excerpted from

Reducing Pandemic Risk, Promoting Global Health

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China is home to the most endemic temperate biodiversity of fauna and contains approximately one-tenth of all known species. More than 4,000 vertebrate species live within the borders of China, and changes in land-use are rapidly altering these animals’ natural environments. Some of China’s most biodiverse areas – in South Guangdong, Guangxi, Hainan, and Yunnan Provinces – are also among its most populous. China’s population is the largest in the world, and the country is undergoing the greatest rate of development (Seto et al. 2000). Demographic changes are yielding a rapid centralization of the population in expanding urban centers accompanied by growing demands for resources, including food (Peng 2011). Extraction of natural resources and shifts in agricultural practices and intensity to meet food demands have resulted in large-scale changes to China’s landscape, especially in southern China where rice and domestic animal production are greatest (Seto et al. 2000). In addition to the growing industrial and small-holder poultry farms located throughout urban and rural China (Rae 2008), the country also significantly contributes to the wildlife trade for food, pets, and luxury items, sourcing products through in-country wildlife farming and importation from around the world.

As one of the largest and most geographically diverse countries with a rapidly developing economy, China is a key player in global wildlife trade and transport with potential concomitant impacts on health and the environment. Countries in Southeast Asia are rich in wildlife biodiversity (Myers et al. 2000) and have experienced some of the most rapid deforestation, bringing human settlements and commercial agriculture into proximity with wildlife (Achard et al. 2002). In addition, illegal wildlife trade is pervasive in Southeast Asian countries, including China, Malaysia, and Thailand (Nijman 2010). Innumerable species are shipped from Southeast

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Asia and southern China throughout China, as demand for wild animals increases with per capita income (Nijman 2010). The wildlife trade played a role in the emergence of SARS, avian influenza, and other diseases of wildlife origin (Karesh et al. 2005; Smith et al. 2012).

Guangdong Province in China is where the first cases of SARS were reported in 2002. Now known to have originated in bats (Li et al. 2005), SARS emerged in humans and other mammals in live animal markets (Guan et al. 2003). The disease spread to 26 countries and infected over 8,000 people; killing nearly 800 (Stadler et al. 2003). SARS shut down trade of domestic animals and resulted in upwards of $30 billion in losses to the global economy. Subsequent outbreaks of H5N1 and more recently H7N9 in 2013 and 2014 demonstrated the realities of the risk of disease transmission and spread in China and the detriments to animal and human health, as well as human livelihoods (Smith et al. 2006; Gao et al. 2013).

The increasing frequency and variety of human-wildlife interactions in China present opportunities for zoonotic disease transmission (Karesh et al. 2005). For example, handling or consumption of hunted or farmed wildlife poses a risk of pathogen spillover into humans (Wolfe et al. 2005). Besides home consumption, in southern China provinces like Guangdong, increasing numbers of individuals are traveling to urban-rural interface areas to eat at restaurants, where many hunted or farmed wildlife are kept alive. In addition, the intermingling of wildlife in wet markets can lead to inter-species transmission of pathogens and may result in spillover into a species that can more efficiently transmit the pathogen to humans (Bengis et al. 2004). China’s rich diversity of industry and culture also present human-animal interfaces through activities such as ecotourism, religious activities, natural resource extraction, and wildlife-human conflict situations (e.g. crop-raiding; Karesh et al. 2005; Chomel et al. 2007). Proactive surveillance of wildlife at these and other high-risk human-animal interfaces is needed to identify zoonotic disease risks for humans.

In China, we aimed to detect, track, and predict the emergence of new infectious diseases in high-risk wildlife taxa that could pose a major threat to human health. PREDICT’s work in China was critical because the diversity of potentially zoonotic pathogens hosted by wildlife is likely to be commensurate with the diversity of wildlife, thus putting China at high risk for zoonotic disease outbreaks. PREDICT increased capacity for a One Health approach to disease outbreak response in China. The program implemented surveillance in high-risk human and animal populations, as well as hospital syndromic surveillance for fevers of unknown origin, in partnership with provincial and local centers for disease control (CDCs) under the Ministry of Health. Particular focus was placed on establishing an enhanced wildlife monitoring capacity in geographic “hotspots” in southern China that pose a particular risk for the emergence of novel infectious diseases.
Wildlife disease surveillance focused on targeted discovery of specific priority viruses, including retroviruses, influenza, coronaviruses, and filoviruses in wildlife sampled in natural habitats and the market trade and from wildlife products and foods. Human disease surveillance targeted individuals with high levels of exposure to wildlife (e.g. butchers) and followed them over time to determine their exposure to zoonotic pathogens. In addition, PREDICT conducted syndromic surveillance by applying PREDICT diagnostic protocols to specimens from individuals with key symptomology (e.g. fever, diarrhea, encephalitis). PREDICT China’s in-country partner laboratories focused on virus discovery, especially viruses causing outbreaks of disease and identifying new potential pathogens of pandemic risk. Surveillance and ecological data in combination with GIS information were used to assess the risk of emerging diseases and evaluate mitigation strategies for decreasing risk of pathogen spillover from animals into people in China.

**PARTNERS**

PREDICT partners and colleagues in China have well-established facilities including infectious disease diagnostics labs with state-of-the-art molecular virology and serology capacity. Dr. Shuyi Zhang, based at East China Normal University, was the PREDICT China Country Coordinator, and has extensive experience working with wildlife and leading investigations of viral diversity in wildlife. He was part of the original investigation team that identified bats as reservoirs for SARS CoV. PREDICT’s partners at Guangdong CDC were at the epicenter of the SARS outbreak, and developed surveillance programs with PREDICT using a One Health framework.

Because of the strengths of its partners, the China PREDICT team had unparalleled access to wildlife trade systems in China spanning all levels of the trade network from hunters in source areas, through conduit routes, markets, consumers, illegal wildlife restaurants, and wildlife department holding facilities (confiscated wildlife). PREDICT was able to obtain detailed information about hunting behavior and work with provincial CDCs to screen blood samples alongside the hunted animal samples for zoonotic pathogens.

In China, PREDICT partnered with USAID and set up long-term collaborations with the Wuhan Institute of Virology (WIV), the Yunnan Institute of Endemic Disease Control and Prevention, Guangxi Normal University, Shanghai Municipal Center for Disease Control and Prevention (SHCDC), the Guangdong Provincial Center for Disease Control and Prevention (GDCDC), the Guangdong Entomological Institute (GDEI), and East China Normal University (ECNU). In addition, PREDICT developed a collaborative relationship with Guangdong Institute of Public Health (GDIPH)/GDCDC, which also bridged joint works with Guangdong Zhanjiang Ratproof Institution. Further, PREDICT developed and maintained closely collaborative relationships with prefecture level CDCs that are located in Fengkai (Zhaoqing), Deqing (Zhaoqing), Yunfu, Yunan (Yunfu), Dabu (Meizhou), Jiaoling (Meizhou), Pingyuan (Meizhou), Xinyi (Maoming), Heping (Heyuan), Lianping (Heyuan), Lianshan (Qingyuan), Lianzhou (Qingyuan), Shaoguan, Zhanjiang, Dongguan, Jiangmen, Huizhou, Zhongshan, Luoding, and Yangjiang.
Other than local CDCs, PREDICT established long-term collaborative relationships with sentinel hospitals located within Guangdong Province. These included Gaozhou People’s Hospital, Maoming; Yunfu People’s Hospital, Yunfu; Luoding People’s Hospital, Yunfu; Deqing People’s Hospital, Zhaoqing; Fengkai People’s Hospital, Zhaoqing; Donghua Hospital, Dongguan; Dongyuan Traditional Chinese Medicine Hospital, Heyuan; Lianping People’s Hospital, Heyuan; Meizhou People’s Hospital, Meizhou; Shaoguan Yue Bei People’s Hospital; Zhanjiang Central People’s Hospital; Jiangmen Central Hospital; Huizhou First People’s Hospital; Zhongshan People’s Hospital; Maoming People’s Hospital; and Yangjiang People’s Hospital. In 2013, an EPT PREDICT-GDIPH/GDCDC collaboration facilitated viral pathogen identification through interprovincial joint activity with Jiangsu Provincial Center for Disease Control and Prevention (JSCDC).

MAJOR ACHIEVEMENTS

• Promoted a One Health approach to human disease surveillance, enhanced laboratory testing capacity, improved inter-sectoral communication, and more broadly facilitated detection of cross-species viral sharing during the H7N9 outbreak. PREDICT tested a total of 167 samples from people with influenza-like illness in addition to 27 environmental samples. The laboratory team implemented protocols developed by PREDICT to expand detection of divergent strains and to improve sequencing capability (see Success Stories for more information).

• Isolated SARS-like coronaviruses from bats for the first time in China and fully characterized the whole genome of two novel bat SARS-like coronaviruses (see Success Stories for more information).

• Implemented PREDICT protocols in a federal virology diagnostic institute (WIV) for viral discovery and at the Guangdong Provincial Center for Disease Control and Prevention (GDCDC) as a diagnostic tool for hospital-based surveillance specimens.

• Improved wildlife field surveillance and diagnostic testing capacity in multiple institutions. Optimized PREDICT surveillance protocols by developing an animal field guide and providing training for all collaborating institutions and individuals.

• Over 3,061 bats, 737 rodents and shrews, and 146 other animals were sampled in animal markets, farms, and rural areas. A total of 1,267 humans were sampled at human-animal interfaces, coupled with animal sampling.

• Enhanced communication among ministries focused on infectious diseases and initiated conversations concerning future collaboration among ministries, including data and sample sharing, as well as identification of new strategies for cooperative research.

• Generated interest among regional Centers for Disease Control in testing samples for plague (rodents) and rabies virus (bats), as well as other zoonotic viruses, using PREDICT protocols. This expansion of testing leveraged existing collection activities to expand wildlife surveillance regionally.

• Identified live animal markets along wildlife trade routes in Southern China, where novel diseases are likely to emerge.
• Conducted a Guangdong Hospital syndromic surveillance study using PREDICT protocols. Patients exhibiting encephalitis symptoms were tested for seadornavirus, flavivirus, paramyxovirus, hantavirus, and arenavirus. Moreover, samples collected from individuals with hemorrhagic fever, or fever with thrombocytopenia, were screened for paramyxovirus, arenavirus, hantavirus, filovirus, and flavivirus.

SUCCESS STORIES

Improving Our Understanding of SARS-like Coronaviruses in Bats

PREDICT isolated for the first time SARS-like coronaviruses from bats sampled in China (Figure 1), fully characterized the whole genome of two novel bat SARS-like coronaviruses, and demonstrated a bat SARS-like coronavirus with 99.98% sequence homology to SARS coronavirus. The virus was found to bind to the human ACE-2 cell receptor, suggesting that direct transmission to humans from bats is possible (Ge et al. 2013). During the 2003 outbreak of SARS in the wet markets of Guangdong province in China, it was thought that bat viruses first infected civets and then evolved to infect people through this intermediate host. However, this study provides compelling evidence that an intermediate host was not necessary. PREDICT has found a surprisingly high number of positives of SARS-like coronaviruses in bats sampled in China. Several of these viruses were novel, and some bats tested positive for multiple novel viruses.

One Health Approach to H7N9 Outbreak Response

The PREDICT team published results demonstrating the first discovery of H9N2 subtype avian influenza virus in wild birds and suggested that these birds may carry H9N2 along migratory routes – highlighting the necessity for continued surveillance of wild birds (Zhu et al. 2013). The PREDICT implementing partners GDCDC and GDIPH organized an expert consulting trip in Guangdong Province during the 2013 H7N9 outbreak, which enhanced surveillance activities, augmented laboratory analysis capacity, and promoted the involvement and coordination of multidisciplinary ministries. PREDICT assisted with the establishment of a Guangdong One Health H7N9 Task Force to coordinate a unified surveillance approach to the H7N9 outbreak among human and animal health sectors. PREDICT facilitated the sharing of expertise and information regarding outbreak response and preparedness between all stakeholders - increasing coordination between human and animal health sectors in China.

CAPACITY BUILDING

One Health Approach to Surveillance and Disease Outbreak Response

PREDICT staff collaborated with scientists and agencies in China to strengthen its public health capacity for identifying new infectious disease threats and early warning disease indicators. PREDICT enhanced surveillance capacity related to pathogen transmission between animals and humans with the goal of incorporating wildlife disease surveillance into standard public health policy in China. Through expanded surveillance and disease modeling, PREDICT
assisted China with developing new tools to target public health resources where they will be most beneficial. After extensive coordinated laboratory analysis with program-engaged partners in China, PREDICT protocols were proven as a valuable viral family level screening tool, as well as a supplemental method to pathogenic-specific real-time PCR. Surveillance activities were coordinated among partners and fostered cross-sectoral collaboration between the human and animal health sectors in China. Information was shared among all partners on a regular basis, which encouraged a One Health approach. Specifically, a hospital-based study and surveillance activities conducted at animal-human interfaces enhanced communication between ministries focused on infectious diseases, which stimulated conversations concerning future inter-ministerial collaborations. These discussions included exchanges regarding efficient strategies for cooperative research and data and sample sharing from both existing and prospective samples and datasets.

PREDICT activities also increased capacity to respond to future disease outbreaks and exerted a positive impact on local and provincial surveillance capacity in Hubei, Yunnan, and Guangdong provinces. In addition, PREDICT China fostered collaboration among provinces and cross-sectoral collaboration between the World Health Organization (WHO), Food and Agriculture Organization (FAO), the Worldwide Scientific Network for Control of Avian Influenza (OFFLU), and the World Organization for Animal Health (OIE).

Training

PREDICT-China trained field and laboratory teams of local scientists in disease outbreak investigation; specimen collection, processing, and preservation; and PREDICT laboratory protocols. Trained personnel followed standardized safety protocols, including use of personal protective equipment, and practiced humane treatment of animals during wildlife sampling activities.

During July 2011, PREDICT staff took part in the Pan Pearl River Triangle Area Emerging Infectious Disease Symposium that was supported by WHO. In August 2012, PREDICT staff attended a ceremony to initiate the modification project of Guangzhou Jiangcun live poultry trade market. This project was supported by both the FAO and China Agriculture Department. In early 2013, the PREDICT China team members participated in the A World United against Infectious Diseases: Cross-sectoral Solutions Conference, which was supported by USAID and WHO, in addition to other organizations and foundations. The PREDICT China team also joined the Sharing Experiences on the Application of One Health Approaches in China meeting, which was organized by WHO and FAO and funded by USAID. To review program success and bring together partners to review the One Health strategy to zoonotic disease control, the PREDICT China team held a forum in Guangzhou on “Surveillance and Epidemiological Research of Zoonotic Diseases & Application of One Health in Disease Control and Prevention in South China”.

SURVEILLANCE

PREDICT primarily conducted zoonotic disease surveillance and research by integrating directly into government laboratories and engaging local CDCs as part of a China public health network. This direct engagement allowed USAID to have the maximum impact and sustainability on local capacity building. PREDICT played a positive role in enhancing capacity building and promoting interprovincial
collaboration surrounding surveillance of zoonotic disease pathogens and viral/bacterial pathogen identification in China.

**Wildlife Disease Surveillance**

Wildlife disease surveillance in China focused initially on pathogens commonly detected in bats but was later expanded to include active surveillance for novel pathogens in a variety of wildlife hosts, in particular those taxa that pose a threat to humans or domestic animals. Surveillance activities were conducted in 19 provinces in addition to Beijing, the capital region of China and targeted a variety of high-risk disease transmission interfaces (Figure 2; Table 1). More than half of the samples were collected in the southernmost Provinces of Guangdong, Guangxi, and Yunnan. A total of 3,944 animals were sampled, and most of them were wild-caught bats from a variety of taxonomic families, including Hipposideridae, Vespertilionidae, and Rhinolophidae (Figure 3). Wildlife surveillance efforts were also largely focused on rodents; the majority of which were farm raised bamboo rats (*Rhizomys sinensis*).

![Figure 2. Sites where PREDICT conducted virus surveillance in wildlife taxa at high-risk disease transmission interfaces between wildlife and humans.](image)

![Figure 3. Number of animals sampled by taxa.](image)
Table 1. Number of animals sampled according to targeted transmission interfaces.

<table>
<thead>
<tr>
<th>Interface</th>
<th>Rodents and Shrews</th>
<th>Bats</th>
<th>Other Taxa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agricultural settings</td>
<td>144</td>
<td>572</td>
<td>4</td>
</tr>
<tr>
<td>Ecotourism and recreational activities</td>
<td>0</td>
<td>1303</td>
<td>4</td>
</tr>
<tr>
<td>Extractive industries</td>
<td>0</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>In or near human dwellings</td>
<td>7</td>
<td>694</td>
<td>0</td>
</tr>
<tr>
<td>Hunted wildlife</td>
<td>0</td>
<td>174</td>
<td>0</td>
</tr>
<tr>
<td>Markets</td>
<td>64</td>
<td>0</td>
<td>127</td>
</tr>
<tr>
<td>Wildlife preying on livestock or their food</td>
<td>93</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Farmed wildlife</td>
<td>247</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pristine habitat</td>
<td>182</td>
<td>235</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>737</strong></td>
<td><strong>3061</strong></td>
<td><strong>146</strong></td>
</tr>
</tbody>
</table>

**Human Disease Surveillance**

PREDICT-China monitored viral pathogens at high-risk animal-human interfaces and also conducted syndromic disease surveillance. In collaboration with regional Centers for Disease Control and Prevention, PREDICT recruited 1,312 human participants at 12 prefecture-level locations throughout Guangdong Province. Subsequently, serosurveillance was conducted to assess exposure to SARS coronavirus, hantavirus, Ebolavirus, and bunyavirus. Supplemental serological assays were also conducted for leptospirosis, brucellosis, and three types of rickettsial diseases: scrub typhus, spotted fever, and typhus. The PREDICT China team worked jointly with experts at the Yale Occupational and Environmental Medicine Program (YOEMP) to investigate the correlation between specific human practices and infection or transmission of zoonotic disease pathogens. In addition, specimens collected from people with influenza-like illness (ILI) were tested with PREDICT protocols for influenza A and various other viruses associated with ILI symptoms: coronaviruses, paramyxoviruses, hantaviruses, henipaviruses, and arenaviruses.

Additional human disease surveillance investigating acute syndromes, including encephalitis/meningitis, hemorrhagic fever, and fever with thrombocytopenia was conducted through collaborative networks that encompassed prefecture level CDCs and sentinel hospitals. Supported by nine participatory hospitals in Guangdong Province, over 169 samples were collected for this effort. Most samples were collected from prefecture level CDCs and sentinel hospitals within Guangdong Province, although additional samples were obtained from extended regional collaboration with Jiangsu Provincial CDC illustrating the broad interest generated by the PREDICT work in-country.

**Disease Outbreak Response and Preparedness**

During the H7N9 outbreak, PREDICT facilitated establishment of a Guangdong One Health H7N9 Task Force to improve coordination of surveillance and disease outbreak response efforts among human and animal health sectors in China. PREDICT also provided support to the Influenza Surveillance network in Guangdong Province, which consists of sentinel hospitals and prefecture-level CDCs. Samples were collected from individuals with serious acute respiratory infections and ILI for testing using PREDICT laboratory protocols. Environmental and fecal samples were also collected from wet markets and poultry markets where live birds are sold.
PREDICT team members assisted with testing of wild bird samples obtained from rural areas of Guangdong Province in collaboration with the Ministry of Forestry. Our team’s involvement in disease outbreak investigations fostered partnership and trust between PREDICT and key stakeholders in the human and animal health sectors in China and served as a case study of an international One Health response to an emerging disease outbreak in China. PREDICT-China’s partners viewed this collaboration as a successful pilot for future international engagement with US partners, particularly during outbreak scenarios.

PREDICT CHINA PUBLICATIONS
PREDICT investigators in China have led and lent support to a number of manuscripts that have been published in peer-reviewed journals. These publications highlight PREDICT’s contributions to characterizing important zoonotic viruses circulating in wildlife and people in Asia (see Highlights of PREDICT Publications section for details).


REFERENCES


