

Surveillance for Febrile Respiratory Infections during Cobra Gold 2003

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The Naval Health Research Center conducted laboratory-based surveillance for febrile respiratory infections at the 2003 Cobra Gold Exercise in Thailand. Seventeen individuals met the case definition for febrile respiratory illness, and diagnostic specimens were obtained from 16. Laboratory testing identified influenza A for 44%; sequence analysis demonstrated that these were Fujian-like influenza strains, which represented the predominant strain found globally in 2003/2004. Other pathogens identified included coronavirus OC43, respiratory syncytial virus, and rhinovirus. Logistical challenges were overcome as laboratory-supported febrile respiratory illness surveillance was conducted during a military training exercise. With heightened concern over the potential for another global influenza pandemic, such surveillance could prove critical for the detection of emerging influenza and respiratory pathogen strains with potential for importation to the United States.

Introduction

The U.S. military is recognized for deploying its service members throughout nearly every continent in the world. Deployments range from small-scale training missions to politically and militarily significant exercises with worldwide joint and combined operational units. One of the largest combined exercises in the Pacific Command is Thailand's "Cobra Gold." This 2-week multilateral exercise allows engaged military forces to work together in a joint/combined environment to conduct numerous operations on land, at sea, and in the air. The 2003 Cobra Gold exercise included ~12,000 troops from participating nations, with 5,200 of those being from the U.S. Armed Forces. The specific focus of the 2003 exercise was to enhance peace enforcement, humanitarian assistance, and disaster relief operations.¹

As plans for Cobra Gold 2003 were unfolding, however, the world was anxiously watching the spread of another powerful force. In February 2003, atypical pneumonia with high mortality

rates was seen in the Guangdong province of China and reported by the Chinese Ministry of Health. Later called severe acute respiratory syndrome (SARS), a newly recognized, highly pathogenic strain of coronavirus was found to be causal.²⁻⁶

Although SARS transmission was not recognized in the country of Thailand before Cobra Gold 2003, a small number of contained imported cases were documented. In anticipation of Cobra Gold 2003, the Kingdom of Thailand was concerned regarding the potential for participants to pass through or come from countries with known SARS transmission. To ease these concerns, the Naval Health Research Center (NHRC), with an 8-year history of surveillance and diagnosis of febrile respiratory illness (FRI) within active duty continental United States and deployed forces, was tasked with conducting laboratory-based, active surveillance for respiratory illnesses (including SARS) during the exercise, with the intent of early recognition and response.^{7,8} As concerns over SARS importation were eased with implementation of surveillance, valuable information on circulating respiratory pathogens during such an exercise was collected.

Methods

With coordination and logistic support from the Armed Forces Research Institute of Medical Sciences (AFRIMS) (a joint U.S. Army-Royal Thai Army research facility located in Bangkok since 1958), respiratory illness surveillance was initiated by NHRC. AFRIMS has conducted routine diarrhea surveillance during Cobra Gold for many years, and researchers were able to easily accommodate respiratory surveillance in this exercise. In addition to the support received from AFRIMS, two main appointed medical care units, i.e., Fort Thanarat (located in the Hua Hin area, southwest of Bangkok) and Camp Samae San (located in Pattaya Beach, southeast of Bangkok), were selected as collection stations because of their U.S. military force proximity. Individual U.S. aid stations throughout Thailand were sent official notification of the surveillance through message traffic; this instructed the aid stations to send all patients meeting the FRI case definition to Fort Thanarat or Camp Samae San. The FRI case definition was oral temperature of $\geq 100.5^{\circ}\text{F}$ and a respiratory symptom (cough, sore throat, shortness of breath, or difficulty breathing) or any diagnosed pneumonia. The surveillance was conducted for 2 weeks for personnel within the political borders of Thailand, from the official commencement of the exercise to its completion.

Supplies, including viral transport medium, swabs (sterile Dacron), preprinted subject identification labels, FRI log sheets, and informed consent/case forms, were provided to both units. Before commencement of the exercise, a NHRC representative

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conducted training on data and specimen collection procedures. To record the number of personnel under surveillance and the number of those who presented with FRI symptoms, the clinicians at each medical care unit completed a daily summary form. Individuals who presented meeting the FRI case definition were asked to complete an informed consent/case form and to permit a throat swab. Travel and contact information was also requested for potential categorization as a "suspect SARS case,"² which required implementation of respiratory isolation precautions with immediate evaluation.

Diagnostic specimens were collected with a sterile Dacron swab and placed directly into viral transport medium. A pre-printed subject identification label was placed on the vial, and the vial was immediately placed in a -70°C freezer or liquid nitrogen tank. Identical preprinted labels were placed on the case report form and the FRI log sheet. Once the exercise ended, Camp Samae San and Fort Thanarat transported all specimens to AFRIMS, and shipment to the NHRC Respiratory Disease Laboratory was arranged.

Samples received at the NHRC Respiratory Disease Laboratory were processed in both the classic virology laboratory, with cell culture techniques (A549 and RMK cells),⁷ and in the molecular laboratory, with standard polymerase chain reaction (PCR) and reverse transcriptase-PCR methods. Testing was performed for influenza A, influenza B, adenovirus, parainfluenza viruses 1 to 3, respiratory syncytial virus, enteroviruses, coronaviruses (229E and OC43), rhinovirus, and human metapneumovirus. All samples positive for influenza A were typed with four additional primer sets (*N1*, *N3*, *H1*, and *H3*). A portion of the *H3* gene was sequenced for all influenza A-positive samples, for phylogenetic comparison. Because viral transport medium was used to collect the specimens, no testing was conducted for bacterial pathogens. If SARS coronavirus testing had been required, NHRC would have used the real-time, reverse transcriptase-PCR assay developed by the Centers for Disease Control and Prevention, with validation by the Centers for Disease Control and Prevention.⁹

Results

The number of troops under surveillance during the exercise was estimated to average 4,800 over a 2-week period; 17 patients were seen who met the case definition, for an attack rate of 0.18 FRI cases per 100 recruit-weeks. Sixteen of the 17 patients provided a diagnostic specimen. The average age of these 16 individuals was 27 years; all were male, seven were U.S. Marine Corps, seven were U.S. Army, one was U.S. Air Force, and one was not determined. The average symptom duration was 3.7 days; one of the 16 patients was hospitalized with pneumonia. None of the patients had a history of asthma, and all except one had been vaccinated with the influenza vaccine within the past 12 months (two unknown). Six of the 16 individuals were smokers, with an average of 2.2 pack-years.

Of the 16 diagnostic specimens received, seven (44%) tested positive for influenza A, 2 (13%) for coronavirus OC43, 2 (13%) for respiratory syncytial virus, and 1 (6%) for rhinovirus. The remaining four (25%) were negative. No case met the case definition for a suspect SARS case during the surveillance; therefore, patient isolation and urgent investigations were not required. Of the individuals meeting the case definition for FRI, only one had significant symptoms necessitating further evaluation and chest radiographs. This individual was one of the two respiratory syncytial virus-positive individuals. Sequence analysis demonstrated that all seven influenza A strains were more closely related to the Fujian/411 lineage than the Panama, as illustrated in Figure 1.

Discussion

Concern over potential SARS transmission provided the momentum for cooperation and facilitation necessary to conduct this surveillance. Although no SARS suspect case was identified, valuable information was gathered regarding circulating respiratory pathogens among our deployed troops in this setting. Most interesting, influenza A was identified for 44% of the presenting patients (7 of 16 patients). Given the potential for

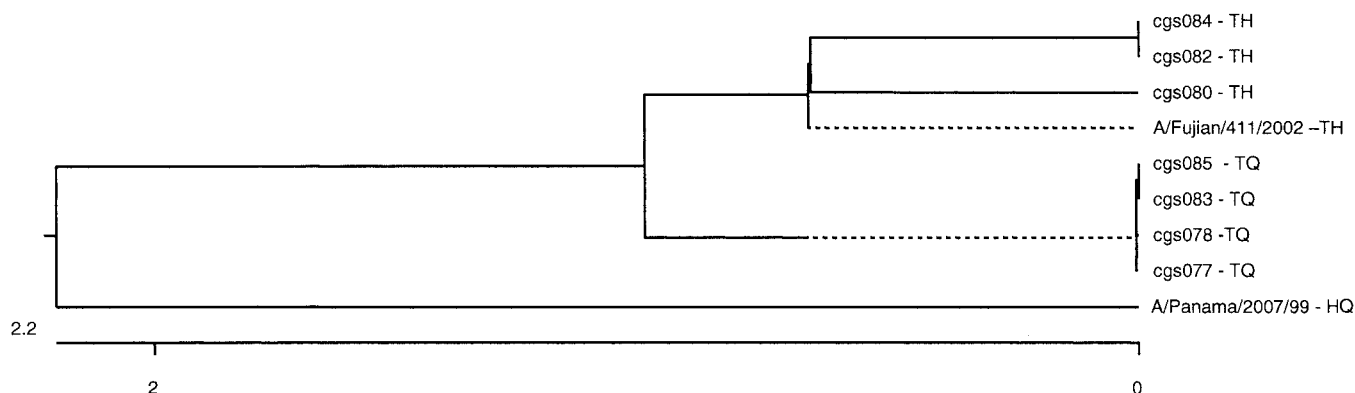


Fig. 1. Phylogenetic tree for the influenza A isolates from Cobra Gold. This is an alignment of a 303-amino acid stretch of the hemagglutinin gene of influenza A (from position 31 to position 333, with position 1 being the first position of the open reading frame of the HA1 gene). Strains that begin with cgs are isolates collected during the Cobra Gold exercise. Notation of TQ, TH, or HQ indicates amino acid identities at positions 155 and 156. Amino acid changes at these positions were previously identified as polymorphic between vaccine strains of A/Panama/2007/99 (HQ) and A/Fujian/411/2002 (TH). The phylogenetic tree was created with DNASTAR software, using the Clustal W alignment algorithm. The alignment illustrates that these sequences are more closely related to the 03-04 circulating strain of A/Fujian/411/2002 than to A/Panama/2007/99. Sequence comparison at positions 155 and 156 indicates that four of the CGS isolates are intermediate between A/Fujian/411/2002 and A/Panama/2007/99.

genetic recombination and drift of influenza A virus and concern over the potential for another influenza pandemic similar in scope to the devastating pandemic of 1918, the global community is renewing efforts to improve global influenza surveillance. Particularly in regions of the Far East where living conditions are often in close proximity to avian and swine populations, the risk for human acquisition of recombined influenza viruses with increased pathogenic potential is real. Indeed, of the influenza A isolates sequenced, all were found to be closely related to the Fujian strain (Fig. 1), which was the predominant influenza strain seen globally in the subsequent 2003/2004 influenza season but was not covered by the 2003/2004 influenza vaccine preparation.^{10,11}

A weakness of this surveillance was lack of data indicating the percentage capture of those meeting the case definition. Given the great concern over SARS transmission, however, we are confident that capture of FRI was better than it would have been in years without this concern. In addition, the surveillance period was relatively short, indicating that individuals in the pre-symptomatic stages of infection likely came back to the United States. Given this risk, real-time knowledge of pathogens in circulation would be useful. To this end, field implementation of diagnostic technologies, such as classic PCR or real-time PCR methods (such as with the LightCycler, Roche Diagnostics, Indianapolis, Indiana), would be a valuable addition to surveillance such as this in remote regions.

Critical surveillance for infectious agents causing FRI during overseas military exercises can be conducted, although logistical barriers must be overcome. Given concern over emerging pathogens such as SARS and the known potential for emergence of newly pathogenic influenza strains such as the highly pathogenic avian influenza strains, opportunities for laboratory-based surveillance for respiratory pathogens among our deployed troops should be sought. Valuable information on the epidemiological features of these pathogens will be gained as we monitor the potential importation of emerging pathogens into the United States.

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