Am. J. Trop. Med. Hyg., 87(6), 2012, pp. 965–971
doi:10.4269/ajtmh.2012.12-0074

Perspective
Capacity Building in Response to Pandemic Influenza Threats: Lao PDR Case Study

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Abstract. The Lao People's Democratic Republic (PDR) committed to pandemic detection and response preparations when faced with the threat of avian influenza. Since 2006, the National Center for Laboratory and Epidemiology of Lao PDR has developed credible laboratory, surveillance, and epidemiological (human) capacity and as a result was designated a World Health Organization National Influenza Center in 2010. The Lao PDR experience in building influenza capacities provides a case study of the considerable crossover effect of such investments to augment the capacity to combat emerging and re-emerging diseases other than influenza.

BACKGROUND

The pandemic potential of highly pathogenic avian influenza (HPAI), and in particular avian influenza virus subtype H5N1,[1] provided the backdrop to an unprecedented global investment in critical preparedness capacities worldwide to combat this emerging disease threat.

In Southeast Asia, considerable differences within and between countries existed in laboratory, surveillance, and outbreak response capacities when H5N1 made its regional mark in 2004. The World Health Organization National Influenza Center (WHO NIC) designation was conferred in the Lower Mekong region as early as 1972 when Thailand was designated a NIC, followed by Vietnam, Cambodia, and Myanmar in 2005, 2006, and 2008, respectively; reflecting recognition of laboratory, surveillance, and outbreak investigative competencies in the region.

First recognized in 1996,[2] H5N1 virus outbreaks in poultry/bird are generally sporadic, with defined seasonal patterns and established endemicity in some countries, e.g., Egypt, Republic of China, Vietnam, and Bangladesh.[3,4] Worldwide, there have been 7,030 avian outbreak reported through July 2011, 60% of which have occurred in Southeast Asia and 56% from the Lower Mekong Region (i.e., Cambodia, Lao People's Democratic Republic (Lao PDR), Myanmar, Thailand, and Vietnam).[5] In Lao PDR, 19 outbreaks of H5N1 virus infection in poultry populations have been documented since 2004, representing eight "waves" of HPAI outbreak occurrence that were temporally and spatially distinct.

The imperative to mobilize international resources in preparing for a H5N1 threat was pragmatically embraced by the Government of Lao PDR (GOL). Although human infection is uncommon, the high human case fatality rates observed from the region, ranging from 50% in Vietnam to 82% in Indonesia,[6] only added to the urgency of advancing credible detection and response capabilities. The pace of pandemic preparedness quickened in February 2007, when seven (out of nine) districts in Vientiane Capital were flagged for H5N1 poultry outbreaks, with two associated human deaths.

The following report describes the Lao national commitment and experience in preparing for and responding to the H5N1 crisis and how the capacity building measures enabled the Government of Lao PDR to successfully mitigate the impact of the 2009 influenza pandemic attributed to A(H1N1)pdm09, and to attain WHO NIC designation of the National Center for Laboratory and Epidemiology (NCLE) in August 2010. Moreover, the generic quality of influenza oriented investments described, framed by the WHO Asian Pacific Strategy for Emerging Diseases (APSED),[7] measurably contributed in the strengthening of WHO International Health Regulations (IHR) core capacity requirements for detection and response in Lao PDR. And although the International Community partnered with the GOL in contributing toward a wide range of multi-sector preparedness actions, the capacity building measures described in this report (with the exception of Institutional Mechanisms) amounted to an estimated four million U.S. dollars over 6 years: 2006 thru 2011.

Institutional mechanisms established to build capacity. The unprecedented assistance by the International Partner Community in advancing pandemic preparedness efforts was a catalyst for the creation of a national coordinating entity in May 2006: National Avian and Human Influenza Coordinating Office (NAHICO). By virtue of its organizational affiliation falling under the Prime Minister's Office, NAHICO was well placed to manage coordination between: 1) multi-sector interests like human and animal health, and 2) the GOL and the International Partner Community. As pandemic threats evolved from H5N1 to A(H1N1)pdm09 to future as yet unknown disease entities, so too did NAHICO, to the National Emerging Infectious Disease Coordinating Office (NEIDCO) in May 2009.

Strategic influenza investments in public health laboratory detection, targeted surveillance, and outbreak response. In support of establishing viable capabilities in fulfilling National institutional pandemic preparedness functions and responsibilities, NCLE convened an International Forum in October 2007 with development partners, principally from the WHO-United

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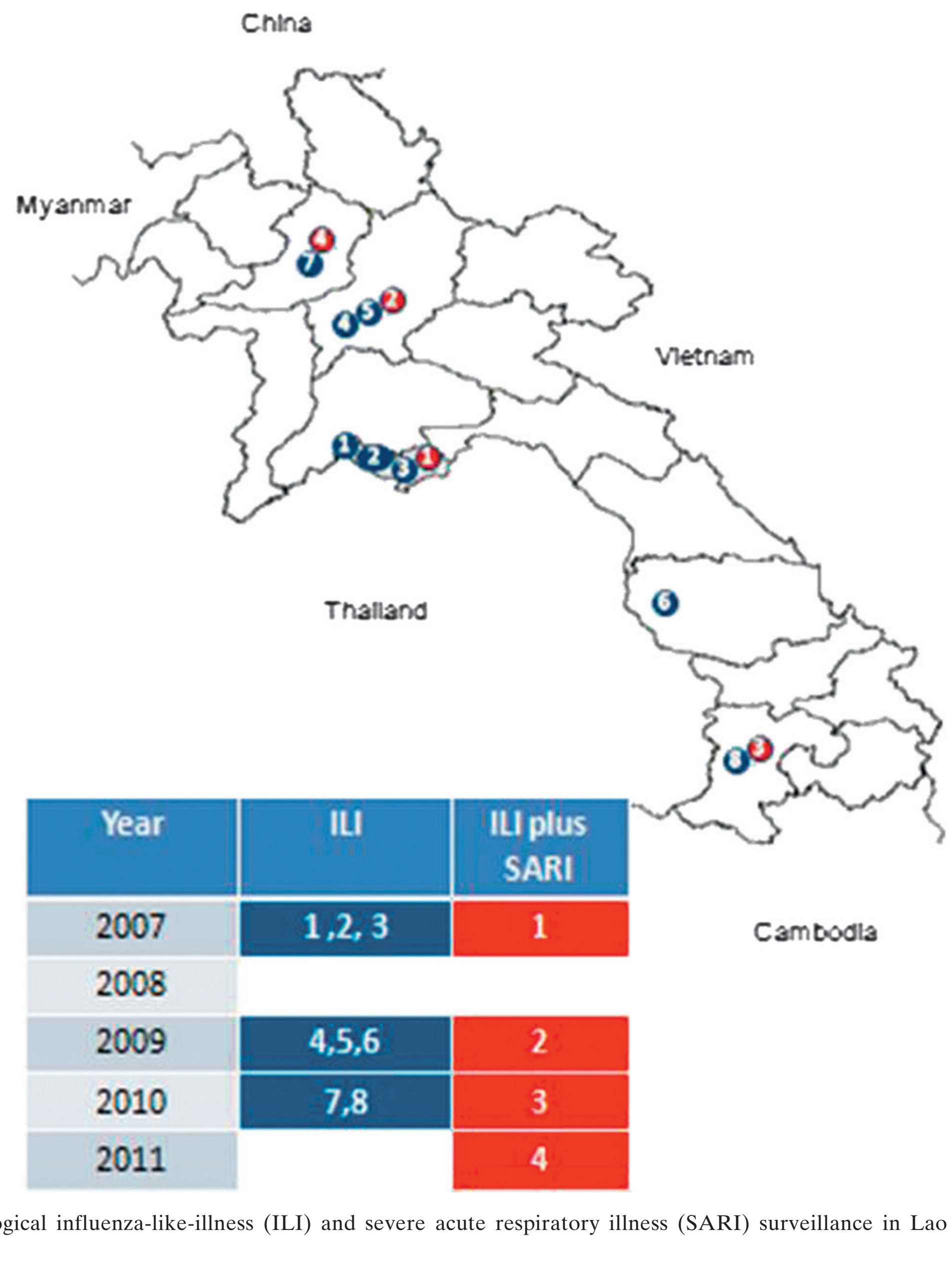
States Centers for Disease Control and Prevention (WHO-USCDC) Lao Collaboration, with the intent of developing a *roadmap toward NIC designation*.

1. Public health laboratory detection. Early recognition of the H5N1 virus in human clusters is critical in managing the potential of viral reassortment, through a prompt response leading to containment. In Laos, however, the absence of laboratory detection capabilities precluded confirmation of suspected cases and initiating targeted virological influenza surveillance. Challenges included: 1) few (N = 5) trained National Laboratory Staff, 2) no existing conventional or real-time (r)-polymerase chain reaction (PCR) capabilities, 3) an absence of systems' management for laboratory procurement and material inventory, 4) no bio-medical equipment expertise, 5) lack of a bio-safety program or practice, 6) no organized routine training, 6) absence of a system of quality assurance, and 7) a 60-year-old facility originally built to house nuns that had been converted to support National Public Health functions. The imperative to move quickly in advancing diagnostic capacity was further appreciated because surveillance and timely detection of H5N1 in humans could not be initiated without credible in-country diagnostic testing capabilities.

Critical to the success of introducing new diagnostic technologies through equipment procurement and laboratory bio-safety enhancements was the use of long-term, on-site foreign expertise to provide for ongoing training, oversight, and quality standards, under the auspices of the NCLE. The placement and integration of technical experts at NCLE from international organizations like USCDC and Institute Pasteur greatly contributed to repeated successes in adopting and adapting new laboratory strategies.

The timeline in developing laboratory detection capabilities for influenza began with the start-up of conventional PCR testing in October 2006. Follow-up training in January and



Year	ILI	ILI plus SARI
2007	1,2, 3	1
2008		
2009	4,5,6	2
2010	7,8	3
2011		4

FIGURE 1. Virological influenza-like-illness (ILI) and severe acute respiratory illness (SARI) surveillance in Lao PDR: temporal and spatial mapping.

February 2007 allowed for the first recognized human H5N1 laboratory detection, with conventional PCR expert assistance from USCDC during in-country training that coincided with the February 2007 H5N1 outbreak in Vientiane Municipality. To date other notable accomplishments include: 1) participation in the WHO External Quality Assurance Program EQAP (March 2007), 2) rPCR and cell culture training and practice (February 2009), and 3) isolation of the first influenza viruses in Lao PDR (July 2009). Laboratory advances allowed NCLE to begin contributing to the WHO Global Influenza Surveillance and Response System (GISRS) in May 2007, and the WHO FLUNET in November 2010.

From 2008 through December 2011, 294 (15 in 2008, 133 in 2009, 42 in 2010, and 104 in 2011) influenza samples and viral isolates have been submitted through the WHO GISRS, principally to National Institute for Infectious Diseases (NIID), Tokyo, Japan, and USCDC (Atlanta, GA). Partial genomic sequencing and hemagglutination inhibition assay have led to characterization of six different circulating virus strains during this period.

The validity of testing accuracy through the WHO EQAP in collaboration with the Center for Health Promotion (Hong Kong) from 2007 to 2011 is reflected in steady proficient qualitative competence ratings: 90–100% for conventional PCR (March 2007–July 2008) and 80–100% for rPCR (Feb 2009–July 2011). The quantity of clinical specimens tested varied yearly, with a high of 2,304 in 2009, a 5-fold increase from 2008 (N = 462) reflecting pandemic influenza occurrence, and would have been higher had not laboratory supply constraints forced changes that resulted in more selective testing criteria.

New diagnostic technologies continue to be introduced, including sequencing capabilities for in-country phylogenic evolution analysis of A(H1N1)pdm09 and H5N1 gene sequences. Notable is a single molecular sequencing platform that will be shared using expertise from both human (NCLE) and animal (National Animal Health Center [NAHC]) health laboratories to make best use of critical and scarce human resource demands with the introduction of new laboratory technologies. This "marriage" has contributed to realization of the WHO inspired "one health" approach driving human and animal health sector cooperation in responding to zoonotic diseases.

Challenges to laboratory diagnostic advancement in Laos continue to demand innovative approaches and multi-sectoral cooperation. The requirement for red blood cells for cell culture work and absence of animal facilities affiliated with either human or animal health laboratories required procurement, breeding, and bleeding arrangements of domestic turkeys, by NAHC, for NCLE. The implementation of systems' intended to support laboratory functions, like quality assurance, bio-safety, and procurement and inventory, have lagged behind diagnostic advancements.

2. Surveillance. Before recognition of the pandemic H5N1 threat, national surveillance efforts were fragmented into a few vertical programs in addition to a routine reporting system based on clinical presumptive diagnoses. Additionally, a syndromic real-time electronically driven "early warning outbreak recognition system" (EWORS) was operating in selected Hospitals. The use of EWORS was however severely limited because it was managed under the Laboratory Branch of NCLE; data were not shared with the Epidemiology Unit responsible for acting upon outbreak alerts, and therefore not acted upon.

Newly established laboratory Influenza diagnostic capabilities encouraged a focus on respiratory illnesses compatible with pandemic and seasonal influenza through the creation of a virological sentinel surveillance network, beginning in 2007; before this year, there was little information regarding

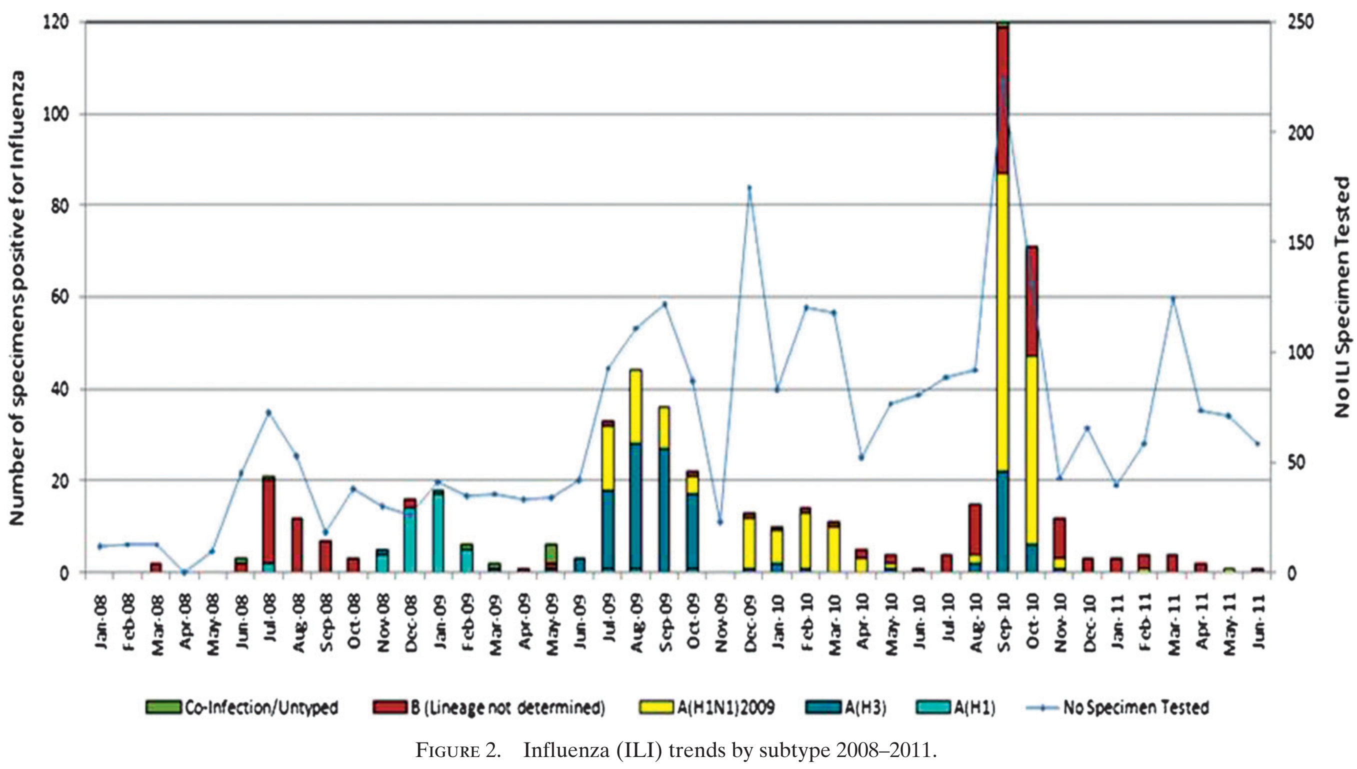


FIGURE 2. Influenza (ILI) trends by subtype 2008–2011.

the disease burden of influenza, or recognition of seasonality.[8] Figure 1 highlights the geographical extent and year of implementation of surveillance for influenza-like-illness (ILI) and severe acute respiratory illness (SARI). New ILI and SARI hospital surveillance sites now cover the central, north and south of country. The power of this network for monitoring the changing patterns of circulating influenza subtypes is depicted in Figure 2.

The National Routine Disease Surveillance System (NRDSS) was challenged early on in the H5N1 crisis to become more responsive in recognizing human cases and unusual case clustering of respiratory illnesses. The transformation of a faxed/phone based "system" to an electronically driven LAO early warning and response network (EWARN) provided for more timely and accurate reporting, with reporting managed by local public health authorities. Since going operational in late 2009, Lao EWARN has expanded from 33 to 144 Districts in all 17 Lao Provinces. Findings shown in Figure 3 reflect the sensitivity of the network in recognizing seasonal trends in acute respiratory illness (ARI) and the impact of pandemic H1N1 in 2009, showing a dramatic increase from 2,657 to 5,779 to 7,176, in 2007, 2008, and 2009, respectively.

Trends in ARI from EWORs show a strong correspondence with seasonal and pandemic occurrence found in Lao EWARN (Figure 3), notwithstanding differences in how cases are captured: EWORS reflecting the aggregate of ILI Syndromes (Fever/Cough, Fever/Cough/Sore Throat, and Fever/Cough/Difficulty Breathing); and Lao EWARN using a Severe Acute Respiratory Infection case definition. In early 2011, EWORS oversight responsibilities were re-organized to improve outbreak recognition and response utility, and facilitate the eventual integration with Lao EWARN in realizing surveillance efficiencies and avoiding duplicative actions. Since 2007, 28 Lao EWARN and no EWORS outbreak alerts have been investigated (Table 1).

The lack of local, village-based reporting mechanisms fueled the need for a more community oriented, event-based surveillance approach. With over 70% of the population residing in rural areas,[9] the H5N1 threat forced the creation of simple toll free reporting "hotlines." Managed by NEIDCO, with monitoring and evaluation databases, the total number of calls for both reporting and requesting information purposes rose from 1,010 in 2008 to 27,593 in 2009, and then fell to 10,111 calls in 2010. The dramatic rise in 2009 call-ins reflects public awareness and concerns during the influenza pandemic (Figure 4). In humans, one respiratory outbreak of Influenza A/H1 was recognized in 2008 and of A(H1N1)pdm09 in 2010 by "hotline" functions. During the 2009 influenza pandemic, no human clusters documenting A(H1N1)pdm09 "community transmission" were identified through "hotline" notifications, and in only one instance was a respiratory outbreak identified through this reporting mechanism (Table 1). However, HPAI H5N1 outbreaks were reported in poultry through "hotline" communications: one in 2008 and one in 2010.

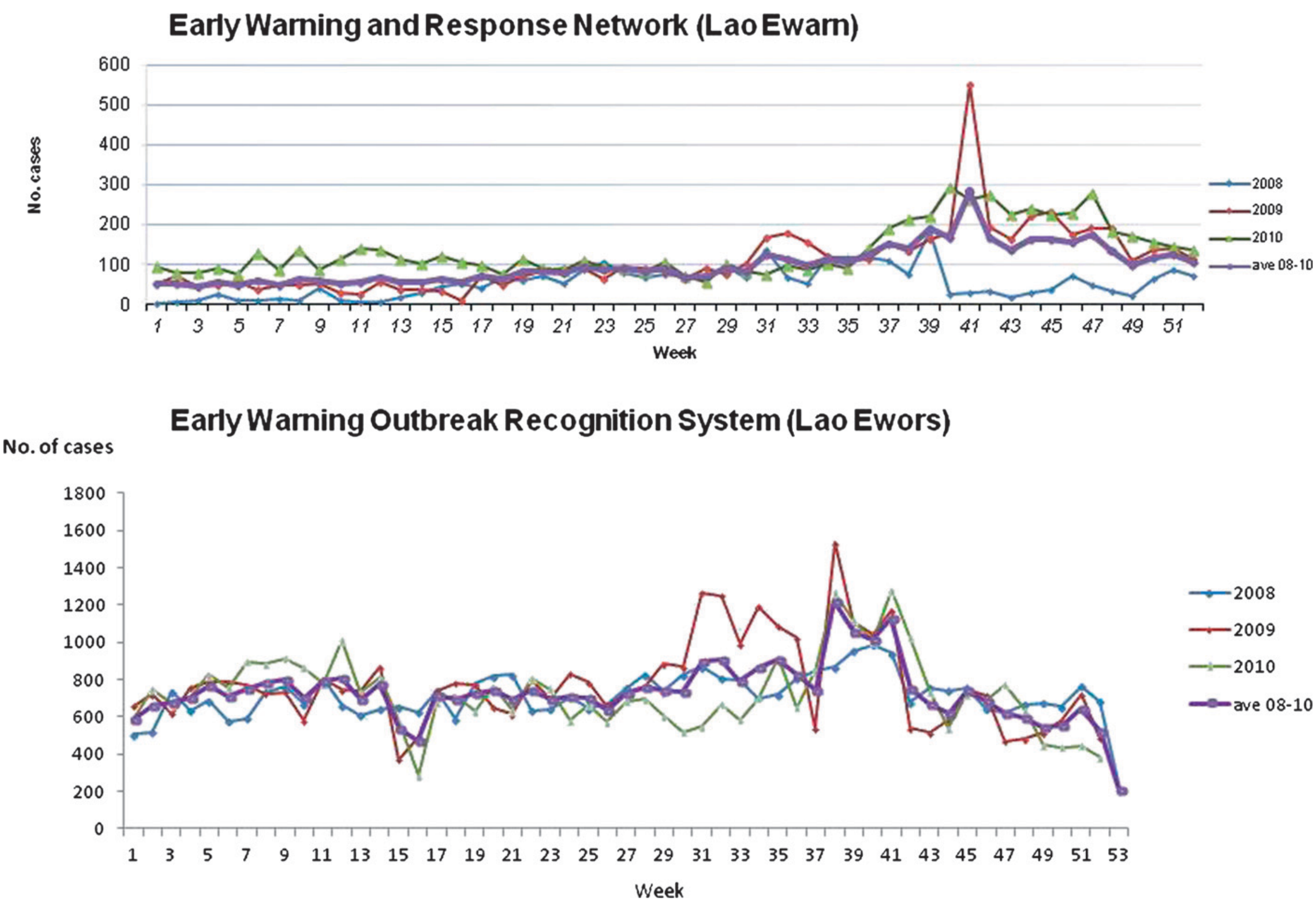


FIGURE 3. Comparison of Lao early warning and response network (EWARN) acute respiratory illness (ARI) and Lao early warning outbreak recognition system (EWORS) (ILI) surveillance findings, 2008–2010.

Table 1
Human respiratory outbreak/cluster recognition, by surveillance mechanism, 2003 thru 2010*

Year	LAO EWARN H1	PH1N1	H3	FLU B	Other	Unknown	**Total**
2003							
2004							
2005							
2006							
2007						1	**1**
2008	2						**2**
2009		12	4		1		**17**
2010		5		3			**8**
Total	**2**	**17**	**4**	**3**	**1**	**1**	**28**

Year	LAO EWORS H1	PH1N1	H3	FLU B	Other	Unknown	**Total**
2003							
2004							
2005							
2006							
2007							**0**
2008							**0**
2009							**0**
2010							**0**
Total	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Year	Hotline H1	PH1N1	H3	FLU B	Other	Unknown	**Total**
2003							
2004							
2005							
2006							
2007							**0**
2008					1		**1**
2009							**0**
2010							**0**
Total	**0**	**0**	**0**	**0**	**1**	**0**	**1**

Year	Other† H1	PH1N1	H3	FLU B	Other	Unknown	**Total**
2003							
2004							
2005							
2006							
2007					1		**1**
2008							**0**
2009			1				**1**
2010							**0**
Total	**0**	**0**	**1**	**0**	**1**	**0**	**2**

Year	Total H1	PH1N1	H3	FLU B	Other	Unknown	**Total**
2003							
2004							
2005							
2006							
2007	0	0	0	0	1	1	**2**
2008	2	0	0	0	1	0	**3**
2009	0	12	5	0	1	0	**18**
2010	0	5	0	3	0	0	**8**
Total	**2**	**17**	**5**	**3**	**3**	**1**	**31**

*LAO EWARN = Lao early warning response network; LAO EWORS = Lao early warning outbreak recognition system.
†Others refer to hospital recognized case reported directly to the Ministry of Health.

3. Response to outbreak/cluster recognition. The importance attributed to timely verification and follow-up of suspect H5N1 cases in identifying possible "human clusters," led to a "train-the-trainer" approach using internationally adapted guidelines[10] in the creation of "rapid response teams" in all 17 Provinces, commensurate with significant decentralization of outbreak resources and responsibilities.

Before 2007, there were no investigations of outbreaks involving "respiratory" illness. During 2007–2011), 31 outbreaks or clusters have been recognized and investigated (Table 1). This dramatic change was largely attributable to three factors: 1) "first time" laboratory diagnostic capacity put in place to detect respiratory pathogens, 2) an appreciation of the H5N1 threat and potential pandemic ramifications, and 3) the 2009 influenza pandemic. During the pandemic, early containment through close-contact follow-up investigations may have slowed the spread of the virus early on, allowing for more lead time between "containment" and "mitigation" phases. Moreover, newly established guidelines have been developed and adopted to insure complete and timely responses to outbreak reports: within 24 hours.

Responding to critical human resource limitations. Findings from an assessment commissioned by the WHO-USCDC Lao Collaboration of Ministry of Health Human Resources were highlighted during a December 2007 meeting intended to map out public health staffing needs, with an emphasis on satisfying anticipated laboratory, surveillance, and outbreak response demands. Critical shortages in skilled public health practitioners in the provinces shaped a strategy to decentralize capabilities from the national level, through the creation of a Field Epidemiology Training (FET) Initiative. The purpose was to develop a cadre of technically capable public health professionals networked throughout the country who could manage surveillance and outbreak response efforts locally. Furthermore, Lao FET was designed to promote the "one health" principle, with students from human and animal disease sectors.

Lao FET was organized to accommodate provincial staffing with little public health training, Lao (only) language skill, against a backdrop of critical human resource shortages. Candidates work through 3-onth training modules over the year-long Lao FET experience, each consisting of practical classroom instruction and project driven field practicums that include strengthening of the national surveillance system and significant exposure to outbreak investigations.

A notable benefit of Lao FET beyond the current nationwide network of alumni, now numbering 23, is the addition of qualified manpower at the disposal of NCLE to conduct investigations of outbreaks caused by influenza as well as other pathogens, pandemic containment, and mitigation, and project driven field studies and activities that have led to tangible public health contributions. These include: 1) measures of adverse events following immunizations (AEFI) following pH1N1 vaccine receipt, 2) expansion and improvements of ILI and SARI surveillance, and 3) investigation of seasonal influenza as an outbreak phenomenon.

The spillover – beyond influenza. The collateral impact of the influenza investment in advancing overall public health capacity in Lao PDR has been pronounced. The investment strategy articulated by the GOL, although remaining influenza focused, continues to be generic in approach. For example, support for investigation of a febrile disease outbreak assists responders in dealing with seasonal, avian, and pandemic

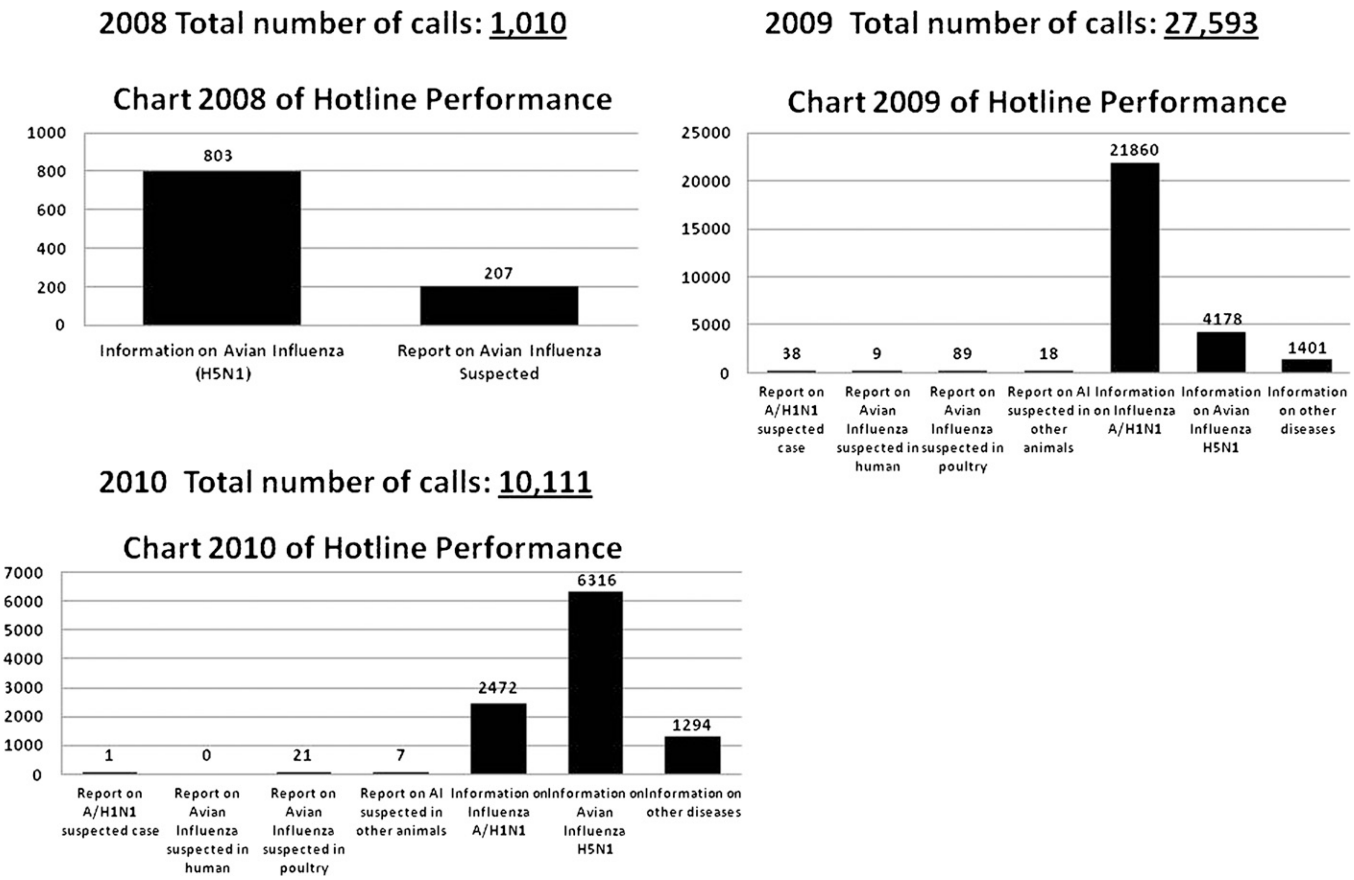


FIGURE 4. Hotline reporting functions: 2008–2010.

influenza threats. New influenza capabilities have been easily adapted to contribute to laboratory detection of other pathogens, surveillance, and outbreak response capabilities; these factors have enabled the country to fulfill its IHR commitments.

Laboratory detection. Real-time PCR testing capacity, instituted in 2009, was adapted for use in anthrax and facilitated detection of human cases for the first time during an outbreak in 2009. Furthermore, this outbreak in the south of Lao PDR was recognized as a result of a FET led investigation, which had been started with influenza investments to address critical human resource shortages. In August 2008, conventional PCR (established in October/November 2006 and used in detection of the two Lao H5N1 cases in March 2007) enabled Lao recognition for the first time of circulating dengue serotypes during epidemic conditions.

Surveillance. Lao EWARN has greatly enhanced early outbreak recognition since 2008, as evidenced by outbreak alerts for epidemic cholera (2009) and dengue (2010). Importantly, before the reworking of NRDSS into Lao EWARN, the haphazard nature of reporting did not have features needed to support early outbreak recognition, including timely automated recognition of syndromic events (for lack of strong clinical and laboratory capacity) and rapid data interpretation. Hotline reporting has also shown a fledgling trend toward more non-avian and pandemic calls: 5% in 2009 and 15% in 2010 (Figure 4).

Outbreak response. The absence of outbreak documentation before 2007 prevents comparison of outbreak-related actions with later years. Nevertheless, the number of respiratory and other outbreak investigations since 2008, is notable (Figure 5). Outbreak findings have led to recognition of Japanese Encephalitis virus and human anthrax. In addition to dengue and cholera, outbreaks of leptospirosis, diphtheria, and measles were verified, investigated, and contained. It is no coincidence that the increase in the number of outbreak investigations coincided with the start-up of Lao FET in 2009.

The Lao FET field work has led to important evidence driven findings that include: figures of rubella susceptibility among woman of child-bearing age; and anthrax knowledge, attitudes, and practices among human and animal health workers.

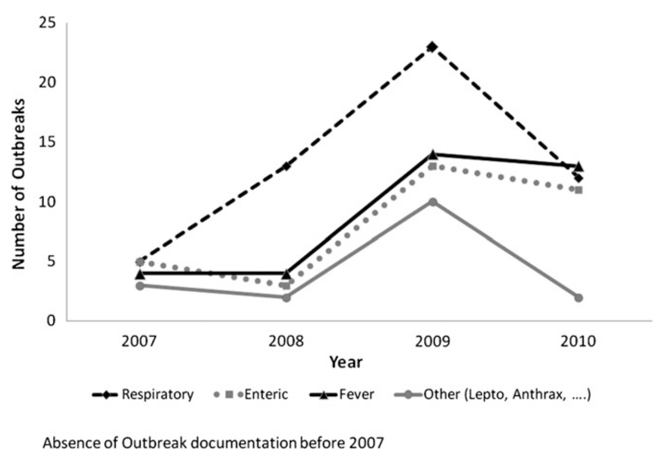


FIGURE 5. Number of outbreak investigations 2007–2010.

Newly established public health capabilities have given rise to research opportunities, from outbreak mapping and recognition of newly emerging infectious disease threats, to phylogenic evolutionary profiling through genomic sequencing of such viral diseases as measles and rabies.

DISCUSSION

Rarely do disease threats present the kind of investment opportunity as did that associated with the emergence of HPAI H5N1 Influenza. The GOL and international partners were able to seize attention and funding focused on influenza to formulate a roadmap with clearly outlined measures leading to detection and response capabilities commensurate with both NIC designation, and a broader IHR agenda.

The Lao example lends credibility to an investment strategy in capacity building that is disease focused, and yet sufficiently generic to be applied in combating a range of emerging diseases. There are few examples of vertical disease programs having had such a dramatic impact on preparedness and response as has the threat of pandemic influenza, owing in large measure to the historical record and perspective, e.g., the Spanish Influenza Pandemic of 1918.[11,12]

Pandemic H5N1 pandemic preparations outlined in this report allowed for 1) immediate diagnostic recognition marking the introduction of A(H1N1)pdm09 into Lao PDR, 2) capable epidemiological investigations of case clusters reflecting "community transmission," and 3) established and on-going ILI and SARI Surveillance that facilitated "trending" of the pandemic: all contributing to GOL decisions on resource allocations and mitigation actions. Indeed, transitioning from enhanced surveillance to containment to mitigation to recovery using WHO guidance for (2009) Global Pandemic Phases was contingent on those capacities put into practice in Lao PDR.[13]

Moreover, the pace of nominally general public health investments was accelerated exponentially caused by reassortment fears of HPAI H5N1. And yet the Lao experience in successfully transforming such investments into practice can be attributed, uniquely so, to national coordination efforts through the establishment of an entity (NAHICO) empowered with the authority to force action.

CONCLUSION

The greatest challenge in realizing influenza (and other) detection and response capacity gains made in the last 5 years is the sustainability of an otherwise fragile system. Complacency in the absence of a pandemic threat is inevitable, anywhere. And yet a Lao PDR armed with an array of new capabilities is poised to leverage their influenza investments in fulfilling their IHR commitments and contribute to regional bio-security efforts.

Received January 31, 2012. Accepted for publication May 7, 2012.

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