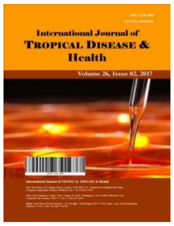

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Associated Signs and Symptoms of Confirmed Influenza Infections in Ghana

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Authors' contributions

This work was carried out in collaboration between all authors. Author MA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EKA, JHKB and SAO were part of the literature searches, editing of manuscript and validation. Authors MN, BS and ED managed the analyses of the study. Author FAB participated in interpretation of results. Author WA participated in the interpretation of results and manuscript writing. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Acute respiratory tract infections are among the most common causes of morbidity and mortality worldwide and rank second among the top causes of health facility attendance in Ghana. A well-positioned case detection system can efficiently identify respiratory illnesses and detect influenza outbreaks early. This study determined clinical signs and symptoms most predictive of confirmed influenza infection among Influenza-Like Illness (ILI) patients.
Study Design: A cross-sectional study was conducted.

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Place and Duration of Study: A data repository of case-based records from the regional sentinel sites available at the Disease Surveillance Department of the Ghana Health Service for the period of January to December 2011 was used as secondary data. The dataset was first accessed in October 2016.
Methods: A cross-sectional study was conducted with 2,089 anonymized case-based records. The associations between the combinations of fever and cough together with other signs and symptoms of an influenza positive infection were explored. Frequencies, sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio were computed using Epi Info 7.0 (CDC, Atlanta, GA).
Results: The median age was 22 years (IQR: 6.5 to 37 years). Twenty-one percent were children under 5 years. Females formed 1,190 (57%) of the total patients studied. Fever and cough together with a sore throat had the highest significant association (ORa: 1.52; 95%CI: 1.15 - 2.02) with a positive influenza laboratory results in the adjusted analysis.
Conclusion: The case definition for Influenza-Like Illness (ILI) was loosely applied considering the variation between the frequencies of patients with fever or a cough. Since an ILI case definition encourages the inclusion of other respiratory signs, observations from this study suggest the inclusion of a sore throat, together with fever and cough as the best predictor of an influenza infection.

Keywords: Influenza; risk factors; surveillance; sensitivity.

1. INTRODUCTION

Acute respiratory tract infections are among the most common causes of morbidity and mortality worldwide. Influenza and respiratory syncytial virus (RSV) account for the top causes of respiratory infections and respiratory-related hospitalizations among children and the aged [1]. It is estimated that 20% of children and 5% of adults are annually infected with influenza infections [2]. Various studies have shown that mortality associated with influenza infections varies by age, virus type, and subtype [3,4]. In seasonal influenza epidemics, 5-15% of the population suffer from upper respiratory tract infections. Although most cases are mild, these annual epidemics cause severe illness in 3–5 million people and 250,000 – 500,000 deaths worldwide [5]. There is a paucity of data on the impact of influenza in the developing world. However, it is known that influenza transmission occurs year-round in the tropics and they tend to present with high attack and case-fatality rates [6]. Poor surveillance or a weak influenza detection system could lead to the late detection of novel viruses or outbreaks [7].

Gavin and Thomson demonstrated that during influenza seasons, acute onset of fever and cough can be highly predictive of influenza (PPV 79–87%; NPV 39–75%) [8]. Due to the uncertainties surrounding the use of only clinical definitions for the diagnosis of influenza, it is important to integrate virological and epidemiological surveillance for the data to be most useful for executing health interventions [9]. A prospective study was conducted over two influenza seasons in Taiwan among outpatients with acute respiratory tract infections. A total of 71 (45%) patients had confirmed influenza from the 158 patients identified. A cough, fever, sneezing, nasal congestion and rhinorrhoea, were significant predictors of influenza infection. Fever and cough showed the best sensitivity (86%; 95%CI: 76%–93%) whereas fever and cough together with sneezing had the best specificity (77%; 95% CI: 62%–88%) [10].

In Slovenia, clinical data from two influenza seasons indicated a total of 211 (16.4%) of the 1,286 patients had confirmed influenza infection. It had a better predictive model for children under 15 years for confirmed influenza: fever (≥38°C), headache, cough, and absence of abnormal breathing sounds. These predictors together had a sensitivity, specificity, positive predictive value and negative predictive value being 5.1%, 98.1%, 57.1% and 80.1% respectively [11].

Data collected from a hospital-based influenza sentinel site in Kenya from the period of January 2007 to July 2010 had 4,800 patients above 2 months with respiratory signs and symptoms, out of which 416 (9%) tested positive for influenza. The symptom combination of a cough with fever (history or measured ⩾38 °C) had a sensitivity of 87·0% (95% CI: 83·3–88·9).

As part of the response to the Avian Influenza and the threat of a novel virus transmission to humans, the Ghana Health Service and the National Influenza Centre (hosted by the Noguchi Memorial Institute for Medical Research, University of Ghana) established sentinel surveillance sites in Greater Accra, Volta and the Brong Ahafo regions of Ghana, where the Highly Pathogenic Avian Influenza H5N1 virus had been detected in poultry. This was later scaled-up to cover all the 10 regional administrative capitals during the 2009 influenza A H1N1 pandemic. The main purpose of the sentinel surveillance system is to detect predominant circulating influenza viruses in the country at any period. This sentinel surveillance for influenza viruses is also utilizing the main Integrated Disease Surveillance and Response (IDSR) approach to disease surveillance in Ghana.

Influenza-Like Illness together with other Acute Respiratory Infections ranks second among the top causes of morbidity for hospital attendances in Ghana. Identifying predominant circulating influenza viruses contributing to the burden of Acute Respiratory Infections should be an objective of every disease surveillance system in especially developing countries. Case detection forms the trigger for the chain of activities or public health response measures within a disease surveillance system.

When clinicians have information that will increase their index of suspicion to detect positive influenza infections among respiratory illness patients, it will go a long way in the early detection of a cluster of influenza cases or outbreaks. It is envisaged that prescribers will be motivated by an evidence-based relative high sensitive and specific surveillance case definition and apply accordingly. This will go a long way to increase the case detection rate of influenza-related suspected infections.

With limited available data on sensitivity, specificity and predictive values of the various signs and symptoms in Sub-Saharan Africa including Ghana, we proceeded to determine clinical signs and symptoms most predictive of confirmed influenza infection among ILI patients.

2. MATERIALS AND METHODS

A cross-sectional study was conducted with 2,089 anonymized case-based records from the regional sentinel sites already available at the Disease Surveillance Department of the Ghana Health Service for the period of January to December 2011. The dataset was accessed in 2016. This dataset was used because of the relative level of completeness of variables. Key demographic variables obtained from the database were sex and age. Clinical signs and symptoms related variables were fever, cough, sore throat, coryza, myalgia, and headache. The date of onset of symptoms, date of specimen collection, date specimen dispatched and laboratory results were the other variables present. Laboratory investigations were conducted at the Noguchi Memorial Institute for Medical Research which is a WHO-accredited institution.

For uniformity in clinical detection of Influenza-Like Illnesses (ILI) within the surveillance system, a standard case definition was used to detect new cases for sample collection and laboratory investigations. The case definition provided for use was the presence of fever (measured ≥37.5°C or history of fever) and cough; with one or more other signs and symptoms such as a headache, coryza, myalgia, and sore-throat with onset within the last 7 days [12].

Whereas some studies evaluated different case definitions in relation to influenza positive infection, this study evaluated the relationship between any of the signs and symptoms presented as part of the case definition for ILI and a positive laboratory result for influenza virus by use of real-time Reverse Transcription-Polymerase Chain Reaction (RRT- PCR) [13,14]. The two conditional signs in the case definition, fever (measured ≥37.5°C or history of fever) and cough, were recombined with the other signs and symptoms; a sore throat, coryza, myalgia, and headache. The proportions of the various signs and symptoms were computed. Furthermore, the sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio were computed with a 95% confidence interval using Epi Info 7.0 (CDC, Atlanta, GA). A significance threshold for a p-value was set at .05 in describing a relationship between a predictor and a positive influenza virus infection.

Oropharyngeal swabs were taken from all the 2,089 patients that met the definition for an ILI patient. Samples were put in specimen carriers with ice packs by trained personnel with triple packaging and then shipped to the laboratory. In some situations where specimens could not be shipped immediately within 48 hours, they were stored in liquid nitrogen tanks till shipment was ready. ILI samples were investigated in the laboratory for influenza viruses. No further laboratory investigations were carried out, irrespective of the primary test outcome being influenza positive or influenza negative according to the protocol used.

The period between sample collection and arrival in the laboratory was evaluated for any association with a confirmed influenza virus. This was categorized into less than 2 days, 2 to 4 days, 5 to 7 days and more than one week. This was largely informed by completion of case-based forms and collected samples reaching the laboratory within 48 hours as per operating procedures for priority conditions but other categories were more arbitrarily done.

We tested the hypothesis that signs and symptoms were predictive for confirmed influenza infection at 95% confidence interval. The comparative groups of interest were Influenza-positive ILIs and Influenza-negative ILIs. The combinations of signs and symptoms that had significant associations with influenza positive infection were all fed into an adjusted model.

3. RESULTS AND DISCUSSION

Among 2,089 ILI patients, 2,072 (99.2%) had a date of birth or age recorded. A total of 1,062 (51.3%) cases were within the age-group of 15 to 49 years. The median age was 22 years (IQR 6.5 to 37 years). Twenty-one percent were children under 5 years (Fig. 1.). Females formed 1,190 (57%) of the total patients studied.

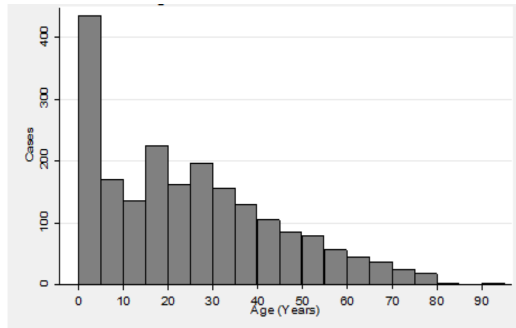

Fig. 1. Age (years) distribution of ILI cases in 2011

The 1,798 (86.1%) ILI cases who had their date of onset indicated were investigated for monthly trends. Influenza-like illness cases peaked in June to July and later saw a gradual decline till December 2011. Of interest was the relatively high percentage of positive rates in the first half of the year and the peak of ILI cases in November which was not accompanied with a rise in the proportion of positive cases (Fig. 2.).

One Thousand Nine Hundred and Fifty-Five (93.6%) of the samples arrived in the laboratory within 7 days. Of the total 134 samples received beyond 1 week, 115 (85.8%) were from institutions outside the Greater Accra Region, where the NIC is located. The odds of having an influenza positive test (using real-time RT-PCR) were not associated with the time between sample collection to arrival in the laboratory (Table 1).

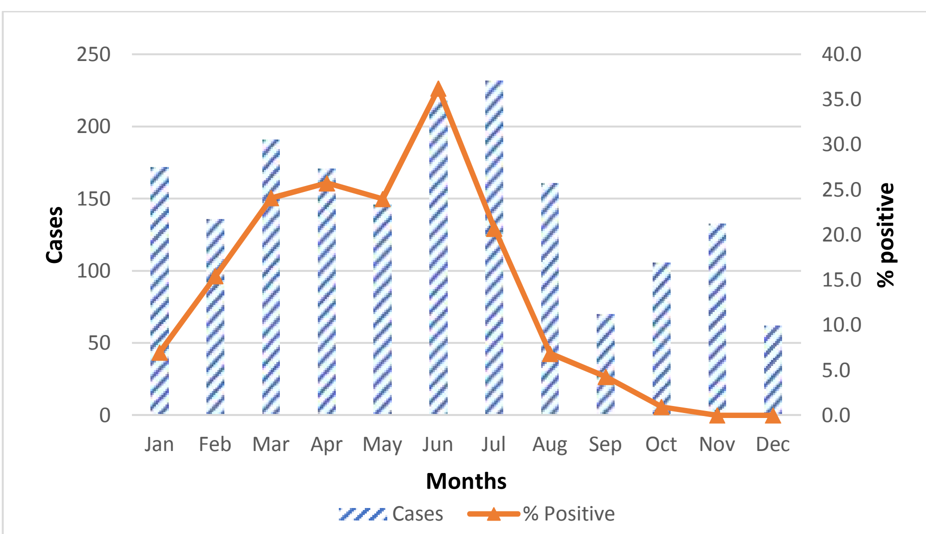

Fig. 2. Monthly onset of ILI cases and proportion of influenza positives, 2011

Table 1. Logistic regression on laboratory results for period between sample collection and arrival in the laboratory

Period	Freq	%	OR	*P*-value
Less than 2 days	1,256	60.1	1.00	-
2 to 4 days	482	23.1	0.90 (0.68, 1.19)	0.48
5 to 7 days	217	10.4	0.94 (0.64, 1.38)	0.76
> 1 week	134	6.4	0.99 (0.61, 1.59)	0.96

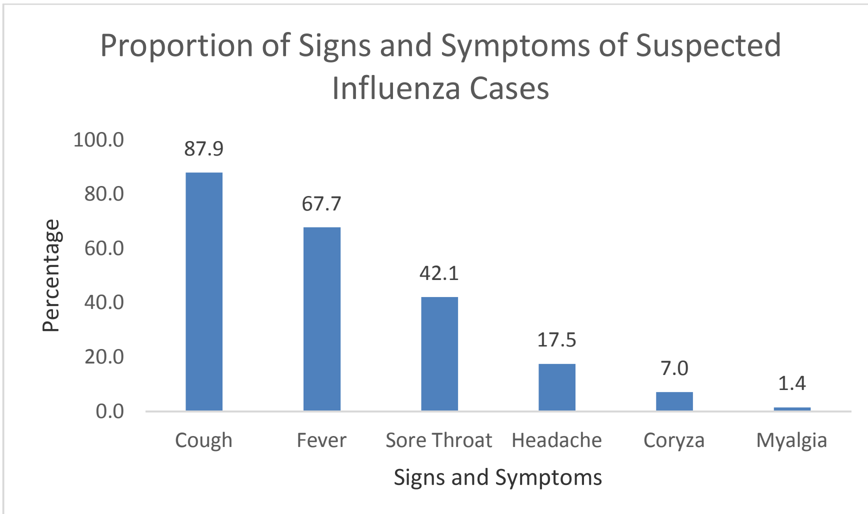

Fig. 3. Proportion of Signs and Symptoms of Suspected Influenza Cases (N=2,089)

Out of the 2,089 observed, 87.9% (95%CI: 86.4% - 89.2%) of cases had cough as part of presentation of signs and symptoms compared with 67.7% (95%CI: 65.0% - 69.0%) being proportion with fever. This is a clear indication that fever and cough were not used as a conditional sign and symptom during screening of patients for influenza-like illnesses (above Fig. 3.).

Three hundred and forty-eight (16.6%) out of the 2,089 cases were laboratory-confirmed for influenza virus infection by real-time reverse transcription–polymerase chain reaction (RT-PCR). The positive results had the following distribution; Seasonal Influenza A(H3N2) - 41 (11.8%), Influenza B – 184 (52.9%) and Influenza A (H1N1)pdm09 – 123 (35.3%).

Considering the various signs and symptoms independently, cough showed a sensitivity of 93.7% (95%CI: 90.4% - 95.9%), which was higher than that of fever (74.1%; 95%CI: 69.1% - 78.5%) and headache (12.1%; 95%CI: 8.9% - 16.0%). The sensitivity of headache was significantly associated with a positive influenza infection but unlike fever and cough, the odds ratio (OR: 0.6, 95%CI: 0.42 – 0.85) was not clinically plausible. Cough had a lower specificity (13.3%; 95%CI: 11.7% - 14.9%) than fever (33.3%; 95%CI: 31.3% - 35.8%).

Fever/cough alone had a significant high sensitivity (69.0%; 95%CI: 64.0% - 74.0%) and specificity (42.0%: 95%CI: 40.6% - 45.3%) values. Patients with fever/cough alone had the highest negative predictive value (87.4%; 95%CI: 85.0% - 89.5%).

Looking at the combination of fever/cough, which is conditional as per case definition, with other signs and symptoms, only that of a sore throat was significantly associated with a positive influenza laboratory result. It had a sensitivity of 34.2% (95%CI: 29.2 – 39.4) and specificity of 77.7%. A sore throat together with fever/cough had the highest negative predictive value of 85.5% (Table 2.).

All the significant associations of the various signs and symptoms with positive influenza virus infection were fed into a logistic regression model. The adjusted Odds Ratio of fever/cough was 1.40 (95%CI: 1.06, 1.86). That for fever/cough/sore throat was 1.52 (1.15, 2.02) in the presence of fever/cough alone (Table 3.).

Table 2. Fever and Cough in combination with other signs and symptoms

Signs & Symptoms	Freq (%)	Odds Ratio (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	P-value *
Fever, Cough	1,234 (59.0)	1.69 (1.32, 2.17)	69.2 (64.0, 74.0)	42.9 (40.6,45.3)	19.5 (17.3,21.8)	87.4 (85.0,89.5)	*P* <.001
Fever, cough & headache	172 (8.2)	1.01 (0.71, 1.43)	8.3 (5.7, 11.8)	91.8 (90.3,93.0)	16.8 (11.7,23.4)	83.4 (83.3,81.5)	*P* = .94
Fever, cough & coryza	90 (4.3)	0.54 (0.27, 1.09)	2.6 (1.2, 5.0)	95.3 (94.2,96.2)	10.0 (4.9, 18.5)	83.0 (81.3,84.6)	*P* = .08
Fever, cough & Myalgia	12 (0.6)	2.51 (0.75, 8.41)	1.1 (0.3, 3.1)	99.5 (99.0,99.7)	33.3 (11.2,64.5)	83.4 (81.7,84.9)	*P* = .12
Fever, cough & Sore throat	506 (24.2)	1.18 (1.42, 2.33)	34.2 (29.2, 39.4)	77.7 (75.7,79.6)	23.5 (19.9,27.5)	85.5 (83.6,87.2)	*P* < .001
Fever, cough, Sore throat & Myalgia	6 (0.29)	5.03 (1.01,25.06)	0.8 (0.2, 2.6)	99.8 (99.4,99.9)	50 (13.9,86.0)	86.3 (81.6,84.9)	*P* = .06 (F)

** - chi-square p-value; F = F-statistics*

Table 3. Logistic Regression on signs & symptoms and laboratory outcome

Signs & Symptoms	Unadjusted Odds Ratio	Adjusted Odds Ratio (95% C.I)	***P*-Value (adjusted)**
Fever/ cough	1.69 (1.32, 2.17)	1.40 (1.06, 1.86)	*P* = .017
Fever/ Cough/Headache	1.01 (0.66, 1.54)	-	-
Fever/ Cough/Coryza	0.54 (0.27, 1.09)	-	-
Fever/ Cough/ Myalgia	2.51 (0.75, 8.41)	-	-
Fever/ Cough/ Sore throat	1.81 (1.41, 2.33)	1.52 (1.15, 2.02)	*P* < .001
Fever/Cough/Sore throat/ Myalgia	5.03 (1.01, 25.06)	-	-

The proportion of common signs and symptoms in this study were a cough (87.9%), fever (67.7%) and sore throat (42.8%) among the 2,089 patients enrolled. Another study of 369 patients conducted in the United States of America documented the predominant signs and symptoms shown among influenza patients to be a cough, coryza, sore throat, and fever in patients with influenza infection [15].

The prevalence of influenza has ranged from 5% to 20% in the United States as estimated by the Centers for Disease Control and Prevention (CDC) [16]. A proportion of 16.6% (95%CI: 15.1% - 18.3%) was positive for influenza virus in this study with a similar study in Western Kenya having 9% as the proportion of laboratory-confirmed influenza infections (14). There are some wider variations though, for instance with the study of 3,744 subjects enrolled by Monto *et al* (2000) with baseline influenza-like symptoms, where 2470 (66%) were confirmed to have influenza in a pooled analysis [17].

The case definition of an ILI, which suggests a person presenting with fever and cough with other respiratory symptoms was not strictly adhered to as the frequency of a cough was more than fever and the variation was significant as per their respective 95% confidence intervals. Sensitivity, specificity and predictive values of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity (9). This study considered only a positive influenza virus infection without recourse to the various subtypes. A patient who reported symptoms of a cough alone (Sensitivity - 93.7%; Specificity - 13.3%; P < .001) was 2.3 times more likely to have a positive influenza laboratory diagnosis as compared with those who did not in this study. The sensitivity obtained with a combination of fever and cough was 69.2% (95%CI: 64.0% - 74.0%). The best multivariate predictors of influenza infections were fever and cough with a positive predictive value of 79% (P < .001) (17).

Recommendations from the Advisory Committee on Immunization Practices indicated that among adult populations, estimates of a positive predictive value (PPV) of a simple clinical definition of influenza (acute onset of a cough and fever) for laboratory-confirmed influenza infection have varied. These have ranged from 79% to 88% (9). The PPV (19.5%; 95%CI: 17.3% - 21.8%) of cough/fever alone for this study, which covered children as well, was relatively lower. cough/fever had a relatively high sensitivity and specificity of 69.2% and 42.9% respectively.

The two combinations of cough/fever and cough/fever/sore throat that were included in the adjusted model remained significant predictors for an influenza positive infection. Of much interest will be the combination of cough/fever, which had a relatively higher sensitivity (69.2%; 95%CI: 64.0 - 74.0) and specificity (42.9%; 95%CI: 40.6 - 45.3) values as against the other combination of signs and symptoms (Table 2.). A study in Western Kenya, on the other hand, had a cough and fever showing a higher sensitivity of 87·0% (95% CI: 83·3-88·9) (14). In the adjusted analysis, cough/fever/sore throat indicated an Odds Ratio of 1.52 (95%CI: 1.15 - 2.02) as compared with 1.40 (95%CI: 1.06 - 1.86) for cough/fever alone. This is important in light of the case definition encouraging the inclusion of other respiratory signs and symptoms in addition to a cough and fever.

In Korea, 372 (44.9%) out of 828 patients were confirmed with H1N1 infection by real-time reverse transcription-polymerase chain reaction (RRT-PCR). A cough was the most common independent symptom in patients with laboratory-confirmed (H1N1)pdm09 infection, and further suggested the combination of a cough plus fever or myalgia as a clinical diagnostic criteria (17) whereas this study identified a sore throat as the additional significant sign.

4. CONCLUSION

With the rapid spread of respiratory virus infections, prompt diagnosis is needed for successful case management and prevention of further transmission. The case definition for ILI was loosely applied considering the variation between the frequencies of patients with a cough or fever. A cough and fever alone were also significantly associated with a positive influenza infection. A combination of signs and symptoms is, however, more useful as that is a more likely scenario and also specified by the case definition. In this vein, fever and cough with a sore throat had the strongest association 1.52 (95%CI: 1.15 - 2.02) with a positive influenza infection in the adjusted analysis. The cough/fever/sore throat had a sensitivity of 34.2%, specificity of 77.7%, PPV of 23.5% and NPV of 85.5%.

Most diseases or infections present with fever, therefore not looking at fever in isolation but in combination with a cough and sore throat will improve the efficiency of clinical diagnosis and laboratory investigations in detecting influenza viruses in the face of limited laboratory resources.

5. RECOMMENDATIONS

It is worth noting that case definitions for influenza-like illness are primarily not intended to capture all cases but to describe trends over time (12). Due to the need for consistency in the use of case definitions for global influenza surveillance, it is strongly recommended that clinicians should stick with the mandatory signs and symptoms of fever and cough in the ILI case definition and consider a sore throat as the most likely combination for influenza-associated respiratory infection at Out-Patient Departments in the study population.

Other respiratory signs aside sore throat should however not be ignored in the ongoing ILI surveillance. This will certainly call for further retraining and orientation on the use of the ILI surveillance case definition.

CONSENT

The study was conducted with anonymized secondary records that formed part of the country's routine sentinel data using the Integrated Disease Surveillance and Response approach.

ETHICAL APPROVAL

The Disease Surveillance Department which is the repository of surveillance data including that of influenza surveillance gave permission for the anonymized dataset to be used.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ucakar V, Socan M, Trilar KP. The impact of influenza and respiratory syncytial virus on hospitalizations for lower respiratory tract infections in young children: Slovenia, 2006–2011. Influ J. 2013;7(6):1093-102. Accessed 19 September 2017. Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634267/pdf/IRV-7-1093.pdf
2. Juárez-Reyes A, Noyola DE, Monsiváis-Urenda A, Alvarez-Quiroga C, González-Amaroa R. Influenza virus infection but Not H1N1 Influenza Virus Immunization is associated with changes in peripheral blood nk cell subset levels. Clin Vaccine Immunol J. 2013;20(8):1291-7. Accessed 20 July 2017. Available:http://cvi.asm.org/content/20/8/1291.full.pdf+html
3. Mizgerd JP. Acute lower respiratory tract infection. New Engl Med J [Internet]. 2009; 358(7):716–27. Accessed 05 October 2016. Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2711392/pdf/nihms109753.pdf
4. Wesseling G. Occasional review : Influenza in COPD : Pathogenesis, prevention, and treatment [Internet]. 2007;2. Accessed 22 October 2016. Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2692115/pdf/copd-2-5.pdf
5. World Health Organization. The Global Burden of Disease: 2004 update [Internet]. Vol. 2010, Update. Switzerland; 2008. Accessed 03 August 2016. Available:http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf
6. World Health Organization. Influenza: Overview. Fact Sheet No. 211. 2003. Accessed 12 August 2016. Available:http://www.who.int/mediacentre/factsheets/2003/fs211/en/
7. Katz MA, Schoub BD, Heraud JM, Breiman RF, Njenga MK, Widdowson M. Influenza in Africa: Uncovering the epidemiology of a long-overlooked disease. J Infect Dis. 2012;206(Suppl 1):4-7. Accessed 14 August 2016. Available:https://academic.oup.com/jid/article/206/suppl_1/S1/984364/Influenza-in-Africa-Uncovering-the-Epidemiology-of-Long-Overlooked-Disease
8. World Health Organization. WHO recommendations on the use of rapid testing for influenza diagnosis. 2005. Accessed 23 August 2016. Available:http://www.who.int/influenza/resources/documents/RapidTestInfluenza_WebVersion.pdf
9. Centers for Disease Control and Prevention. Clinical Signs and Symptoms

of Influenza; 2008. Accessed 22 August 2016.
Available:http://www.cdc.gov/flu/professionals/acip/clinical.htm

10. Yang J-H, Huang P-Y, Shie S-S, Yang S, Tsao K-C, Wu T-L, et al. Predictive symptoms and signs of laboratory-confirmed influenza: A prospective surveillance study of two metropolitan areas in Taiwan. Medicine (Baltimore). 2015;94(44):e1952. Accessed 05 September 2017.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4915903/pdf/medi-94-e1952.pdf
11. Socan M, Prosenc K, Nagode M. Differences in clinical predictors of influenza in adults and children with influenza-like illness. Central European Journal of Medicine; 2010. Accessed 07 September 2017.
Available:https://link.springer.com/article/10.2478/s11536-009-0089-3
12. WHO Global Influenza Programme Surveillance and Epidemiology Team. WHO Interim Global Epidemiological Surveillance Standards for Influenza; 2012. Accessed 25 August 2016.
Available:http://www.who.int/influenza/resources/documents/INFSURVMANUAL.pdf?ua=1
13. Nyawanda BO, Mott JA, Njuguna HN, Mayieka L, Khagayi S, Onkoba R, et al. Evaluation of case definitions to detect respiratory syncytial virus infection in hospitalized children below 5 years in Rural Western Kenya , 2009 – 2013. BMC Infect Dis. 2016;16(218):1-10. Accessed 30 July 2016.
Available:http://dx.doi.org/10.1186/s12879-016-1532-0
14. Murray EL, Khagayi S, Ope M, et al. What are the most sensitive and specific sign and symptom combinations for influenza in patients hospitalized with acute respiratory illness? Results from western Kenya, January 2007-July 2010. 2013. Accessed 24 July 2016.
Available:https://www.ncbi.nlm.nih.gov/pubmed/22417876
15. Babcock HM, Merz LR, Dubberke ER, Fraser VJ. Case-control study of clinical features of influenza in hospitalized patients. Infect Control Hosp Epidemiol. 2008;29(10):921-6.
16. Swierzewski SJ. Flu overview, incidence and prevalence of influenza; 2016. Accessed 15 August 2017.
Available:http://www.healthcommunities.com/influenza/overview-of-flu.shtml
17. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Archives of Internal Medicine. 2000;160:3243–7. Accessed 23 September 2016.
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