Several dominant clinical symptoms associated with Influenza A in Indonesia

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Abstrak

Latar belakang: *Pada tahap awal infeksi, influenza A yang dapat menimbulkan pandemi, sangat sulit dibedakan dengan influenza-like illness (ILI) yang lain. Oleh karena itu gejala klinik sangat penting untuk mendiagnosis secara dini influenza A. Tujuan penelitian ini untuk mengidentifikasi gejala klinik dominan yang berkaitan dengan influenza A di Indonesia.*

Metode: *Penelitian potong lintang. dilakukan di 20 puskesmas sentinel yang dipilih secara purposif di 19 propinsi di Indonesia tahun 2009. Data dan spesimen dikumpulkan oleh petugas paramedik atau medik puskesmas dari subjek rawat jalan dengan gejala ILI (batuk dan demam). Pemeriksaan Spesimen dilakukan di Pusat Rujukan Influenza Nasional di Jakarta. Penentuan Influenza A dengan real time RT-PCR.*

Hasil: *Sebanyak 1802 subjek berdata lengkap untuk analisis influenza A dari 2728 subjek dengan gejala ILI, dan 23,1% (416 subjek) didiagnosis positif influenza A. Pada model terakhir terungkap bahwa subjek dengan pilek dibandingkan dengan yang tidak pilek berisiko 3,6 kali lipat Influenza A [risiko relatif suaian (RRa) = 3,59; 95% interval kepercayaan (CI) = 1,34-9,63]. Subjek dengan nyeri tenggorok dibandingkan dengan yang tanpa nyeri tenggorok berisiko 54% lebih besar menderita Influenza A (RRa = 1,54; 95% CI = 0,95-2,58; P = 0.082). Seangkan, subjek dengan riwayat demam dibandingkan tanpa riwayat pernah demam dalam dua hari terakhir berisiko 42% lebih besar menderita Influenza A (RRa = 1,42; 95% CI = 0,97-2.,7; P = 0,069).*

Kesimpulan: *Selain demam dan batuk, keluhan pilek dan nyeri tenggorok, serta riwayat pernah demam dalam dua hari terakhir merupakan faktor risiko dominan yang berhubungan dengan Influenza A.* ***(Health Science Indones 2011;2:96-100)***

Kata kunci: *Influenza A, cough, muscle pain, runny nose, sore throat*

Abstract

Background: Influenza A has a potential to become a pandemic, in the early stages is difficult to differentiate influenza to influenza-like illnesses. Therefore, the dominant clinical symptoms are the important keys to predict influenza A infection in patients with influenza-like illnesses (ILI). The aim of this study is to identify additional dominant symptoms associated to influenza A in Indonesia.

Methods: The eligible subjects of this study were outpatient who had ILI symptom, i.e. who had fever (38^{o} or more) and coughing in purposive selected 20 Health Centers in 19 provinces of Indonesia during year 2009. Paramedics and medical staff identified the ILI cases and collected specimens. Laboratory tests for RT-PCR were performed at the National Influenza Center in Jakarta.

Results: Of 2728 specimens, 1802 had complete data for this analysis, and 23.1% (416 subjects) diagnosed positive influenza A. Those who had than did not have runny nose symptom had 3.6-fold risk of influenza A [adjusted relative risk (RRa) = 3.59; 95% confidence interval (CI) = 1.34-9.63). In term of sore throat, those who had than did not have it had 54% more risk of influenza A (RRa = 1.54; 95% CI = 0.95-2.58; P = 0.082). Furthermore, those who ever had than did not have fever for the last two days had 42% more risk of influenza A (RRa = 1.42; 95% CI = 0.97-2.07; 0,069).

Conclusion: In addition to fever and coughing, runny nose, sore throat, and ever had fever are dominantly associated with influenza A. ***(Health Science Indones 2011;2:96-100)***

Key words: influenza A, cough, muscle pain, runny nose, sore throat

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Influenza-like illness (ILI) is a medical diagnosis of possible influenza or other illness with a set of common symptoms and therefore a significant source of morbidity and mortality worldwide. Influenza is an infectious disease caused by *Orthomyxoviridae* viruses that affects birds and mammals. The initial symptoms of influenza are similar to ILI, such as fever or history of fever accompanied by cough, runny nose, sore throat, muscle pain and or dyspnea.[1,2]

There are three types of influenza based on the main virus that caused, they are A, B, and C. Influenza type A dan B have similar early symptoms that can cause epidemics and have high case fatality rates as well. Additionally, influenza type A is more threatening because it can cause pandemics.[3] Influenza type A viruses are divided into subtypes (strains) based on two proteins on the surface of the virus. These proteins are called hemagglutinin (HA) and neuraminidase (NA). Currently, there are 16 different HA subtypes and 9 different NA subtypes. New subtypes of influenza viruses may occure through processes called antigenic drift and antigenic shift. In 2005, influenza virus subtype H5N1 pandemic (bird flu) occured in Indonesia. Another pandemic occured in 2009 caused by a new subtype of H1N1 (swine flu). The symptoms were similar with common seasonal influenza. There are little known about factors related to influenza A.[3,4]

Since influenza A has similar symptoms with ILI, further examination in laboratory is needed to reveal the type of influenza and the sub-type if the result is influenza A. Influenza A viruses can cause diseases with common symptoms that mostly will be neglected by people. Doctors seldom tell patients to confirm the result to the laboratory tests such as rapid test, RT-PCR and Culture test as the gold standard for influenza[2]. It has been known that laboratory tests are very expensive, even for the rapid test that has low specivicity and sensitivity for influenza A. Additionally, RT-PCR and Culture test are taking much time. Furthermore, it will be too late to realize that patients have influenza A viral infections.

Since influenza A viral infection can cause severe influenza-like illness among exposed people, virological and epidemiological surveillance are needed to understand the impact of influenza A virus among people with ILI symptoms in Indonesia. Therefore, we need clinical symptomps to give us high predictions about influenza A in patients. This study aimed to identify additional dominant symptoms associated to influenza A in Indonesia.

METHODS

A cross sectional study was conducted on cases that included into the ILI surveillance in 19 provinces in Indonesia in 2009. For each provinces appointed one health center except Papua which had two health centers that were chosen purposively. The criteria to select the health centers included: (1) high prevalence of upper respiratory track infection; (2) human resources availability for ILI surveillance; (3) cooperative and willingness to participate; (4) well documented reporting system; (5) and close to airport for easiness shipping to the regional laboratory or the nasional referral laboratory.

Procedures: Subjects with symptoms of fever (38° C or more) and cough who presented at primary health centers (outpatients) were enrolled once a week. Informed consents were obtained from subjects. Trained paramedics collected nasal and throat swabs from the patients. They also obtained demographic data and clinical symptoms from patients. All of the specimens were shipped to the regional laboratory in four provinces or to the national referral laboratory in Jakarta. A confirmed case was efined by a positive result of a realtime reverse-transcriptase polymerase chain reaction (rRT-PCR) test. Before shipping, swab of specimens were placed into sterile Hanks' Balanced Salt Solution (HBSS) as viral transport media (VTM). Specimens were refrigerated (4°C) and shipped weekly with a strick condition.

All of the specimens were tested for influenza by realtime reverse-transcription polymerase chain reaction (rRT-PCR) assay. The QIAamp Viral RNA kit (QIAGEN, Valencia, CA) was used to extract viral RNA according to the manufacture manual. Positive specimens were inoculated into cell culture using Madin Darby Canine Kidney (MDCK).

All of the virological and epidemiological data were collected and analized at the Virology Laboratory in Center for Biomedical and Basic Technology of Health: For this analysis age were categorized into five groups (6-12, 13-17, 18-34, 35-49, and 50-82 years old). We also collected the other symptoms which occured among the subjects: history of fever, runny nose, sore throat, muscle pain and dyspnea. These symptoms were obtained by observation and or asked by special trained paramedic or medical doctor during the subjects visited the health centers.

Statistical analysis: Of the people enrolled (n=2728), only 1802 samples can be included in this study. We

excluded uncomplete data and patients under 6 years old because we could not acquire information from them about muscle pain. We performed data analyzed using Cox regression using Stata released 9.

RESULTS

Of 2728 specimens, 1802 had complete data for this analysis, and 23.1% (416 subjects) diagnosed positive influenza A.

Table 1 shows that in general, those who had and did not have influenza A was similarly distributed with respect to dyspnea. Similar condition is shown between subjects age 18-34 years and 6-12 years old. Male subjects and those who had muscle pain than sore throat more likely had increase risk to be influenza A. Compared to age 6-12 years old, subjects of age 13-17 and 35 or more had more likely increase risk to be influenza A.

Our final model (Table 2) reveals runny nose, sore throat, and ever had fever are dominantly associated with influenza A. Those who had and did not have runny nose symptom had 3.6-fold to be Influenza A. In term of sore throat, those who had than did not have it is 54% more risk to be influenza A. Furthermore, those who ever had fever than did not have fever had 42% more risk having influenza A.

Table 1. Several demographic, clinical symptoms and risk of Influenza A

	Influenza A		Relative risk	95% confidence interval	P
	Negative (n=1386)	Positive (n=416)			
Gender					
Female	725	197	1.00	Reference	
Male	661	219	1.16	0.96-1.41	0.120
Age group					
6-12	643	210	1.00	Reference	
13-17	141	70	1.34	1.02-1.76	0.031
18-34	322	94	0.91	0.71-1.17	0.490
35-49	176	34	0.65	0.45-0.94	0.023
50-82	104	8	0.29	0.14-0.58	0.001
Muscle pain					
No	455	113	1.00	Reference	
Yes	931	303	1.23	0.99-1.53	0.056
Dyspnea					
No	30	400	1.00	Reference	
Yes	56	16	0.96	0.58-1.58	0.876
Sore throat					
No	374	97	1.00	Reference	
Yes	1,012	319	1.16	0.93-1.46	0.191

Tabel 2. Relatioship between clinical symptoms and risk of Influenza A

	Influenza A		Adjusted relative risk*	95% confidence interval	P
	Negative (n=1386)	Positive (n=416)			
Runny nose					
No	190	27	1.00	Reference	
Yes	1,196	389	3.59	1.34-9.63	0.011
Sore throat					
No	374	97	1.00	Reference	
Yes	1,012	319	1.54	0.95-2.58	0.082
Ever had fever for the last 2 days					
No	410	45	1.00	Reference	
Yes	258	47	1.42	0.97-2.07	0.069

*Adjusted each other among risk factors listed n this Table

DISCUSSION

In interpreting our finding there are some limitation that must be considered. First, we did not include fever and cough as examined symptoms because those symptoms had been included in CDC protocol for influenza. Therefore, every subject must have fever and cough. Second, we only studied five symptoms. It is a very small number if we compare to the number of symptoms that have been known. Third, for this study we did not analyze for combination of symptoms.

Symptoms of influenza can start quite suddenly one to two days after infection.[5] These symptoms may include fever, cough, body aches, especially muscle and throat, and dyspnea.[1,2] It is difficult to differentiate influenza to *influenza-like illnesses* in the early stages of these infections.5 One study suggested that during local outbreaks of influenza, the prevalence will be over 70%.[6]

Rapid laboratory tests can be used to detect influenza A, especially during the influenza season. However, it is not frequently experienced because the test itself is usually expensive.[6] According to the CDC, rapid diagnostic tests have a sensitivity of 70–75% and specificity of 90–95% when compared with viral culture.[7,8] Unlike viral culture or rapid test, RT-PCR test has more sensitivity in detection and ability to identify which influenza A subtypes. Therefore, CDC recommends RT-PCR for influenza for surveillance purposes.[9]

Our study reveals that among individuals with influenza A, the most frequent reported symptoms were runny nose (n=389), sore throat (n=319), and muscle pain (n=302). In contrary, Monto et al. in a study stated different result. They said that the most common symptoms for influenza feverishness, cough, myalgia, and weakness.[10] Another study imply that malaise, fever, and cough are the most common symptoms for influenza.[11] In addition, Eccles and Cao et al. also stated fever and cough as the best predictors.[5,8] However, in our study we could not use fever and cough as variables because they are included in ILI definition.

Furthermore, similar distribution is shown between subjects age 6-12 years and 18-34 years old (P = 0.490). Male subjects had more likely increase risk to have influenza A. Dyspnea are distributed similarly between those who had and did not have influenza A. Male subjects and those who had muscle pain than sore throat more likely had increase risk to be influenza A. Compared to age 6-12 years old, subjects of age 13-17 and 35 or more had more likely increase risk to be influenza A. Moreover, Govaert et al. in a study analyzed combination of symptoms and revealed that combination of fever, cough, and acute onset had a high predictive value of influenza.[11]

In conclusion, close observation into ILI surveillance in 2009 offered some dominant symptoms (runny nose, sore throat, and ever had fever) that can be used in order to predict influenza A in patients.

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