, electricians, and some construction workers may enter various buildings or sited that have rodent infestations. These recommendations are likely to be considered case by case after each working environment has been assessed.

The SARS outbreak initiated an important nosocomial transmission pattern, unlike HPS. The peak viral loads of SARS-CoV were shown to be reached at 12-14 days of illness when patients were probably in hospital care, explaining why hospital workers were more prone to infection [96]. Also, since the initial outbreak of SARS, two laboratory incidents have occurred in which SARS cases were reported in Singapore and China. Despite the differences in occupational risk for HPS, some fundamental HPS prevention measures can be applied to SARS including:

- Baseline serum samples collected for all employees involved in potential SARS-CoV or SARS case contact
- Healthcare workers and laboratory workers should be educated thoroughly about SARS and be given strict guidance and prevention measures
- Healthcare workers and laboratory workers developing SARS symptoms (i.e. fever, respiratory illness, etc) should seek medical attention and inform local health authorities if SARS is suspected. A blood sample should also be taken and tested for SARS-CoV

- Personal protective equipment for SARS will be slightly different than HPS. During aerosol generating procedures, personal protective equipment is required including a disposable isolation gown, a full body isolation suit (option), surgical hoods, disposable gloves, and eye goggles.
- Persons completing necropsies of SARS-CoV infected animals should follow detailed safety precautions recommended by the WHO and CDC

Outdoor Activities

Another at risk group for HPS is individuals engaged in outdoor activities such as camping or hiking. The following are recommendations and precautions to help reduce the likelihood of rodent exposure [68, 69, 81, 93]:

- Avoid coming in contact with rodents, and rodent burrows or disturbing dens (such as pack rat nests).
- Do not use cabins or other enclosed shelters that are rodent infested until they have been appropriately cleaned and disinfected.
- Do not pitch tents or place sleeping bags in areas in proximity to rodent feces or burrows or near possible rodent shelters.
- If possible, do not sleep on the bare ground. Use a cot with sleeping surface at least 12 inches above the ground.
- Keep food in rodent-proof containers.
- Promptly bury or burn all garbage and trash, or discard in covered containers.
- Use only bottled water or water that has been disinfected by filtration, boiling, chlorination, or iodination for drinking, cooking, washing dishes, and brushing teeth.

In the case of SARS, these specific precautions for HPS are not applicable since the SARS reservoir(s) is currently unknown. Therefore, these activities would only represent importance if the close contact with which you were hiking or camping had SARS-CoV or if you were exposed to the reservoir(s).

6.3 PUBLIC HEALTH AWARENESS

Surveillance activities are an important component contributing to overall awareness of disease. There are a few key components that are important for understanding HPS patterns in a community. First, consistent monitoring of hantavirus prevalence in rodent populations may indicate warning of expected increases in the number of human HPS cases [80]. Second, attention to environmental factors which may indirectly increase the risk of hantavirus exposure may be an important component for disease prevention [80]. For example, an increase in precipitation in 1992-1993 from El Nino may have been a key factor for the increase in rodent numbers, hence HPS cases.

With surveillance activities initiated for HPS, general public health awareness of risk can be determined. Health education programs for the public may be an essential component to enhance recognition and management of HPS and to prevent cases by reducing human contact with rodents. There are two key knowledge based areas that are essential for recognition of HPS risks, involving both health care providers and the general public.

First, early recognition of an HPS case may improve the patient's chance of survival; therefore, physicians and other health care workers play an important role in early case identification [68]. As a result, educational programs should be targeted to all health care professionals focusing on the clinical features of disease, diagnosis, and

patient management and treatment. In order to maintain an active surveillance system and develop effective community-based programs, other health professionals including epidemiologists, laboratorians, and public health educators also should be educated on the latest HPS research. These health professionals should have such information available for the general public upon request.

Secondly, health education programs for the general public are essential for HPS awareness and can be divided into two types [68]:

1. Prevention during nonoutbreak situations

Health education programs for the general public should focus on informing the public about the disease, helping to identify personal risk factors, and providing prevention recommendations.

2. Rapid response when there is a suspected HPS case

Once the risk factors associated with HPS transmission are determined and preventative measures have been initiated, the population at risk can be targeted with education materials and campaigns. Many materials and services can be utilized to educate the public and health care professionals about HPS, including videotapes, slide sets, print materials, internet, mass media news coverage, public service announcements, national campaigns, audio conferences, seminars, and telephone hot lines.

Public health awareness initiatives for SARS are both unique and parallel to HPS. Since the recognition of HPS, cases have continued to occur sporadically, allowing for specific surveillance procedures. However, since the SARS outbreak of 2003, SARS cases have only occurred from laboratory incidents and it is not known whether SARS

will return in an outbreak pattern. The public health approach for this area of SARS presents a gray area of understanding; therefore, it is difficult to initiate specific procedures. Until more knowledge is obtained about the possible pattern of SARS cases, case reporting of individuals that present with similar symptoms may be a means to trace the emergence of SARS in a specific community and initiate prompt isolation or control procedures.

Another distinction from HPS is the focus of health education programs for SARS knowledge. HPS programs focus on reducing human contact with rodents. However, SARS procedures would include eliminating close contact with possible SARS cases or known carriers of the SARS-CoV. Early recognition of cases becomes an important role for physicians to potentially break the chain of transmission to close contacts and other hospital patients.

There are some fundamental parallel public health awareness measures initiated in HPS that can also be applied directly to SARS if needed in the future. Targeting educational programs to healthcare professionals, epidemiologists, laboratorians, and public health educators becomes essential for these individuals to understand the latest SARS research and features of the disease. The health education programs initiated for HPS awareness for the general public are also important for SARS by integrating prevention during nonoutbreak situations and rapid response if a SARS case is suspected. The many diverse forms of materials and services used to educate the public on HPS could also be integrated in SARS educational programs. These various strategies and public health awareness techniques used in HPS in application to SARS in the future may

be beneficial mechanisms to educate and motivate healthcare professionals and the public to protect themselves, their families, and their community from the threat of SARS.

Chapter 7

DEFICIENCIES IN SARS KNOWLEDGE

Despite current epidemiological investigations into the SARS outbreak of 2003, there are still important deficiencies present in the overall SARS knowledge. Three key epidemiological concepts that are important to understand more thoroughly involve the possible seasonal pattern of the disease, the study of outlying incubation period values, and the difference in SARS cases reported in the United States.

Currently, the number of newly reported cases of SARS in 2004 is insufficient to accurately determine any seasonal variation. The seasonality is important for two reasons, recurrence of disease and the sporadic nature of cases. It's important with any disease to understand if specific seasons or months are more prone to producing cases of disease or if the cases are sporadic in nature. With an understanding of seasonality, public health measures and precautions can be implemented more predominately during these time periods.

The incubation periods for SARS have produced some outlying values beyond 10 days. Currently, there have not been any thorough investigations addressing these incubation period outliers. This is problematic since other coronaviruses have shown a long right-tail incubation range. Therefore, it is feasible that SARS-CoV may also show a similar pattern for the incubation period. Studies should consider these outlying values primarily for the fact that if the SARS incubation period indeed includes a wider range, public health practice and control techniques would change drastically.

The difference in secondary transmission of SARS in the United States is an important consideration to understand particularly if application of prevention can be

utilized in other regions. In the United States, cases were mostly limited to those who had traveled to SARS infected areas with limited spread to close contacts and health-care workers. The difference in transmission may be explained by various levels of surveillance and early detection procedures, however this distinction warrants more understanding and assessment. If a public health measure was detrimental in decreasing SARS transmission in the United States, it becomes essential to investigate these practices and procedures for complete understanding of the possible SARS control measures. An alternative hypothesis for the difference in SARS cases reported may be that individual super-spreaders may not have been present in the United States. The role of individual transmission of SARS in other countries, as mentioned previously, was a detrimental factor in the transmission of SARS.

An important component lacking in SARS knowledge is related to the causative agent of SARS. How long has the SARS-CoV been circulating in China and how has the virus genetically evolved so uniquely from previous coronaviruses? The first question is difficult to answer since the virus may have been present in animals asymptomatically before it crossed over to develop into a human disease. The second question still warrants some research and understanding, but one possible explanation is that once the virus crossed the interspecies barrier to humans the virus may have genetically altered itself for enhancing negative outcomes in the human host. If an individual is likely to have symptoms of SARS, they are also at a higher risk of being admitted to the hospital setting in which SARS transmission is enhanced. This idea may explain why SARS-CoV has a higher mortality rate and contagiousness than any other known human or animal coronavirus. Is there an explanation why other human coronaviruses such as those that

are responsible for the human cold are not as severe? Likely, the transmission of these viruses seems to depend on mobility of the host in comparison to specific settings for SARS. However, more research is needed to fully understand and address these questions.

The primary deficiency in SARS knowledge is the insufficient identification of the natural reservoir of the disease or the species that may be responsible for the cross-species transmission to humans. To date, a range of species have been shown to harbor the virus including animals in the wild animal markets of China (Himalayan palm civet cats, raccoon dogs), wild animals such as foxes, domestic cats, and ferrets. Studies have also shown the virus to be promiscuous with capabilities not only of human-to-human transmission, but also an animal-to-animal threat. The problem is that there are other possibilities to consider related to the natural animal reservoir of SARS. First, one or more animals in the wild may be the natural reservoir for SARS-CoV. Second, the animals investigated and shown to harbor the virus may simply have been infected from another unknown animal source, which may be the true reservoir for the virus. With these considerations, it seems unjustified that an estimated 10,000 civets were slaughtered to prevent the spread of SARS, because the Chinese government was initiating an effort to cut of the source of disease. Again, the question must be asked, were the animals in China slaughtered without sufficient cause by the Chinese government? This question can only be answered once knowledge of the true reservoir(s) is obtained.

Another key distinction for SARS knowledge is the lack of understanding related to the Amoy Gardens outbreak in China. The point-source nature and temporal and

spatial progression of SARS in the community is unlikely to have been distinctly caused only by respiratory droplet and close contact transmission. There have been both circumstantial evidence and speculation related to the possibility of a rat vector for this specific SARS cluster. It is interesting that this specific SARS case group was more severe than others, with more diarrhea, greater ICU admissions, and higher mortality. For a complete parallel assessment of SARS to HPS, this piece of information is quite necessary and could be important if the rat vector hypothesis is confirmed through investigations. However, the key point to this specific SARS deficiency is that SARS investigators must explore all possible SARS reservoirs and transmission mechanisms to have a thorough understanding for public health prevention.

A recent deficiency in the SARS knowledge stems from the previous SARS cases reported in 2004. As mentioned in Chapter 1, investigation of the source of the current SARS cases continues to focus on the National Institute of Virology in Beijing. Investigations are still ongoing in the laboratory with the institute closed on April 23, 2004 with most of the staff quarantined for medical observation [97]. Interestingly, since the SARS emergence in 2003, more than 50 laboratories in the United States and elsewhere around the world have obtained samples of the SARS-CoV from the United States government [98]. This fact has been quite controversial among scientists as to why the virus is so widely available, since the viral outbreak of 2003 is considered under control? Concerning this, the CDC remarks that they are not exactly sure who has access to the virus since it is currently not on the nation's list of strict security rule organisms, such as anthrax [98]. The WHO has strongly recommended that any work using the SARS-CoV be conducted in biosafety level 3 facilities. This precaution would help

minimize the risk of laboratory-acquired infections. More precise guidelines regarding possession and handling of SARS Co-V are clearly necessary to prevent any unnecessary transmission of SARS into the United States population or in any other region of the world.

Chapter 8

FUTURE RECOMMENDATIONS FOR SARS FROM HPS UNDERSTANDING

By examining both the parallel and the distinct aspects of HPS and SARS, important conclusions have been formulated for applying the previous experience of HPS public health responses to future SARS outbreaks. The following provides a summary of these recommendations with additional comments for future consideration:

Detection of causative agent

- Integrating the modern technology of molecular biology and epidemiology with a multidisciplinary approach to a new disease, such as SARS, may be an integral component for identifying the causative agent of the illness. With this information, laboratory tests can be used to detect carriers of the virus in those who are suspect SARS cases.

Laboratory handling/biosafety

- Following biosafetly level 2 and level 3 guidelines for handling SARS clinical specimens and any material derived from laboratory investigations may be an important means for controlling an unexpected laboratory incident of SARS.
- When a laboratory incident occurs, SARS produces a greater threat to the public than HPS since it is transmitted from person-to-person. As a result, more stringent guidelines for eliminating this possibility may be necessary.

For the future it may become important for public health officials to restrict access to SARS-CoV. Currently, approximately 50 known laboratories in the United States and elsewhere around the world have obtained samples of the SARS-CoV from the

United States government. Many officials and researchers are questioning why the virus is so widely available considering its potential global outbreak potential. Since SARS-CoV is currently not on the list of strict security rule organisms (example: anthrax), the CDC is not exactly sure who has access to the virus. Based upon this information provided, it seems clear that there should be more precise guidelines regarding possession and handling of the SARS-CoV to prevent any unnecessary transmission of SARS in the United State population or in other regions of the world. This statement is purely based on the current understanding of the level of severity that SARS presents to the population since spread primarily from person-to-person.

Health Professional Education

- Since SARS was a newly emerging disease in 2003, the first educational material should have been targeted to health care professionals and epidemiologists instead of being delayed for several months.
- Education must be prioritized during similar outbreak situations to ensure optimal control and prevention practices from all those directly or indirectly involved with the situation.
- A "gold standard" of education for health care professionals and epidemiologists should be implemented in the emergence or recurrence of an infectious disease such as SARS. The "gold standard" would be defined as prioritizing training beginning with in-person instruction course information, videotapes, printed materials on the management of patients with the designated infectious disease, infection control, and the proper use of any necessary protective equipment.

- Since SARS is transmitted from person-to-person, additional education is necessary, particularly since the healthcare setting presented a major epidemiological component in the SARS outbreak. Important education for SARS may include:
    - risk of exposure to SARS-CoV as a healthcare worker
    - importance of reporting personal illness to eliminate spread to patients and other healthcare workers
    - use of personal protective equipment (PPE)
    - basic infection control procedures
    - proper hygiene/cough etiquette
    - quarantine/isolation procedures and practices
    - cleaning and disinfecting environmental surfaces
    - use of droplet and aerosol generating devices and proper procedures
    - communication within the healthcare setting

As mentioned in Chapter 6, addressing professional education practically from a hospital perspective becomes extremely important for SARS since the healthcare setting became an important area of risk. Two important additional recommendations to condense are the use of personal protective equipment and communication within the healthcare setting.

Creating a distinct classification of respiratory diseases is essential for determining the necessary PPE to use. A surgical mask simply does not provide adequate respiratory protection to the healthcare worker if the infection is airborne. This is likely due to the fact that basic surgical masks cover the user's nose and mouth providing only a

physical barrier to fluids and particulates. Within the healthcare setting a N95 mask along with rigorous use of gloves, gowns, and hand washing seem appropriate for prevention of SARS transmission. The distinction of the N95 surgical mask is that it is fitted to the users face, forming a seal that provides a physical barrier to fluids, particulate matters, and aerosols blocking about 95% of particles 0.3 microns in size or larger. By following stringent guidelines for the use of PPE, not only is the healthcare worker reducing risk of SARS infection for themselves, but they are also protecting their personal contacts by eliminating a second and third generation of spread.

The second key component to address is communication within the hospital setting. By following a proactive approach through communication between all specialties and departments within the hospital, overall awareness is produced. For example, if a physician from the emergency department has drawn blood from a suspected SARS case, it is important for them to communicate to the laboratory workers that they are sending such a sample. By addressing this information, the laboratory can follow the necessary guidelines to protect from SARS-CoV transmission. From a hospital perspective understanding the importance of PPE usage and communication among workers, one can produce the best possible outcome for prevention and control of SARS.

Surveillance

- Integrate a passive surveillance system (telephone hotline), like that existing for HPS, for reporting suspected cases of SARS and provide information to persons on recommendations to help eliminate transmission among contacts.

- Produce a comparison of passive surveillance system recorded cases to other surveillance procedures to determine the effectiveness of this type of system for a disease such as SARS. This technique may provide a means for future public health measures.

The primary disadvantage of applying a passive surveillance system for SARS is that the global spread resulted from a sentinel event, which typically wouldn't be appropriate for passive surveillance techniques.

Travel

- Due to the global potential of SARS transmission, strict travel guidelines and advisories are essential in future outbreaks to eliminate SARS internationally.
- Transit surveillance may be a means to monitor the SARS situation within a given region. The cost to benefit ratio may become an important factor if SARS returns at outbreak levels.

When addressing the issue of continuing transit surveillance for SARS, it becomes important to develop a cost to benefit perspective. Does the cost of maintaining a transit surveillance system outweigh the benefits of continuing such a system? From the cost perspective, one would argue that to continue a system with costs of employees, equipment, and organization is not practical or economically feasible since of the 14 million people screened at these sites, only 12 probable SARS cases were identified. However, on the opposing side, the benefit would be potentially eliminating the possibility of a sentinel event of SARS producing a global spread as in 2003. It may only take 12 probable SARS cases for a serious global threat to occur again, so the benefit of a transit system may outweigh the cost.

Both perspectives produce convincing arguments, however, an alternative is to have a transit system initiated and guidelines to follow if SARS cases recur in the future. For example, it likely is not cost effective to continue the transit surveillance of SARS when no cases are being reported. However, if an area reports a single case, initiation of the proposed transit system and guidelines should be initiated. From these recommendations, both arguments are recognized and the most efficient scenario produced.

Risk Reduction

- More research is essential to understand fully the natural reservoir(s) of SARS-CoV and the species responsible for the cross-species transmission to humans. With a more thorough understanding of the disease to human reservoir contact, public health measures can be implemented to help break the chain of transmission.
- Limited **extreme** public health measures, such as killing a large number of civet cats, should be initiated until more research is completed on the SARS-CoV reservoir(s). Any decisions to do so are likely to be under scrutiny by public health officials and the public since it seems that these actions are currently not justified. However, this recommendation could be under scrutiny by those who think that it is more important to consider all measures when human life is at risk. Both arguments are essential to consider in this situation.
- Using HPS's primary prevention of risk reduction through environmental modification and hygiene practices may not be applicable to SARS unless the

rodent reservoir/carrier hypothesis shows further support or "until an animal reservoir is clearly identified".

Quarantine/Isolation

- Federal, state, and local governments must work closely in coordinating any quarantine actions as needed for SARS in the future.
- Public education on quarantine is essential to aid with understanding that this extreme public health measure may be a key component in preventing transmission of SARS, as proven in the 2003 SARS outbreak.

Virus eradication

- Inactivation of SARS-CoV on environmental surfaces may be a necessary part of future control and prevention strategies.
- Guidelines for use of chemicals to inactivate SARS-CoV are important to eliminate unnecessary contact with the virus.

Occupational exposure

- Strict guidelines and prevention measures should be required for individuals with an occupation that may put them at higher risk. Fundamental HPS prevention measures can be effectively applied to SARS including:
    - Requiring baseline serum samples of employees
    - Education and overall risk of SARS within the working environment
    - Blood sample taken if suspected of developing SARS
    - Personal protective equipment is slightly different than HPS, but should be strictly enforced

Public health awareness

- SARS public health strategies can strongly follow the lessons of HPS.
- Target education programs to healthcare professionals, epidemiologists, laboratorians, and public health educators in a timely manner providing the most recent research and information on SARS.
- Health education programs for the general public is essential, including prevention during nonoutbreak situations and rapid response measures needed when a SARS case is suspected.
- Use a diversity of educational material to educate the public (i.e. videotapes, slide sets, print materials, internet, mass media coverage, public service announcements, national campaigns, audio conferences, seminars, telephone hotlines, billboards, advertisements, red neighborhood banners, etc.).
- Provide the most accurate and recent SARS information to the public.

These recommendations include means for control and prevention of SARS in future outbreak situations based upon the extensive experience of HPS in 1993. By providing a parallel comparison of HPS and SARS, future knowledge can be acquired and utilized. The process of examining two diseases in parallel for public health practices proved to be a beneficial strategy in various areas as reflected in the above summary. However, the main limitation to this specific parallel comparison is the mode of transmission associated with both diseases. An infectious disease like HPS transmitted from a rodent host is clearly distinct from SARS, which is transmitted from person-to-person. Also, SARS knowledge is still limited particularly with understanding the animal reservoir(s). If the rat hypothesis produced further scientific or epidemiological support, the parallel nature of the two diseases would be strengthened. The overall logic of

paralleling two diseases is supported from some of the similar public health control measures recommended and may be considered as a future public health mechanism for other newly emerging/identified diseases.

To summarize, it is important to illustrate some of the important lessons learned from the SARS outbreak of 2003 [99-101]:

- Infectious diseases remain a serious global threat.
- An outbreak such as SARS requires attention in advance to clarity, collaboration, communication, coordination, and capacity.
- A global public health system is essential.
- The SARS outbreak has likely better prepared the world's public health authorities for a major influenza or other similar pandemic.
- The SARS epidemic produced a negative light on the Chinese public health system and the consequences of suppressing health care information.
- Global operations proved important for containing an infectious disease like SARS.
- SARS reaffirmed the "moral center" [99] of the medical profession, meaning it confirmed health care worker's ethical duty and obligation to care for sick patients at risk of death regardless of their own personal risk.
- Prompt use of isolation and quarantine was an integral part of SARS control in various settings with extensive transmission, and these measures are acceptable if appropriately explained.

- Public health programs need specific communicable disease investigational units and surveillance and technology information systems to ensure optimal outbreak investigation facilities and technology.
- Though some clinical features are suggestive of SARS; its signs and symptoms overlap too much with those of other respiratory pathogens for firm diagnoses to be made exclusively on a clinical basis.
- Risk of exposure is essential to considering the likelihood of SARS as a diagnosis, since SARS clinical features often overlap other respiratory pathogens.

These lessons learned from SARS may be important considerations if SARS were to reappear with outbreak potential in the future. Continuing research on SARS and the virus's development into a serious human illness are key epidemiological components that may become instrumental in any future SARS outbreaks.

In summary, there are several likely reasons for the size of the SARS outbreak in 2003 including: multiple imported cases, lack of knowledge about healthcare setting spread, lack of awareness about proper use of personal protective equipment while treating SARS cases, delays in hospitalizing patients with symptoms, the population density of Beijing, and the failure to communicate the SARS problem to the public and healthcare professionals earlier. With these disadvantages, the efficiency of outbreak resolution was impressive to some extent. However, future recommendations, as listed above from the parallel comparison of HPS and SARS, may produce even more beneficial outcomes if SARS recurs in the future.

Figure 1. Worldwide Epidemic Curve of Probable cases of SARS by week of onset [1]

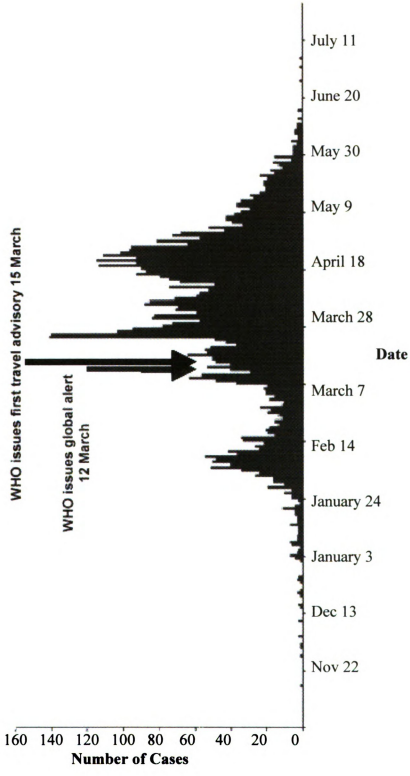


Figure 2. Worldwide Epidemic Curve of Probable cases of SARS by date of report [102]

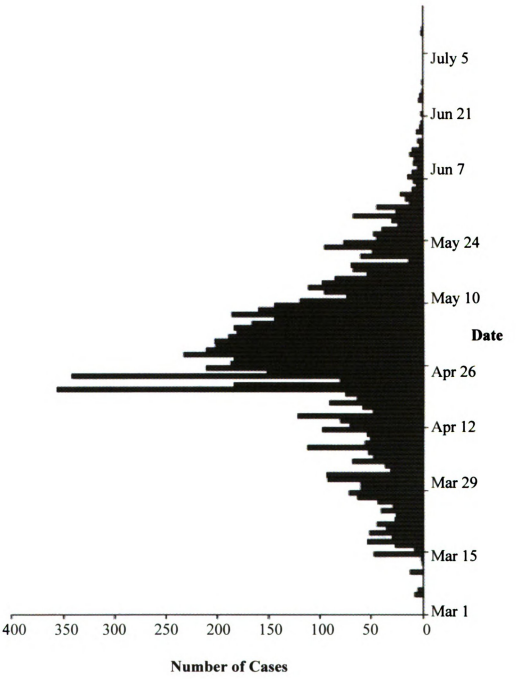


Figure 3. SARS: Cumulative Number of Probable Cases Worldwide, June 16, 2003 (Total: 8460 cases, 799 deaths) [12]

Figure 4. China Epidemic Curve for Probable SARS Cases by Date of Report [102]

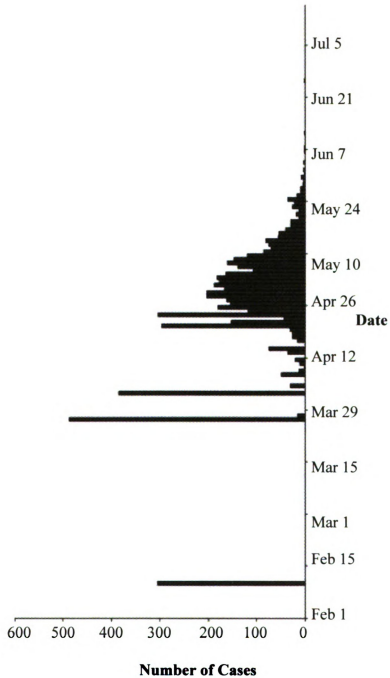


Figure 5. Probable cases of SARS in selected regions [1]

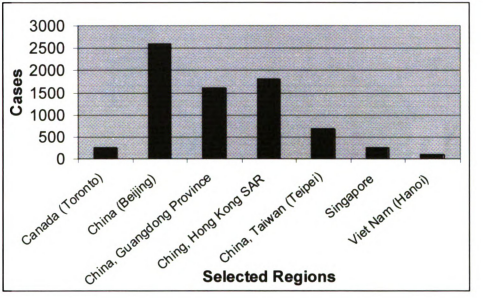


Figure 6. Map of China and Provinces [103]

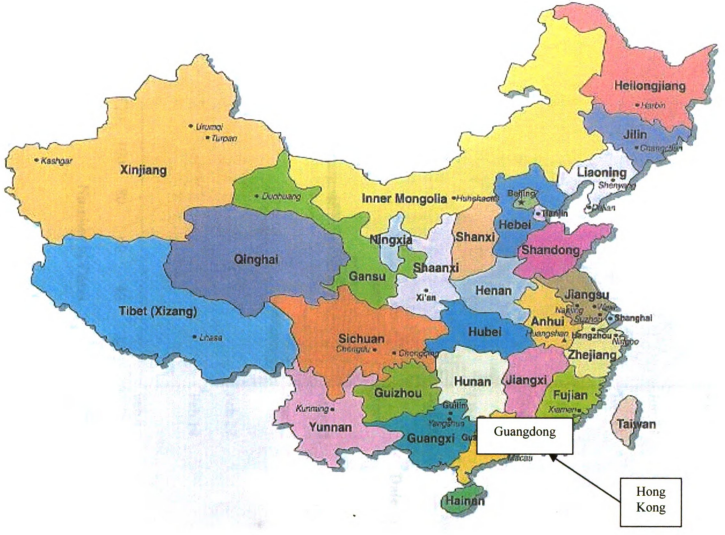


Figure 7. Hong Kong, China Epidemic Curve for Probable SARS Cases by Date of Onset [102]

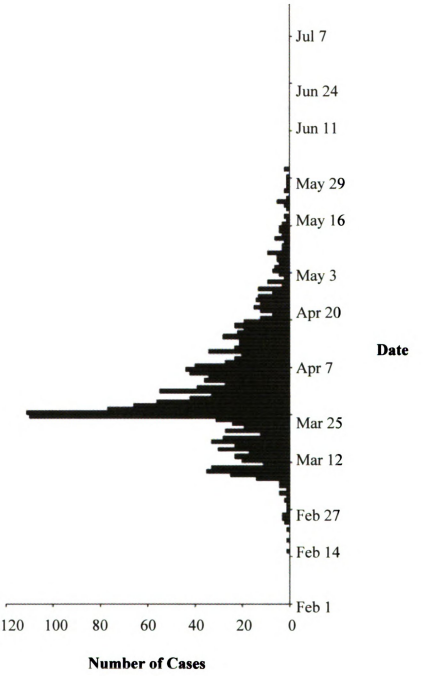
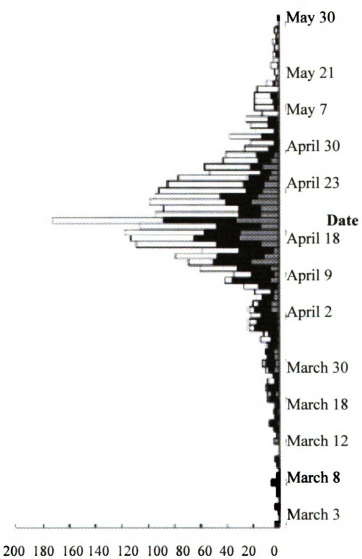


Figure 8. Beijing, China Epidemic Curve for Probable SARS Cases by Date of Hospitalization and Type of Exposure [13]



Open bars indicate healthcare workers without contact with a SARS patient; dark bars indicate non-healthcare workers with contact with a SARS patient; light filled bars indicate healthcare workers.

Figure 9. Taiwan, China Epidemic Curve for Probable SARS Cases by Date of Onset [102]

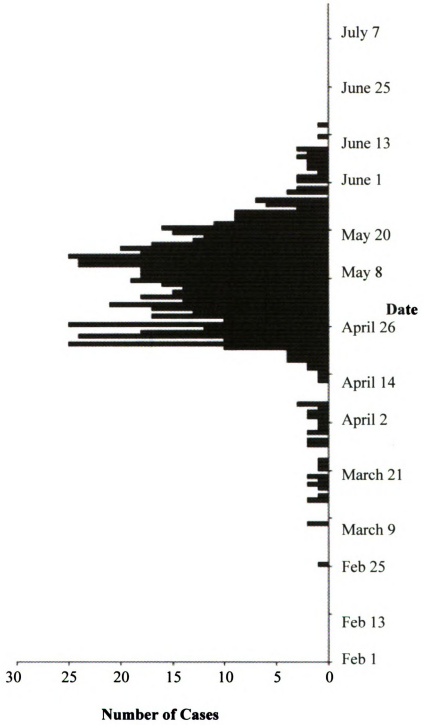


Figure 10. Taiwan Geographic Distribution of Probable SARS Cases, 2003 [14]

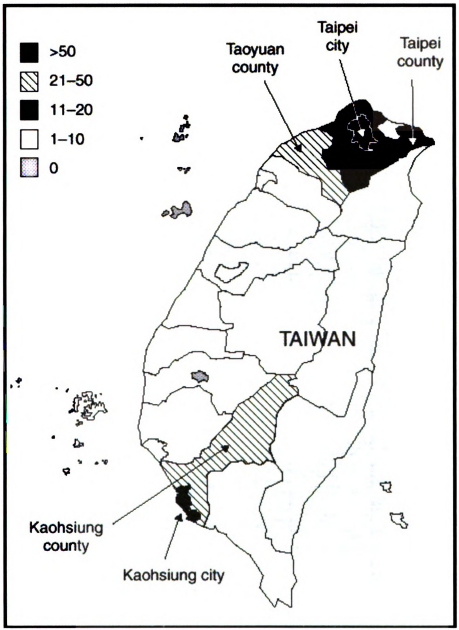


Figure 11. Canada Epidemic Curve for Probable SARS Cases by Date of Onset [102]

Figure 12. Singapore Epidemic Curve for Probable SARS Cases by Date of Onset [102]

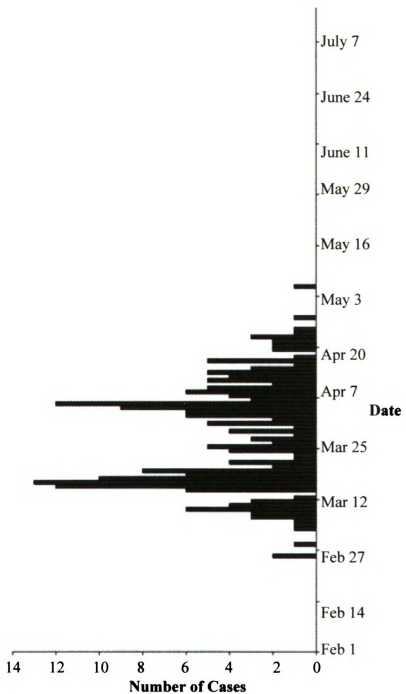


Figure 13. Viet Nam Epidemic Curve for Probable SARS Cases by Date of Onset [102]

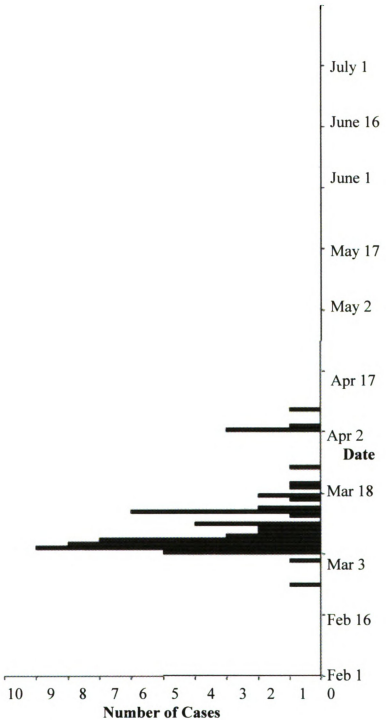


Figure 14. United States Epidemic Curve for Probable SARS Cases by Date of Onset [102]

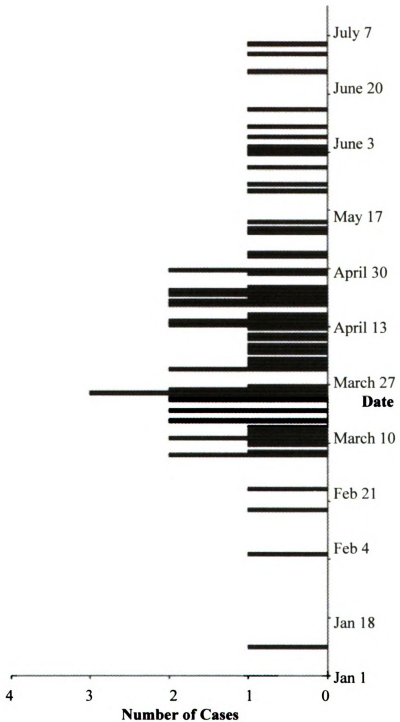
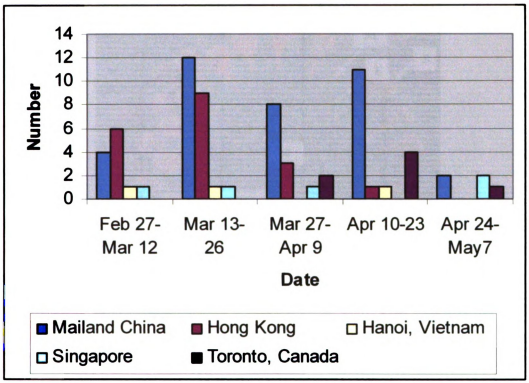


Figure 15. Number of Probable SARS Patients Reporting Travel to Areas with Community Transmission of SARS, by Date of Illness Onset, United States, February 27 – May 7, 2003 [19]



*N=61. The total number of visits to areas with documented or suspected community transmission of SARS exceeds the number of probable SARS patients reporting travel exposure because some patients traveled to two or more of these areas.

Figure 16. Structure of SARS-associated coronavirus (SARS-CoV) [11]

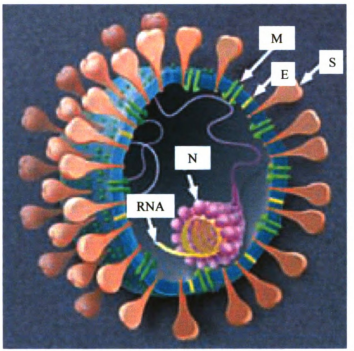
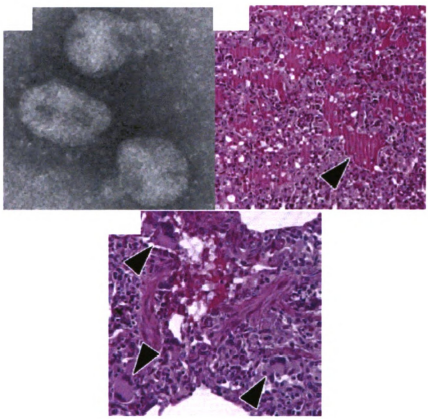


Figure 17. SARS-associated coronavirus (SARS-CoV) and associated lesions in macaque lungs [30]

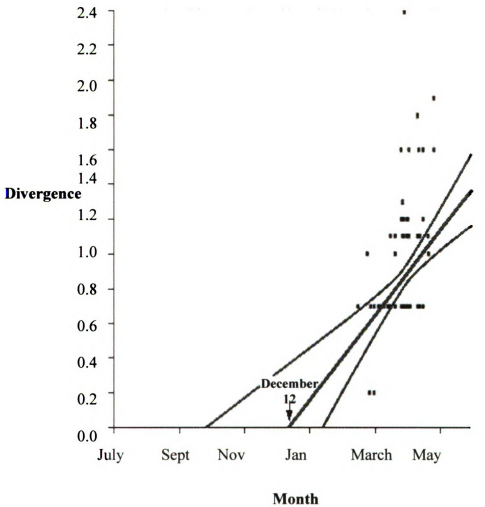


Top Left: Virus particles re-isolated from nasal swabs of infected macaques display typical coronavirus morphology

Top Right: Diffuse alveolar damage in the lung; alveoli are flooded with highly proteinaceous fluid (arrowhead) that stains dark pink

Bottom: Several synctia (arrowheads) are present in the lumen of bronchiole and surrounding alveoli

Figure 18. Timing of the Most Recent Common Ancestor of the Hong Kong SARS-CoV [35]



*The divergence of the sequence of ancestral sequence was plotted against sampling time. The middle line represents the best-fit line obtained by linear regression, and the outside lines indicate the 95% confidence intervals.

Figure 19. Proposed Mechanism of SARS-CoV transition from animals to humans [104]

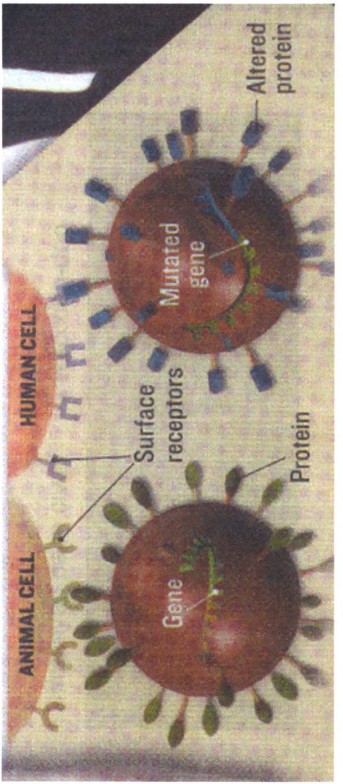


Figure 20. Himalayan palm civet and a Raccoon-dog [37]

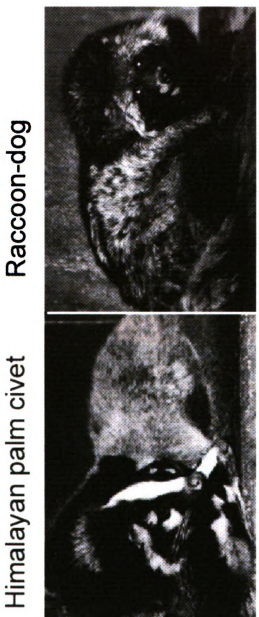
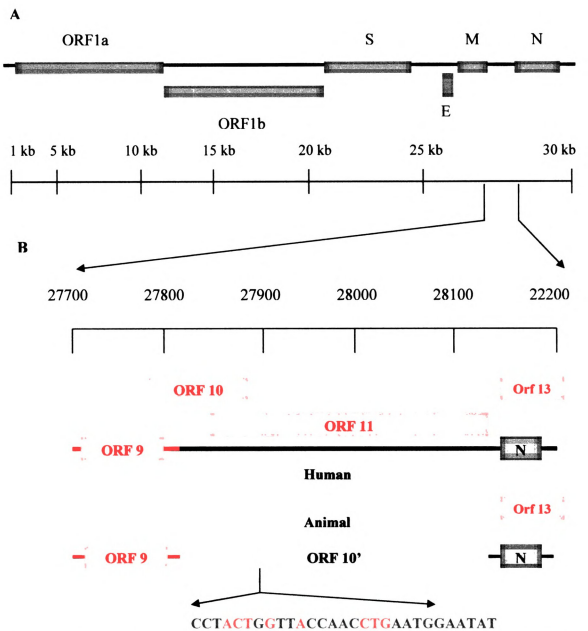


Figure 21. A 29-nucleotide deletion in human SARS-CoV compared to animals SARS-CoV [44]



A. Genetic organization of SARS-CoV found in humans and animals. ORFs 1a and 1b, encoding the nonstructural polyproteins, and those encoding the S, E,M, and N structural proteins are indicated (green boxes)

B. Expanded view of the SARS-CoV genomic sequence. ORFs for putative proteins and for N in human isolates are indicated in brown and green boxes, respectively. An extra 29-nt sequence is present downstream of the nucleotide of 27868 of the animal SARS-CoV. The presence of this 29-nt sequence in animals isolates results in fusing the ORFs 10 and 11 (top) into a new ORF (bottom: light blue box)

Figure 22. Phylogenetic Analysis of the Nucleotide Acid Sequence of the Spike Gene of Human and Animal SARS-CoV [44]

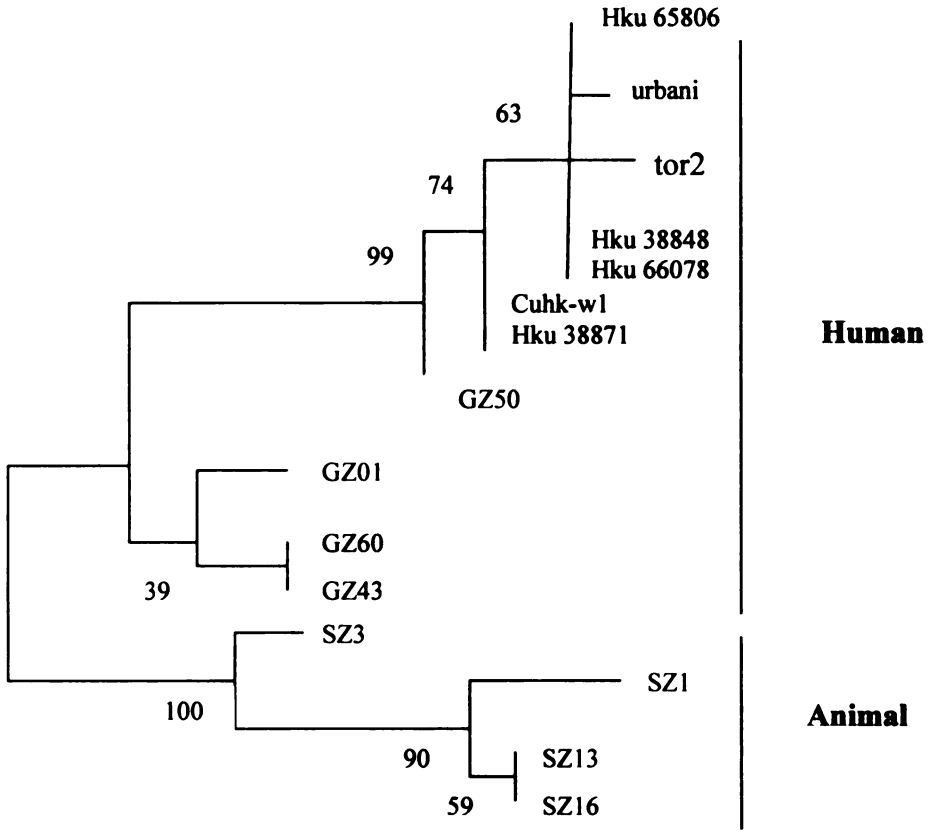


Figure 23. Chain of SARS Transmission for Hotel M in Hong Kong Leading to International Spread of SARS [12]

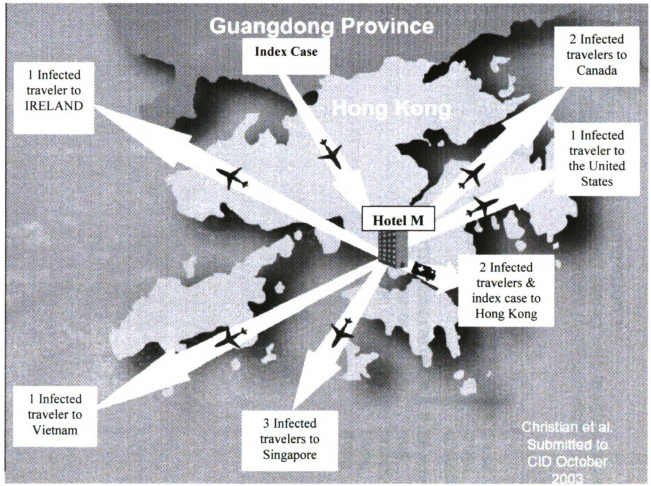


Figure 24. Generational Transmission of SARS [12]

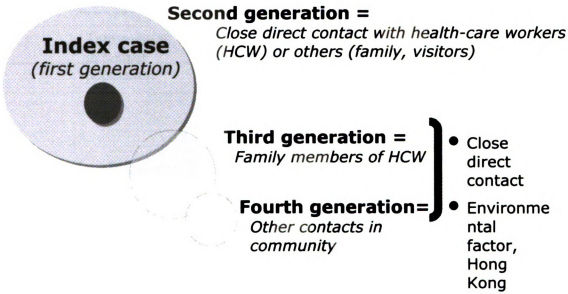
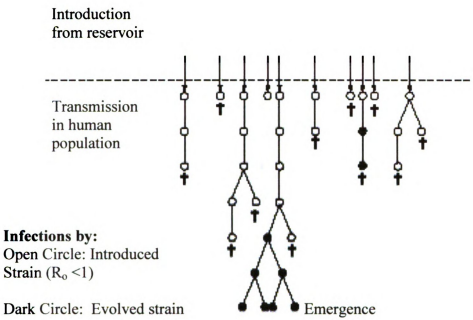


Figure 25. Schematic for the new emergence of an infectious disease [51]



***Introductions from the reservoir are followed by chains of transmission in the human population. Infections with the introduced strain (open circles) have a basic reproductive rate number R_0 <1. The infections caused by the evolved strain can go on to cause an epidemic. Daggers indicate no further transmission.**

Figure 26. Secondary Cases of SARS by days to isolation of the source case, Singapore, April 15, 2003 [1]

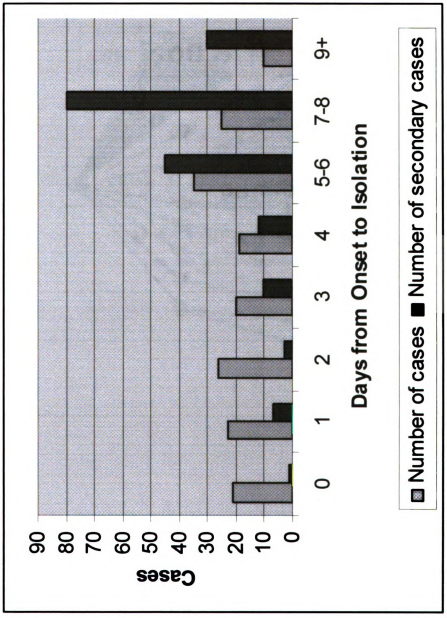


Figure 27. Probable Cases of SARS by Source of Transmission in chain of 77 cases in Beijing, 2003 [105]

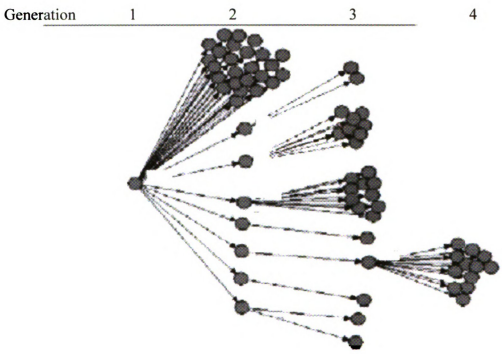


Figure 28. Hantavirus Pulmonary Syndrome Cases by Region, United States, as of January 6, 2004 (N=358) [71]

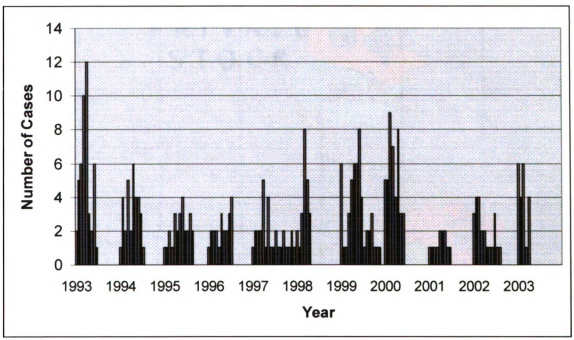


Figure 29. Geographic Distribution of HPS Cases in the Americas [77]

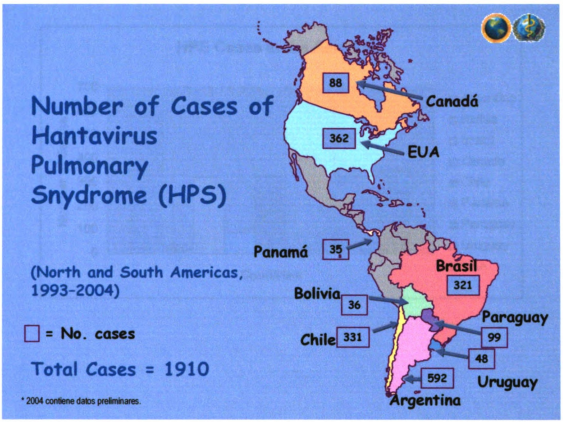


Figure 30. HPS Cases in North and South America by Country, 1993-2004 [62, 67]

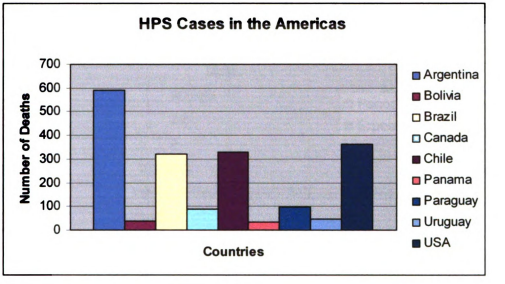


Figure 31. Exposure Period in days before onset of 11 case-patients with well-documented HPS exposures [70]

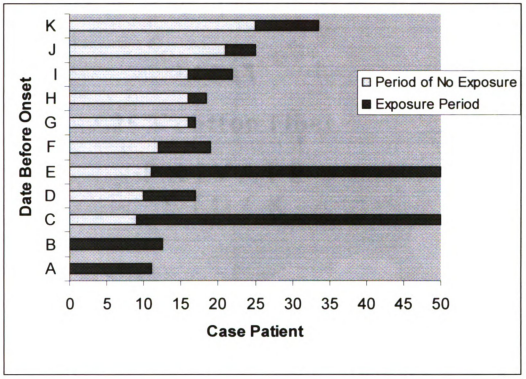


Figure 32. Hantavirus Pulmonary Syndrome Cases by State of Residence, United States, January 6, 2004 [71]

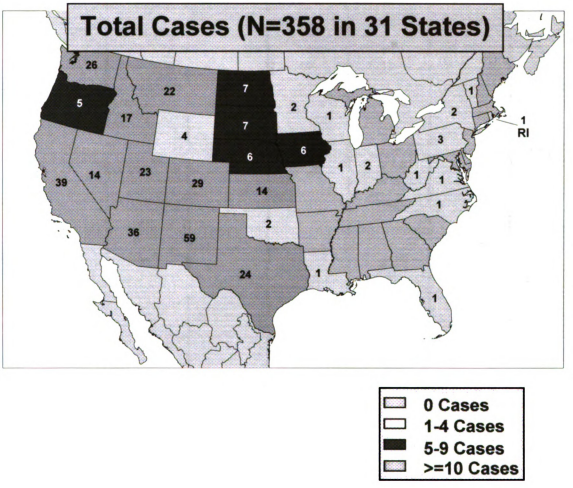


Figure 33. New World Hantaviruses Geographic Distribution [77]

Figure 34. Sin Nombre Virus [76]

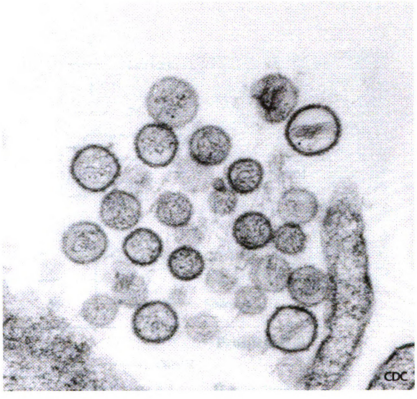
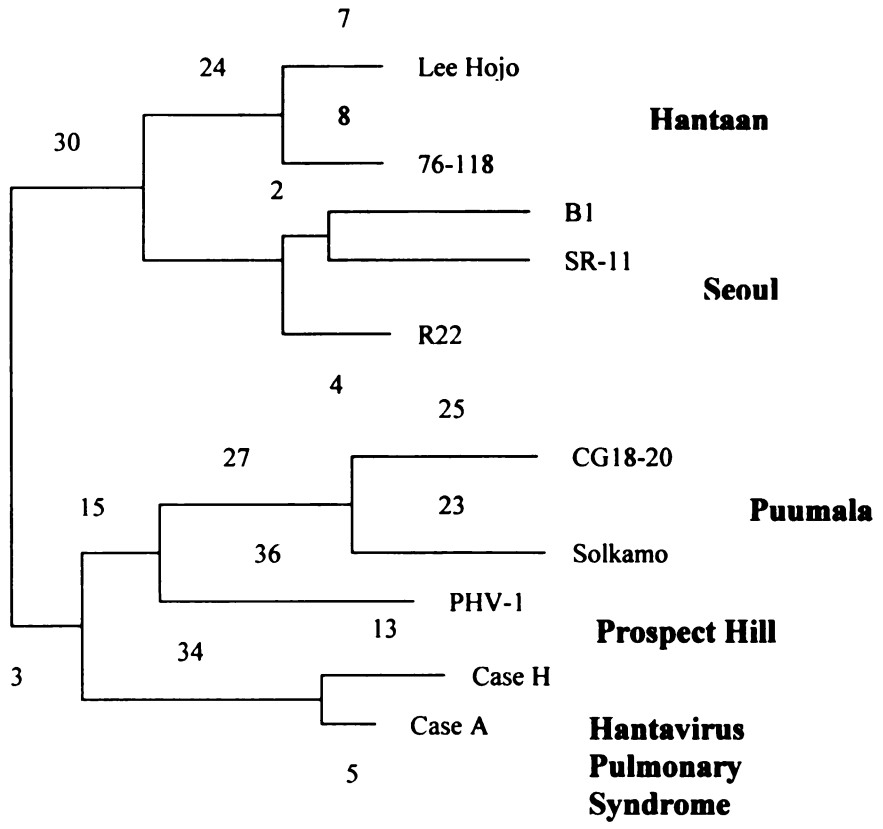


Figure 35. Phylogenetic relation of the Adult Respiratory Distress Syndrome (ARDS)- associated hantavirus from the Four Corners region to previous characterized hantaviruses [106]



Phylogenetic analysis of the virus sequence differences within 241 bp of the amplified fragment was performed by the maximum parsimony method. The horizontal distances represent the number of nucleotide step differences (indicated adjacent to the lines) present between branch nodes and taxa (that is, viruses). Bootstrap confidence limits exceeding 50% are indicated in ovals next to each branch node.

Figure 36. The Deer Mouse (*Peromyscus maniculatus*) [107]

Figure 37. Deer Mouse Population Range, United States, June 6, 2002 [81]

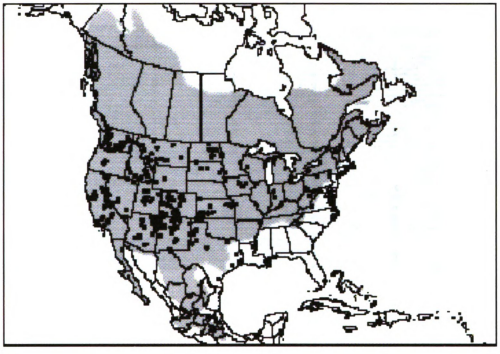


Figure 38. White-footed Mouse (*Peromyscus leucopus*) [107]

Figure 39. Cotton Rat (*Sigmodon hispidus*) [107]

Figure 40. Rice Rat (*Oryzomys palustris*) [107]

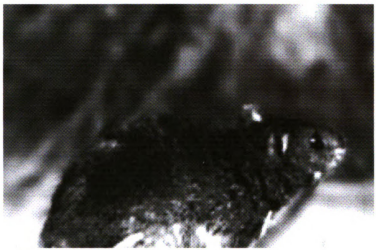


Figure 41. HPS Transmission Schematic

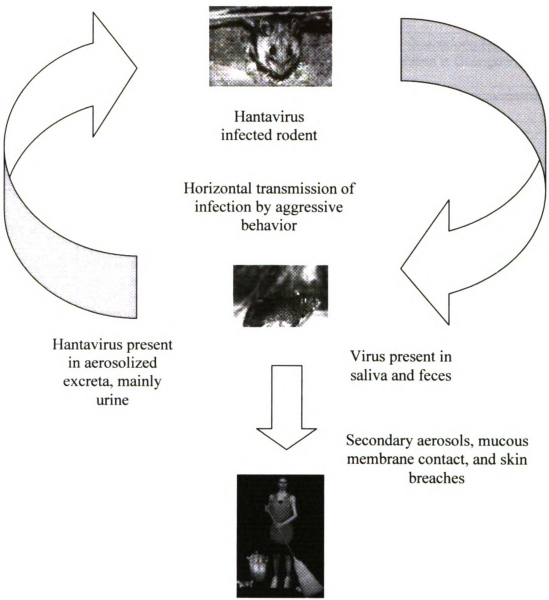


Table 1. SARS Chronology of Events [6, 12]

Date	Key Events
Nov 16, 2002	Unusual atypical pneumonia documented in Foshan, Guangdong Province, China.
Jan 2003	Outbreaks of pneumonia in Guangzhou (capital city of Guangdong Province)
Feb 11	WHO receives reports of an outbreak of respiratory disease in Guangdong Province: 305 cases and 5 deaths
Feb 12	WHO is informed that the outbreak in the Guangdong affected 6 municipalities. Laboratory analysis is negative for influenza.
Feb 14	The Chinese Ministry of Health informs the WHO that the outbreak in Guangdong is clinically consistent with atypical pneumonia. Investigations rule out anthrax, pulmonary plague, leptospirosis, and hemorrhagic fever.
Feb 20	Fatal Influenza (H2N1 subtype) identified in family returning to Hong Kong from Fujian Province, China.
Feb 21	65-Year-old Physician for Guangdong Province checks in at "Hotel M" in Hong Kong (index patient); he has been ill since February 15. His health deteriorates further; he is admitted to the hospital on February 22. He infects at least 17 other guests and visitors at the hotel, some of whom travel to Vietnam, Singapore, and Toronto, where they initiate transmission of local clusters of cases.
Feb 26	A Hotel M contact, a 48-year-old businessman, is admitted to a private hospital in Hanoi and is the source of an outbreak there; 7 health care workers at this hospital become ill by March 5.
Feb 28	Dr. Carlo urbane, a WHO official based in Viet Nam, observes several cases of atypical pneumonia in the French Hospital, where he has asked to assist. He informs the WHO Regional Office for the Western Pacific. WHO moves into a heightened state of alert.
March 1	26-Year-old former flight attendant is admitted to a hospital in Singapore with respiratory symptoms. She was a guest on the 9th floor of Hotel M in Hong Kong.
March 4	A Hotel M contact, a 26-year-old local Hong Kong resident, is admitted to the Prince of Wales Hospital in Hong Kong. By March 7, health care workers at this hospital report a respiratory illness.
March 5	A Hotel M contact, an elderly woman, dies in Toronto; 5 family members are affected.
March 7	Health care workers at the Hong Kong Prince of Wales hospital begin complaints of respiratory tract infections, progressing to pneumonia
March 8	Fourteen staff at the French hospital in Hanoi are ill with an acute respiratory syndrome. A WHO team arrives to provide support.

Table 1 (continued). SARS Chronology of Events

March 10	At least 22 staff at the Hanoi hospital are reported ill with respiratory symptoms. The Chinese Ministry of Health asks WHO to provide technical and laboratory support to clarify the cause of the Guangdong outbreak.
March 12	WHO issues a global alert about cases of severe atypical pneumonia following numerous reports of cases among staff in the Hanoi and Hong Kong hospitals.
March 14	Singapore and Toronto report clusters of atypical pneumonia. In retrospect, both groups have an epidemiological link to Hotel M. During travel, symptoms develop in on of the doctors who treated patients in Singapore; he is quarantined in transit on arrival in Germany.
March 15	WHO has received reports of more than 150 cases of the new disease, now named Severe Acute Respiratory Syndrome (SARS). A travel advisory is issued. WHO issues a travel advisory and is declaring SARS a "worldwide health threat".
March 17	WHO multicenter laboratory network established for the study of SARS causation and diagnosis.
March 18	A cumulative number of 210 cases with 4 deaths are reported to WHO from 7 countries.
March 20	The cumulative total climbs to 306 cases with 10 deaths.
March 24	In Hanoi, WHO epidemiologists determine that 63% of SARS cases are in health care workers. All can be linked to the index case at the French Hospital.
March 26	A WHO team reviews the case definition. The world cumulative total soars to 1323, with 49 deaths
March 27	A novel coronavirus is identified in patients with SARS by scientists from the WHO.
March 28	China joins the WHO collaborative networks. Media reports describe SARS as greater threat than the war in Iraq.
March 30	Hong Kong health officials announce a large and almost simultaneous cluster of probable cases among residents in a single building in the Amoy Gardens housing estate, pointing to a possible environmental source of exposure. The cumulative global total reaches 1622 cases and 58 deaths.
April 2	WHO recommends persons planning to travel to Hong Kong and the Guangdong Province considers postponing all but essential travel. Cumulative total surpasses 2000 cases.
April 4	China begins daily electronic reporting of SARS cases and deaths, nationwide by Province
April 9	WHO team in Guangdong Province presents interim report to the Ministry of Health. Addressed concern of the capacity of some provinces to cope with the health challenge posed by SARS due to lack of a strong health system.
April 12	Mapping of the full genome of SARS-associated coronavirus (soon called SARS-CoV) is completed.

Table 1 (continued). SARS Chronology of Events

April 16	WHO announces that SARS-CoV is the causative agent of SARS.
April 20	Chinese authorities announce 339 previously undisclosed cases of SARS, bringing the cumulative total of SARS cases in China to 1959.
April 23	WHO advises travelers to Beijing and Shanxi Province, China, and Toronto, Canada to consider postponing all but essential travel.
April 25	Outbreak in Hanoi, Hong Kong, and Toronto show signs of peaking.
April 28	Viet Nam becomes the first country to contain its SARS outbreak. The cumulative total surpasses 5000.
April 30	China, accounting for 3460 probable cases of the global SARS total of 5663, now has more cases than the rest of the world combined. WHO lifts its travel advisory to Toronto.
May 2	Cumulative total surpasses 6000.
May 3	WHO sends team to Taiwan, which is now reporting a cumulative total of 100 probable cases.
May 7	WHO estimates that the case-fatality ratio of SARS ranges from 0%-50% depending on the age group affected, with an overall estimate of 14%-15%.
May 8	Cumulative total of cases surpasses 7000, with cases now reported in 30
	countries.
May 13	Outbreaks at the remaining initial sites show signs of coming under control, indicating SARS can be contained.
May 17	The first global consultation of SARS epidemiology concludes its work. Cumulative total of 7761 probable cases with 623 deaths. Of the total, 5209 cases and 282 deaths are reported from mainland China.
June	A virus related to SARS-CoV is isolated from animals.
July 5	The absence of further transmission in Taiwan signals the end of the SARS outbreak.

Table 2. Summary Table of SARS by Country, November 1, 2002 through August 7, 2003 [26]

Areas	Female	Male	Total	Median Age Range	Number of Deaths	CFR(%)	Number of HCW affected	Date onset first probable case	Date onset last probable case
Australia	4	2	6	15 (1-45)	0	0	0	24-Mar	1-Apr
Brazil	1		1	4	0	0	0	3-Apr	3-Apr
Canada	151	100	251	49 (1-98)	41	17	105	23-Feb	12-Jun
China,	Pending	Pend	5327	Pending	349	7	1002	16-Nov	25-Jun
Hong Kong	977	778	1755	40 (0-100)	300	17	386	15-Feb	31-May
China, Macao	0	1	1	28	0	0	0	5-May	5-May
China, Taiwan	349	319	685	46 (2-79)	180	27	86	25-Feb	15-Jun
Colombia	1	0	1	28	0	0	0	2-Apr	2-Apr
Finland	0	1	1	24	0	0	0	30-Apr	30-Apr
France	1	6	7	49 (26-61)	1	14	2	21-Mar	3-May
Germany	4	5	9	44(4-73)	0	0	1	9-Mar	6-May
India	0	3	2	25 (25-30)	0	0	0	25-Apr	6-May
Indonesia	0	2	2	56 (47-65)	0	0	0	6-Apr	17-Apr
Italy	1	3	4	30.5 (25-54)	0	0	0	12-Mar	20-Apr
Kuwait	1	0	1	50	0	0	0	9-Apr	9-Apr
Malaysia	1	4	5	30 (28-54)	2	40	0	14-Mar	22-Apr
New Zealand	1	0	1	67	0	0		20-Apr	20-Apr
Philippines	8	6	14	41 (29-73)	2	14	4	25-Feb	5-May
Ireland	0	1	1	56	0	0	0	27-Feb	27-Feb
Korea	0	3	3	40 (20-80)	0	0	0	25-Apr	10-May
Romania	0	1	1	52	0	0	0	19-Mar	19-May

Table 2 Continued. Summary Table of SARS by Country, November 1, 2002 through August 7, 2003 [26]

Areas	Female	Male	Total	Median Age Range	Number of Deaths	CFR(%)	Number of HCW affected	Date onset first probable case	Date onset last probable case
Russia	0	1	1	25	0		0	5-May	5-May
Singapore	161	77	238	35 (1-90)	33	14	97	25-Feb	27-Feb
South Africa	0	1	1	62	1	100	0	3-Apr	10-May
Spain	0	1	1	33	0	0	0	26-Mar	23-Mar
Sweden	1	2	3	33	0	0	0		
Switzerland	0	1	1	33	0	0	0	9-Mar	9-Mar
Thailand	5	4	9	42 (2-79)	2	22	1	11-Mar	27-May
United Kingdom	2	2	4	59 (28-74)	0	0	0	1-Mar	1-Apr
United States	16	17	33	36 (0-83)	0	0	1	9-Jan	13-Jul
Viet Nam	39	24	63	43 (20-76)	5	8	36	23-Feb	14-Apr
Total			**8422**		**916**		**1725 (20%)**		

Table 3. Summary of SARS Incubation Period Estimates [1]

Area	Min	Mean	Median	Max	Comments
Canada	2	4.8	4.2	10	Based on 42 cases with a single exposure to a source case. The median and mean were calculated using a parametric fit, while the minimum and maximum are from the data.
People's Republic of China	1	4	4	12	Based on 70 cases from Guangdong. 5 cases with an incubation period of >10 days.
				14	Beijing and Guangdong.
China, Hong Kong, SAR	*	6.37 (95% CI 5.29-7.75	*	*	Based on 57 cases with one exposure to SARS over a limited time scale. Incubation period of <= 14.22 days in 95% of cases (parametric fit)
China, Taiwan	*	*	*	10-14	Based on household transmission studies
Singapore	1	5.3	5	10	Based on 46 cases with a single exposure.
Viet Nam	5	6-7	*	10	Based on health care associated exposure to a source case.
WHO European Region	5	7.2	7	10	Based on two episodes (5 cases) with a single exposure to a source case.

Table 4. Number of Cases and Deaths from HPS (Regions of the Americas), 1993-2004 [62, 67]

Country	93	94	95	96	97	98	99	00	01	02	03	04	Total
Argentina													
Cases	21	10	10	42	51	67	81	68	92	86	52	12	**592**
Deaths						11							**11**
Bolivia													
Cases	3		1	1	7	6	2	1	5	8	11	4	**36**
Deaths													**17**
Brazil													
Cases	3		1	3		11	26	58	71	73	75		**321**
Deaths	2		1	3		8	12	20	25				**71**
Canada													
Cases		8	3	3	7	6	2	1		44	14		**88**
Deaths													**0**
Chile													
Cases			1	3	30	35	26	31	81	65	59		**331**
Deaths					18	20	11	12	29	17	17		**124**
Panama													
Cases							3	21	5	2	4		**35**
Deaths									1		2		**3**
Paraguay													
Cases		16	15	5	4	5	4	15	27	4	4		**99**
Deaths			2	1	1	0	2	2	5				**13**
Uruguay													
Cases					2	3	12	8	4	9	10		**48**
Deaths					1	2	1	1	0	3	5		**13**
USA													
Cases	48	32	24	22	23	33	33	34	6	11	17	79	**362**
Deaths													**132**
Total													
Cases	**75**	**66**	**55**	**79**	**124**	**166**	**189**	**237**	**291**	**302**	**246**	**95**	**1910**
Deaths	**2**	**0**	**3**	**4**	**20**	**41**	**26**	**35**	**60**	**20**	**24**	**0**	**384**

Table 5. Hantaviruses

Hantaviruses in the Old World			
Subfamily Murinae associated viruses			
Virus	**Host**	**Location**	**Disease**
Hantaan	*Apodemus agrarisu*	Asia, Far East Russia	HFRS
Dobrave	*Apodemus flavicollis*	Balkans	HFRS
	Apodemus agrarius	Europe	
Seoul	*Rattus norvegicus*	Worldwide	HFRS
	Rattus rattus		
Subfamily Arvicolinae associated viruses			
Virus	**Host**	**Location**	**Disease**
Puumala	*Clethrionomysglareolus*	Europe	HFRS
Hantaviruses in the New World			
Subfamily Sigmodontinae associated viruses			
Virus	**Host**	**Location**	**Disease**
Sin Nombre	*Peromyscus maniculatus* (deer mouse)	West and Central US and Canada	HPS
Monongahela	*Peromyscus maniculatus* (white-footed mouse)	Eastern US and Canada	HPS
New York	*Peromyscus leucopus*	Eastern US	HPS
Bayou	*Oryzomys palustris (rice rat)*	Southeastern US	HPS
Black Creek Canal	*Sigmodon hispidus* (cotton rat)	Florida	HPS
Andes	*Oligoryzomys longicaudatus*	Argentina and Chile	HPS
Oran	*Oligorozomys longicaudatus*	Northwestern Argentina	
Lechiguanas	*Oligoryzomys flavescens*	Central Argentina	
Hu39694	*Unknown*	Central Argentina	
Laguna Negra	*Calomys laucha*	Paraguay and Bolivia	HPS
Bermejo	*Oligoryzomys chacoensis*	Northwestern Argentina	
Juquitiba	*Unknown*	Brazil	HPS
Choclo	*Oligoryzomys fulvescens*	Panama	HPS

*other hantaviruses have been identified but not linked to human disease in these areas

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