Case Definitions for Influenza: Need for standardization in the Indian settings

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Abstract

Influenza is a major cause of ill health and fatality in India. The present study evaluates the performance of case definitions for Influenza enabling these to be used as a screening tool. The study includes patients with any acute medical illness of recent onset, including acute exacerbations of underlying chronic conditions. The authors have employed appropriate methodology and a good study design. The validity of the study is questionable since the authors have included only hospitalised patients. Though the authors have calculated relative risk to determine the symptoms which predict Influenza closely, but multivariate logistic regression would have been a better approach due to multiplicity of comparisons. Receiver operating characteristic (ROC) curves could have been plotted for all the case definitions and sign/ symptom combinations to determine their diagnostic accuracy.

Introduction

The case definitions employed for the surveillance of Influenza vary worldwide and are often different from those recommended by the World Health Organization (WHO). According to WHO, the case definition for influenza-like illness includes measured fever and cough or sore throat whereas that for severe acute respiratory illness (ARI) the inclusion criteria is cough or sore throat, measured fever, shortness of breath and need for hospitalization. However, there is no international consensus on the use of the WHO case definition due to the extremely varied clinical syndrome of Influenza infection and the objectives of the surveillance. Therefore, efforts are being undertaken to standardize influenza case definitions.

Methodology

The present study evaluated the WHO case definitions for Influenza among hospitalized patients including those patients with atypical clinical presentations, particularly caused by acute exacerbations of underlying chronic diseases.

This study was conducted in Pune district of India among patients hospitalized in any of the 29 public or private hospitals for any acute medical illness from May 2009 to April 2011. Clinical information was obtained from medical records and interviews. Nasal or throat swabs were collected and results of reverse-transcription polymerase chain reaction (RT-PCR) were used to determine the accuracy of Influenza case definitions. A risk-factor analysis was conducted to estimate predictive value of various clinical symptoms in the identification of influenza.

Sensitivities, specificities, positive and negative predictive values were estimated.

Of the 3,179 patients, 21% were PCR-positive for influenza virus and 3.1% had at least one chronic condition. Among patients <5 years, vomiting (RR-0.49, *P*=0.047) and diarrhoea (RR-0.37, *P*=0.011) were more common among PCR-negative patients whereas in patients ≥5 years, cough (RR-2.38, *P*=0.00), sore-throat (RR-2.01, *P*=0.00) were more common in PCR-positive patients than their counterparts.

For severe ARI, WHO definition had sensitivity of 11% among patients < 5 years and 3% among those aged ≥5 years. On exclusion of shortness of breath, the sensitivities increased to 69% in < 5 years patients and 70% in ≥5 years patients, while specificities reduced to 43% and 53%, respectively. The inclusion of cough and reported or measured fever in WHO definition for influenza-like illness among patients aged ≥ 5 years increased sensitivity from 70% to 80% but decreased specificity from to 42% from 53%.

Discussion

Influenza infection is characterised by an extremely varied clinical syndrome, which partly explains why case definitions used for the investigation of Influenza vary worldwide. Though WHO has recommended case definitions for surveillance of Influenza, they are not universally adopted in national and regional surveillance programmes[1].

Influenza is a viral infection which is highly prevalent world-wide and is a major cause of ill-health, disease and fatality even

in India. It has posed a serious public health challenge and created tremendous adversity on the already over-strained health system in India[2]. The current gold standard to identify patients infected with Influenza virus is RT-PCR[3]. However, in light of the limited resources and financial constraints, the diagnosis of Influenza remains questionable. The present study evaluates the validity of the Influenza case definitions enabling these to be used as a screening tool to identify these patients, thereby reducing the burden on the already overstretched health system in developing countries like India[4]. The use of validated case definitions would limit the use of expensive investigations to confirm the Influenza infections in patients screened positive[5].

This study has several strengths as compared to previous studies. The most striking feature of the study which sets it apart from the previously conducted studies is that patients with any acute medical illness of recent onset, including acute exacerbations of underlying chronic conditions were enrolled. All the previous studies have evaluated the Influenza case definitions among patients presenting with fever or respiratory symptoms and missed patients with atypical presentations.

It is a large study of public health importance with a good sample size. The study plan, methodology, analysis and results meet the objectives of the study. The authors have specified the exclusion and inclusion criteria as well as the laboratory methods in detail. Trained research staff was selected for screening and trained study physicians were used for carrying out clinical examinations which increased the credibility of the study[6].

However, there are certain limitations in this study. For the present study, surveillance for hospitalized influenza cases was conducted in 29 hospitals in Pune district of Western India. The internal validity of the study is dubious due to the fact that the study design and sampling method have not been explained in detail. Population set is not representative as only one district was selected for the study. External validity of the study is also questionable since the study is restricted to in-patients only[7].

In determining influenza positivity among patients with chronic diseases, the authors have included asthma, chronic lung disease, cardiovascular disease, diabetes, tuberculosis and neurological disorders. The authors have not explained the reason for excluding other chronic diseases like chronic liver disease, chronic renal disease, neuromuscular disease, haematological disorders and immunodeficiency (including HIV) mentioned in the "WHO Interim Global Epidemiological Surveillance Standards for Influenza (2012)" for surveillance of atypical Influenza cases[3].

"WHO Interim Global Epidemiological Surveillance Standards for Influenza (2012)" have recommended criteria for major age grouping in reporting of data to ensure uniformity in reporting, analysis, and comparison of patterns of Influenza world-wide. Recommended major age groupings for reporting are: 0 to <2 years; 2 to <5 years; 5 to <15 years; 15 to <50 years; 50 to <65 years; and ≥ 65 years. The authors have not given the reason for using unequal intervals for age groups[3].

In the study, the percentage of PCR positives in <5 years patients, has been mentioned as 22% in one section and 13% in another part of the article. Also, percentage of patients < 5 years reporting fever as one of the symptom has been calculated as 93% while the true value is 88 % and percentage of patients <5 years reporting fast breathing has been mentioned as 14% whereas the true value is 13%. The authors have not explained the reasons for discrepancy in results.

In this study, 2% of children had missing information of any symptom or sign and 5% of children had missing history of any danger signs. These children with incomplete data were also included in the study. Unbiased results would have been generated if data for patients with missing information of any sign or symptom had been excluded from the study. Further, the authors have not given any information regarding blinding of the investigators and analysts which could have affected the results.

In determining the clinical predictors of Influenza in hospitalized patients, the authors calculated Relative Risk in the patients with symptom/sign and in those without symptom/sign using the information from only PCR positive patients. The authors have not given any information about patients who were PCR negative for Influenza virus to calculate relative risk[8].

Furthermore, in making a particular symptom responsible for Influenza positivity by calculating its relative risk may generate a bias. This is because the results could be positive due to some other symptom, if the patient had multiple signs and symptoms. Due to multiplicity of comparisons, a better approach would have been to do multivariate logistic regression to determine the symptoms which predict Influenza more accurately[9].

To evaluate the performance of standard case definitions and sign/ symptom combinations in the identification of influenza among hospitalized patients using RT-PCR as the reference, the authors calculated Sensitivity, Specificity, Positive and Negative predictive values. The authors should also have calculated Likelihood Ratio (LR) for a positive test and LR for a negative test with 95 percent confidence intervals (CI) to determine the diagnostic accuracy of the case definitions[10].

Receiver operating characteristic (ROC) curves could have been plotted for all the case definitions and sign/ symptom combinations and then the diagnostic accuracy assessed by calculating area under ROC. The best case definition for surveillance could then be considered using Youden Index (sensitivity + specificity – 1) which is the difference between the true positive and false positive rates. Applying this Index, the most valid and accurate case definition could be found in the study settings[11].

Conclusion

In the end, it can be concluded that the WHO case definitions for Influenza performed poorly in the Indian scenario. The pros and cons of the level of sensitivity and specificity that should be achieved in Indian settings needs to be fully explored.

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