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Original Article

Surveillance of Influenza in Indonesia, 2003–2007

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Background Longitudinal data are limited about the circulating strains of influenza viruses and their public health impact in Indonesia. We conducted influenza surveillance among outpatients and hospitalized patients with influenza-like illness (ILI) across the Indonesian archipelago from 2003 through 2007.

Methodology Demographic, clinical data, and respiratory specimens were collected for 4236 ILI patients tested for influenza virus infection by RT-PCR and viral culture.

Principal Findings Influenza A and B viruses co-circulated year-round with seasonal peaks in influenza A virus activity during the rainy season (December–January). During 2003–2007, influenza viruses were identified in 20·1% (4236/21 030) of ILI patients, including 20·1% (4015/20 012) of outpatients, and 21·7% (221/1018) of inpatients. One H5N1 case was identified retrospectively in an outpatient with ILI. Antigenic drift in circulating influenza A and B virus strains was detected during the surveillance period in Indonesia. In a few instances, antigenically drifted viruses similar to the World Health Organization (WHO) vaccine strains were detected earlier than the date of their designation by WHO.

Conclusions Influenza A and B virus infections are an important cause of influenza-like illness among outpatients and hospitalized patients in Indonesia. While year-round circulation of influenza viruses occurs, prevention and control strategies should be focused upon the seasonal peak during rainy season months. Ongoing virologic surveillance and influenza disease burden studies in Indonesia are important priorities to better understand the public health impact of influenza in South-East Asia and the implications of influenza viral evolution and global spread.

Keywords Indonesia, influenza, surveillance.

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Introduction

While the disease burden and seasonality of influenza virus activity in temperate regions of the Northern and Southern Hemispheres have been well characterized with clear peaks during winter months,[1,2] such data are limited for developing countries with tropical and subtropical climates.[3] Recent studies suggest that South-East Asia is an important region in the global ecology and evolution of influenza viruses.[4,5] The ongoing epizootic of highly pathogenic avian influenza A (H5N1) virus among poultry with sporadic transmission to humans further highlights the importance of influenza virus surveillance and response measures in South-East Asia.[6,7]

In tropical and subtropical developing countries, influenza is often under-diagnosed and the disease burden and clinical severity are under-estimated.[3] However, recent studies have revealed that influenza virus infections in tropical climate countries, including in South-East Asia, cause similar severity and disease burden as in temperate countries.[8,9] Beginning in 2003, a widespread, ongoing epizootic of highly pathogenic avian influenza A (H5N1) virus has impacted poultry in Indonesia. First detected in 2005, sporadic H5N1 virus transmission to humans has resulted in high mortality.[7] Since H5N1 virus infection can also cause severe influenza-like illness (ILI) among exposed persons, virologic surveillance is needed to understand the relative impact of H5N1 virus and seasonal influenza A and B viruses among persons with ILI in Indonesia.

Influenza surveillance was implemented among outpatients at six sentinel sites in three districts in Java, Indonesia between September 1999 and January 2003.[10] In this

report, we describe the findings of expanded influenza surveillance at additional sites across the Indonesian archipelago, including among hospitalized patients, during 2003–2007.

Methods

Surveillance sites

We conducted surveillance for influenza-like illness (ILI) among patients seeking care at primary health centers (outpatients) and hospitals (outpatients and inpatients) across Indonesia during January 2003 to December 2007. The number of participating facilities expanded from five sentinel sites in five districts in 2003–22 sites in 18 districts in 2004–2005 and 48 sites (28 outpatient sites at primary health care centers and hospitals, and 20 inpatient sites) in 26 districts in 2006–2007, covering 22 of 33 Indonesian provinces (Figure 1).

Surveillance methods

Patients' enrollment and specimen collection

We enrolled patients who presented at primary health centers (outpatients) and hospitals (outpatients and inpatients) who met the inclusion criteria of ILI, defined as a measured axillary temperature of ≥37·8°C or history of feverishness, and either cough or sore throat without any other diagnosis. Among patients meeting the ILI case definition, a convenience sample of up to 20 ILI cases per week was enrolled. Clinicians or trained nurses obtained demographic data and clinical symptoms, performed physical examinations, and collected nasal and throat swabs from enrolled ILI cases. Swab specimens were placed into sterile Hanks' balanced salt solution (HBSS) viral transport media (VTM) that contained gelatin, 100 U/ml penicillin, 100 μg/ml streptomycin, and 25 U/ml mycostatin. Specimens were refrigerated (4°C) and shipped weekly to laboratories in Jakarta for testing. Specimens from suspected H5N1 patients were shipped to laboratories in Jakarta within 24 hours of collection for urgent H5 testing.[6]

Laboratory evaluation

From 2003 to September 2005, all respiratory specimens were tested for influenza viral RNA by conventional reverse transcription polymerase chain reaction (RT-PCR) assay. The QIAamp Viral RNA kit (QIAGEN, Valencia, CA, USA) was used to extract viral RNA from prepared samples. Samples were assayed using multiplex nested reverse transcription RT-PCR (MnRT-PCR) to detect human influenza viral RNA. In the MnRT-PCR, viral RNA was amplified utilizing cocktails of oligonucleotide primers[11] directed collectively against the matrix protein (MP), hemagglutinin (HA), and neuraminidase (NA) genes for influenza A (H1N1) and A (H3N2) viruses, and the MP and HA genes for influenza B virus. Primers targeting H5 were not included in the nested MnRT-PCR. Amplicons were separated by electrophoresis on 2% agarose gel containing ethidium bromide for virus type and sub-type identification. Positive specimens were inoculated into Madin–Darby canine kidney (MDCK) tissue cells for viral isolation.

Beginning in October 2005, all specimens were first screened for influenza A (H5) viral RNA using real-time RT-PCR (rRT-PCR) as described below. Negative H5 specimens were tested for influenza A (H1N1) (H3N2) and influenza B viral RNA using conventional RT-PCR as described above. Specimens testing positive for seasonal influenza A or B viruses were placed into MDCK tissue cells for viral isolation. Virus isolates were characterized by hemagglutination inhibition (HAI) assay as previously

	Sumatera	Java	Kalimantan	Bali	Lombok	Sulawesi	Maluku	Timor	Papua	Total
Number of health facilities and (districts), by year										
2003	0	3(3)	0	1(1)	0	1(1)	0	0	0	5(5)
2004 – 2005	3(3)	9(5)	2(2)	1(1)	1(1)	2(2)	1(1)	1(1)	2(2)	22(18)
2006 – 2007	9(6)	23(8)	4(3)	1(1)	1(1)	4(2)	1(1)	1(1)	4(3)	48(26)
Total population, million										
	50·7	136·6	13·8	3·9	2·6	17·4	2·6	1	3·6	232·2

Figure 1. Location of Indonesia influenza surveillance sites (blue) and provinces with surveillence sites (red), 2003–2007.

described.[12] All influenza virus testing was performed at the National Institute of Health Research and Development, Ministry of Health (NIHRD, MoH), Indonesia, and U.S. Naval Medical Research Unit #2 (NAMRU#2), Jakarta, utilizing the same standard operating procedures. A convenience sample of approximately 45% of isolates was sent for confirmation and antigenic characterization at the World Health Organization Influenza Collaborating Center (WHO-CC) at the U.S. Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, periodically until mid-2006.

rRT-PCR assay

Starting in October 2005, all specimens were first screened for H5 by rRT-PCR. Ribonucleic acid (RNA) was extracted from nasal and throat swabs using QIAamp viral RNAmini kits (QIAGEN, Hilden, Germany) following the manufacturer's instruction and stored at −70°C. For detection of A (H5) viral RNA, rRT-PCR was initially conducted using an H5 primer set,[13] and then later in 2006, using primers and probes designed by the CDC to specifically recognize the subclade 2·1 viruses circulating among poultry with sporadic transmission to humans in Indonesia. One-step rRT-PCR was performed in a final volume of 25 μl containing 5 μl of extracted RNA, 12·5 μl of buffer mix and 0·5 μl Superscript III/Platinum Taq-Enzyme mix, 20 unit of RNase-out (Invitrogen, Carlsbad, CA, USA), 0·8 μm for each primer, and 0·2 μm of each probe. H5 cDNA positive controls were provided by the CDC and used to quantify each rRT-PCR assay. An ABI 7900 real-time thermocycler was used for all rRT-PCR reactions. The thermocycling parameters for all targets consisted of 50°C for 30 minutes, 95°C for 2 minutes, and 45 cycles with 95°C for 15 seconds, 55°C for 30 seconds.

Virus culture, isolation, and identification

For virus culture, a 0·2-ml aliquot of each specimen was inoculated onto MDCK cells that had been prepared in sterile 24-well plates, and resulting viruses were reacted with type-specific monoclonal antibodies as previously described.[14] To identify the strains, HAI assay was performed using turkey red blood cells. All isolates were tested against standard reference antisera, which were regularly updated by the CDC.

Data storage and analysis

Questionnaires consisting of demographic, epidemiology, and clinical data, along with laboratory data (RT-PCR and virus isolation results) and available climate data (rainfall, temperature, and relative humidity provided by the Climatology, Meteorology, and Geophysics Agency, Jakarta, Indonesia) from 18 districts were entered into an Access (Microsoft, Bellevue, WA, USA) database. Data were analyzed using Stata software (Stata Corporation, College Station, TX, USA). Chi-squared test was used for comparison between two proportions of categorical data. Non-parametric tests were used to assess the correlation between numerical and proportional data.

Human subjects approval

The protocol was approved by the ethical research committees at NIHRD and NAMRU# 2 (DoD protocol 1999-30849).

Results

During the 5-year surveillance period, a total of 21 030 participants, including outpatients (n = 20 012) and inpatients (n = 1018), who presented to surveillance sites with ILI were enrolled. The median age of participants was 17 years (mean age, 21·1 years; range, 1 month to 90 years). Among all participants, 1851 (8·9%) were aged <2 years, 2936 (14·1%) were 2–4 years, 4435 (21·3%) were 5–12 years, 1220 (5·9%) were 13–17 years, 8589 (41·3%) were 18–49 years, 1413 (6·8%) were 50–64 years, and 359 (1·7%) were 65 years and older (Table 1).

Overall, 20·1% (4236/21 030) of ILI cases throughout the study period tested positive for influenza viruses. The proportion of ILI cases that tested positive for influenza viruses by age-group was highest in school-aged children (Table 1). The percentages of outpatients (20·1%) and inpatients (21·7%) testing positive for influenza viruses were similar. The proportion of seasonal influenza-associated pneumonia, diagnosed by clinicians based on clinical manifestations and chest radiography results, among hospitalized ILI cases sampled was 18% (23/128). Among all ILI cases that tested positive for influenza viruses, influenza A virus and influenza B virus were identified in 64·9% (2749) and 35·1% (1487) of cases, respectively. Among the influenza A viruses that were subtyped (n = 2314 viruses), 64·6% were identified as H3N2, 34·9% as H1N1, and 0·4% as H5N1.

The proportion of ILI cases that tested positive for influenza viruses per year was generally consistent throughout the study period and varied from 18·7% (in 2003) to 23·8% (in 2004). However, the proportion of ILI cases that tested positive for influenza viruses varied considerably across island sites, ranging from Bali (14·2%) and Timor (15·3%) to Papua (25·9%) and Maluku (26·6%). Across the surveillance sites, influenza viruses were detected year-round. The distribution of influenza virus types and influenza A virus subtypes varied temporally (Table 2).

All influenza viral isolates (n = 1264) were first characterized at NAMRU#2 and then a subset (n = 473 isolates from 2003 to mid-2006) was further characterized at CDC. In 2003, surveillance was conducted in five sites, and 111 influenza virus infections were identified; influenza A (H3N2) viruses predominated, followed by influenza B and

Table 1. Distribution of influenza specimens testing positive by RT-PCR (by type and influenza A subtype) by age groups, clinical setting, and location. 2003–2007

Factor	Total ILI patients tested	Influenza A not further sub typed		H1N1		H3N2		H5N1		B		Total	
		Positive	% positive	Positive	% positive	Positive	% positive	Positive	% positive	Positive	% positive	Positive	% positive
Age, years													
0–1	1851	50	2.7	24	1.3	47	2.5	0	0	56	3	177	9.6
2–4	2936	64	2.2	122	4.2	154	5.2	0	0	166	5.7	506	17.2
5–12	4435	110	2.5	228	5.1	278	6.3	2	0.05	499	11.3	1117	25.2
13–17	1220	32	2.6	52	4.3	102	8.4	2	0.2	125	10.2	313	25.7
18–49	8589	148	1.7	334	3.9	768	8.9	6	0.1	561	6.5	1817	21.2
50–64	1413	20	1.4	35	2.5	101	7.1	0	0	53	3.8	209	14.8
≥65	359	4	1.1	4	1.1	20	5.6	0	0	16	4.5	44	12.3
Clinical setting													
Inpatient	1018	3	0.3	49	4.8	86	8.4	9	0.9	74	7.3	221	21.7
Outpatient	20 012	432	2.2	759	3.8	1410	7.0	1	0.004	1413	7.1	4015	20.1
Sumatra	2456	59	2.4	132	5.4	167	6.8	1	0.04	188	7.6	547	22.3
Jawa	10 481	253	2.4	388	3.7	747	7.1	7	0.1	639	6.1	2034	19.4
Bali	1202	0	0	23	1.9	51	4.2	1	0.1	96	8.0	171	14.2
Lombok	849	1	0.1	28	3.3	101	11.9	0	0	71	8.4	201	23.7
Kalimantan	1392	40	2.9	43	3.1	81	5.8	0	0	130	9.3	294	21.1
Sulawesi	1768	77	4.4	43	2.4	89	5.0	1	0.1	116	6.6	326	18.4
Timor	816	1	0.1	36	4.4	52	6.4	0	0	36	4.4	125	15.3
Maluku	443	0	0	19	4.3	56	12.6	0	0	43	9.7	118	26.6
Papua	1623	4	0.2	96	5.9	152	9.4	0	0	168	10.4	420	25.9
Total	21 030	435	2.1	808	3.8	1496	7.1	10	0.05	1487	7.1	4236	20.1

A (H1N1) viruses. The most frequent strains identified were A/Fujian/411/2002-like H3N2, B/Hongkong/330/2001-like (B/Victoria/2/87 lineage, 2002–2003 Northern and 2003 Southern Hemisphere vaccine strain), and A/New Caledonia/20/99-like H1N1 (2002–2003 Northern and 2003 Southern Hemisphere vaccine strain) viruses. The number of surveillance sites expanded during 2004–2007. In 2004, A (H3N2) viruses also predominated, with A/California/7/2004-like H3N2, B/Sichuan/379/99-like, and A/New Caledonia/20/99-like H1N1 (2003–2004 Northern and 2004 Southern Hemisphere vaccine strain) viruses the most frequently detected strains. In 2005, influenza B viruses of the B/Victoria/2/87 lineage predominated and most viruses were related antigenically to the reference strain B/Ohio/05/2005. The frequency of circulating A (H3N2) viruses was slightly less than influenza B viruses and most were identified as A/California/7/2004-like. Influenza A (H1N1) viruses were detected at low frequency and all isolates were A/New Caledonia/20/99-like (2004–2005 Northern and 2005 Southern Hemisphere vaccine strain). In 2006, influenza A (H1N1), A (H3N2), and type B viruses were detected at similar frequencies; most H1N1 viruses were related antigenically to A/New Caledonia/20/99-like (2005–2006 Northern and 2006 Southern Hemisphere vaccine strain); the majority of H3N2 viruses were related antigenically to the A/California/7/2004 (2005–2006 Northern and 2006 Southern Hemisphere vaccine strain); and the majority of influenza B viruses belonged to the B/Victoria/2/87-lineage and were identified as B/Malaysia/2506/2004-like. In 2007, influenza A (H3N2) and B viruses were identified in similar frequencies. The majority of H3N2 viruses were related antigenically to A/Wisconsin/67/2005 virus (2006–2007 Northern and 2007 Southern Hemisphere vaccine strain); and the majority of B viruses were of the B/Victoria-lineage viruses and related antigenically to B/Malaysia/2506/2004 virus (2006–2007 Northern and 2007 Southern Hemisphere vaccine strain). Overall, during 2003–2007, influenza A (H3N2) viruses were isolated less frequently (18·7%) than A (H1N1) (39·9%) or B (50·5%) viruses.

Table 2. Influenza virus types and influenza A subtypes detected by year

Year	ILI cases		RT-PCR # Influenza Positive	RT-PCR % of all Influenza Positives	# Isolates	# and (%) of Influenza Positives with isolates
2003	593	Influenza A				
		H1N1	10	9.0	7	7/10 (70)
		H3N2	75	67.6	34	34/75 (45.3)
		Influenza B	26	23.4	9	9/26 (34.6)
		Total	111/593	18.7	50	50/111 (45)
2004	1403	Influenza A				
		H1N1	12	3.6	8	8/12 (66.7)
		H3N2	219	65.6	94	94/219 (42.9)
		Influenza B	103	30.8	70	70/103 (67.9)
		Total	334/1403	23.8	172	172/334 (51.5)
2005	3964	Influenza A				
		H1N1	59	7.9	22	22/59 (37.3)
		H3N2	303	40.5	47	47/303 (15.5)
		H5N1	1	0.1		
		Influenza B	336	51.5	233	233/386 (60.4)
		Total	749/3964	I8.9	302	302/748 (40.4)*
2006	6926	Influenza A				
		A Not further tested	108	8.6		
		H1N1	422	33.5	196	196/422 (46.4)
		H3N2	343	27.2	54	54/343 (15.7)
		H5N1	3	0.2		
		Influenza B	384	30.5	167	167/326 (51.2)**
		Total	1260/6926	18.2	417	417/1091 (38.2)*
2007	8144	Influenza A				
		A Not further tested	327	18.4		
		H1N1	305	17.1	89	89/305 (29.2)
		H3N2	556	31.2	51	51/556 (9.2)
		H5N1	6	0.3		
		Influenza B	538	32.9	183	183/470 (38.9)**
		Total	1782/8144	21.9	323	323/1331 (24.3)*

*Excludes H5N1 viruses and specimens not further tested.
**Denominator differs from all influenza B virus positive specimens detected by RT-PCR.

Influenza A (H5N1) virus infection was identified in one outpatient and nine inpatients from six surveillance sites (five cases from Tangerang, and one each from Bali, Padang, Jakarta, Makassar, and Yogyakarta). Initial diagnoses in these cases included severe bronchopneumonia, dengue, or typhoid fever. All nine confirmed H5N1 hospitalized cases presented with severe illness late in the clinical course, received late oseltamivir treatment, and all died. One H5N1 case presented with ILI to a hospital outpatient surveillance site, was not suspected with H5N1 at clinical presentation, was neither treated nor hospitalized, and subsequently died. H5N1 virus infection was retrospectively confirmed from a respiratory specimen collected through ILI surveillance. These 10 cases represented 8·5% of all confirmed H5N1 cases (n = 117) identified in Indonesia between 2005 and 2007.

Influenza virus detection by RT-PCR and subsequent viral isolation were higher in ILI patients presenting with a measured temperature of ≥37·8°C (22·6% and 44·7%, respectively) compared to those with a history of feverishness, but without a documented fever at presentation (17·4% and 38·3%). Among 4236 patients who tested positive by RT-PCR, 62·5% were positive in both nasal and throat swab specimens, compared to 19·6% of nasal swabs only, and 16·9% of throat swabs alone. Nasal swabs yielded slightly higher isolation of influenza viruses compared to throat swabs [1225/3043 (40·3%) versus 1155/3054 (37·8%), P = 0·04, chi-squared test].

Figure 2 shows the monthly proportion of influenza-positive ILI cases identified by RT-PCR. Seasonal peaks in influenza A virus activity, especially with H3N2 virus

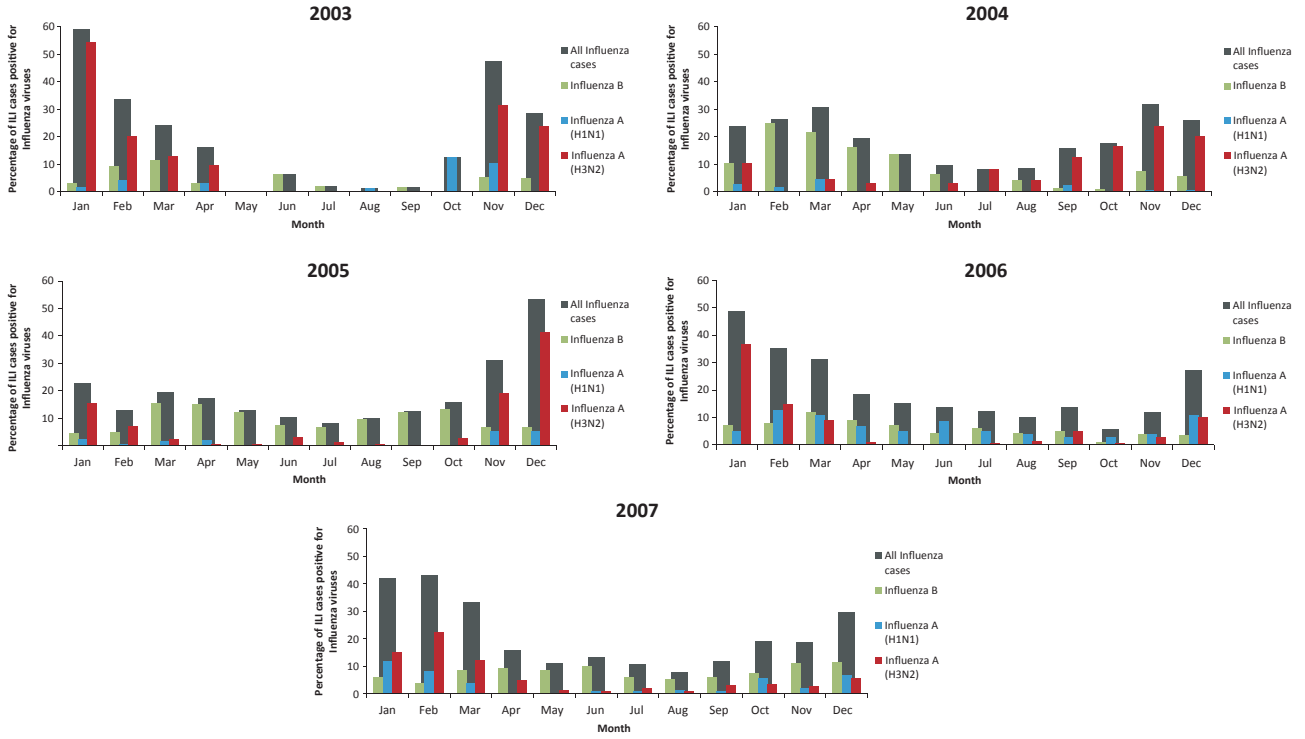

Figure 2. Percentage of ILI cases testing postive for influenza viruses by RT-PCR by month, 2003–2007.

strains, were observed during December and January, followed by increases in influenza B virus activity during March to May. The seasonality of influenza A virus was largely consistent across all nine islands although some had increased activity during May and July (Sumatra, Maluku, and Papua). Two eastern provinces of Indonesia appeared to have a bimodal peak in influenza activity during December-January and June-July although data were limited (data not shown). We observed a high correlation between the mean proportion of influenza A positives among ILI cases and mean precipitation from 18 districts (Figure 3; $r = 0{\cdot}87$). When assessed per district, influenza A virus activity appeared to correlate well with rainfall in 10 districts (in one district, $r > 0{\cdot}8$; in nine districts, $r = 0{\cdot}6$–$0{\cdot}8$); poor-to-moderate correlation was observed in other districts (in one district, $r = 0{\cdot}4$–$0{\cdot}6$; in two districts, $r = 0{\cdot}2$–$0{\cdot}4$; in three districts, $r = 0$–$0{\cdot}2$; and in two districts, $r = -0{\cdot}01$ to $-0{\cdot}2$.) The last five districts are located in Kalimantan and two eastern islands of Indonesia (Maluku and Papua). Influenza A virus activity did not appear to correlate with mean monthly temperature or relative humidity (data not shown). Influenza B virus activity did not appear to be correlated with mean monthly temperature, mean monthly rainfall, or monthly relative humidity for any sites (data not shown).

Retrospective analysis identified a small number of influenza A viruses that were isolated from respiratory specimens collected through surveillance in Indonesia

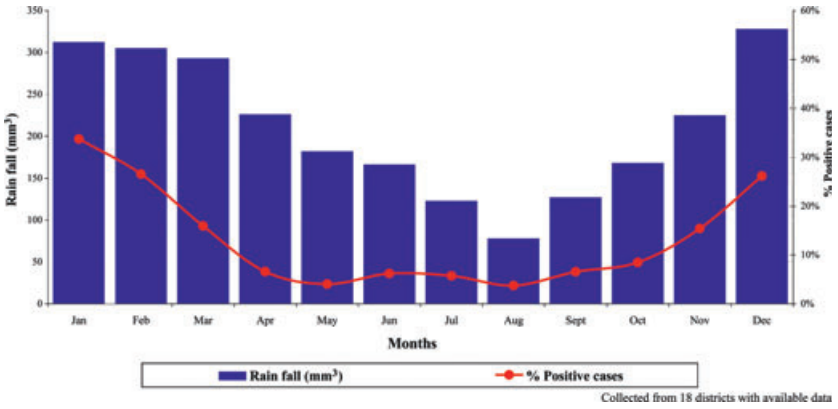

Figure 3. Comparison of rainfall precipitation and the proportion of ILI cases that tested positive for influenza A, 2003–2007 Indonesia*.

Table 3. Detection of Influenza A Virus Strains in Indonesia and Temporal Relationship to Global Detection of WHO Designated influenza A Vaccine Virus Strains, 2003–2007

Influenza vaccine strain	Month, year selected as WHO vaccine strain	Date of collection of influenza vaccine virus	Date of collection of Indonesia virus	Indonesia virus name	Antigenic characterization*
A/California/07/2004 (H3N2)	February 2005	Sept 16, 2004	Sept 16, 2004	Indonesia/1857/2004	A/Califomia/07/2004 (H3N2)-like
A/Wisconsin/67/2005 (H3N2)-like	February 2006	Aug 31, 2005	Feb 18, 2005	Indonesia/1711/2005	A/Wisconsin/67/2005 (H3N2)-like
A/Solomon Islands/03/2006 (H1N1)-like	February 2007	Aug 21, 2006	March 3, 2006	Indonesia/3208/2006	A/Solomon Islands/03/2006 (HlNl)-ike

*With sequence confirmation.

before the collection of specimens elsewhere that yielded influenza A (H1N1) and (H3N2) viruses that were subsequently recommended as WHO influenza vaccine strains (Table 3). A/Solomon Islands/3/2006 (H1N1) virus was first identified in August 2006; this antigenic variant virus spread widely and was selected as the Northern Hemisphere H1N1 vaccine component in February 2007 to replace A/New Caledonia/20/99 (H1N1). An H1N1 virus detected in Indonesia during March 2006 was identified as A/Solomon Islands/3/2006-like (in early 2007), suggesting detection of this virus in Indonesia approximately 5 months earlier than the designated WHO Northern Hemisphere vaccine strain. Similarly, a few H3N2 viruses were identified in Indonesia earlier or at the same time as antigenically equivalent H3N2 vaccine strains that were recommended as WHO H3N2 vaccine strains (A/California/7/2004-like and A/Wisconsin/67/2005-like viruses).

Discussion

Surveillance conducted at sites across the Indonesian archipelago during 2003–2007 identified a substantial proportion of influenza virus infections among patients presenting with influenza-like illness. While influenza activity was detected year-round, the proportion of ILI patients with influenza and predominant viruses varied from year-to-year and geographically. There was evidence for a mixed seasonal distribution of influenza viruses in some parts of eastern Indonesia (Maluku and Papua). However, the observed seasonality of influenza A virus activity among ILI cases at our surveillance sites in most regions of Indonesia, particularly in the western and middle islands which are more densely populated, indicated a peak in December and January, which correlates with the rainy season. Seasonality for influenza B virus was less apparent.

Similar to our surveillance findings, influenza A (H1N1) virus activity was low during 2003–2005 in Australia[15–17], Malaysia[18], and Thailand[19]. However, in 2006, A (H1N1) viruses were the predominant subtype in Malaysia[18], Thailand[19], and Indonesia. In 2007, A (H1N1) activity increased in Australia[20]. Between 2003 and 2007, A (H3N2) virus was the most predominant subtype in Indonesia and in neighboring countries[15–21]. Similar to our findings, influenza B viruses were less frequently detected than influenza A viruses, but still were identified in a moderately high proportion of ILI cases in Malaysia and Thailand (approximately 20% to 40% each year)[18,19], except in 2005 when B viruses predominated in Malaysia and Indonesia (approximately 52%)[18]. In Australia, influenza B virus activity was variable during 2003–2007 (6% in 2003 to 29% in 2006 and 9% in 2007).[15–17,20,21]

Influenza A and B viruses, including antigenically drifted strains as observed in other countries, were also detected in Indonesia during the surveillance period, and in a few instances were detected earlier than designated WHO representative reference or influenza vaccine strains. A sink-source model in which evolution of influenza A (H3N2) virus strains circulating in the tropics seed winter epidemics in temperate region has been proposed; this model emphasizes the importance of South-East Asia for the emergence of new variants and novel strains.[4,5] Although we did not conduct comprehensive antigenic characterization of influenza viruses circulating in Indonesia or compare our limited results with global data, we believe that improved influenza surveillance in Indonesia, the 4th most populated country, can inform better understanding of the evolution of influenza viruses in South-East Asia.

Given the influenza virus seasonality observed among ILI cases at most Indonesian sentinel sites, use of influenza vaccine in Indonesia should target the December-January winter seasonal peak. For this reason and the similarity with most circulating A (H1N1) and A (H3N2) virus strains during 2003–2007, the timing of the availability of Northern Hemisphere influenza vaccine is best suited for Indonesia. This timing of peak influenza activity is different than that found in other countries in the region which also experience year-round activity, but generally experience a mid-year peak, although the timing of peak activity may vary from year-to-year.[18,22–24]

Historically, influenza vaccine use is quite low in Indonesia with fewer than 300 000 doses administered every year.[25] With very limited data on influenza disease burden in Indonesia and no data on cost-effectiveness of influenza vaccination, the Ministry of Health recommends influenza vaccine for high-risk populations such as the elderly, those with underlying chronic diseases, Hajj pilgrims, and healthcare workers.[26] The main reasons for low influenza vaccine coverage are the cost of vaccine and the wide belief that influenza virus infection only causes mild illness.[25] Oseltamivir is the only antiviral for influenza used in Indonesia, but is not widely available. Although oseltamivir has been provided in limited quantities at government primary health centers and hospitals since 2006, it is not available at pharmacies and its use is restricted to treatment of persons with suspected or confirmed H5N1 virus infection.[27]

Among samples tested, the percentage of ILI cases testing positive for influenza viruses was highest among school-age children in Indonesia. While health utilization data for Indonesians of all ages with influenza-like illness are needed, the high burden of influenza among school-age children presenting to surveillance sites is consistent with reports from other countries in the region and underscores the potential of this group as a source of transmission and the importance of influenza vaccination.[23,24] Furthermore, seasonal influenza represented 21·7% of all ILI cases tested in the inpatient setting, among which 18% were associated with pneumonia. Since influenza diagnostic testing is generally not performed as part of clinical management of outpatients or hospitalized patients, the findings in this work can inform physicians in Indonesia who are not aware of the public health impact of seasonal influenza. Furthermore, given the relatively high frequency of influenza among hospitalized ILI patients, both healthcare personnel and other hospitalized patients may be at risk of and contribute to nosocomial influenza virus transmission; the role of influenza vaccination and importance of infection control must be emphasized.

We identified 10 H5N1 cases from patients' respiratory specimens collected at hospital surveillance sites, 8·6% of the 116 H5N1 cases reported in Indonesia during the surveillance period[28]. Nine cases were in suspected H5N1 patients with severe illness admitted to hospitals that were surveillance sites, while one H5N1 case presented with ILI and was not suspected with H5N1. This highlights the value of laboratory-based influenza surveillance to detect human infections with seasonal influenza viruses as well as H5N1 virus[29]. As our surveillance network relied upon a convenience sample of ILI cases among outpatients and inpatients, it is possible that other H5N1 virus infections were missed.

We recognize several limitations to our surveillance findings. First, denominator data on the catchment population for sentinel sites were not collected and data on the total number of outpatient and inpatient visits and total ILI cases were not collected to calculate the incidence of ILI and influenza. We utilized a convenience sample of ILI cases, not a systematic sample. Therefore, influenza disease burden could not be estimated. Nevertheless, we documented a substantial proportion of outpatients and hospitalized patients with influenza. Second, we did not follow the outcomes of our inpatients to estimate seasonal influenza-associated mortality. Third, sentinel sites were selected based on the population density. More sentinel sites existed on two islands, Sumatra and Java in the West, and our findings may not be representative of all of Indonesia, including less populous eastern islands. Finally, the yield of viral isolation was lower over the surveillance period because of cold-chain issues and difficulties in isolating H3N2 viruses. However, as we utilized RT-PCR as the primary method of identification, we believe that our findings accurately reflect influenza virus activity among our surveillance sites.

In conclusion, our findings demonstrate that influenza is an important public health problem among outpatients and hospitalized ILI patients in Indonesia. This has implications for understanding the public health impact of influenza in tropical climates as well as the development of policies for the use of influenza vaccines in Indonesia. In addition to strengthening and improving epidemiological data collection for patients with influenza, collecting more data on influenza disease burden is needed, especially among hospitalized patients and high-risk groups for influenza complications. Also, data are needed on the economic impact of influenza and the role of climactic factors (such as absolute humidity, rainfall, and temperature) in influenza activity and seasonality in Indonesia.

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