Influenza case definitions need to be fit for purpose

P Priest (patricia.priest@otago.ac.nz)¹, H Kelly²

1. Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, New Zealand

2. National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia

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To the Editor: The recent paper by Jiang et al. [1] provides an in-depth analysis of the performance of different case definitions for detecting influenza A(H1N1)pdm09 among adults in the community, including those who have not presented for medical attention.

The authors concluded that the revised World Health Organization (WHO) influenza-like illness (ILI) definition was an improvement on alternative definitions used by the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC), based on its higher positive predictive value (PPV) and higher likelihood ratio for a positive test. However, these are not necessarily the most important measures of success for all ILI case definitions, and different definitions will be required for different purposes. Identifying influenza for surveillance, for case finding during activities to prevent spread during an epi-demic, and for case finding for participation in research studies of treatment or prevention of transmission will require different case definitions.

As the authors of the paper and accompanying editorial [2] note, important characteristics of a case definition for routine surveillance are sufficient sensitivity to identify the beginning of the influenza season or an epidemic, high specificity and consistent application over time. PPV is less relevant, because it varies with the prevalence of disease and the likelihood ratio is more relevant to clinical consultation rather than surveillance.

When almost complete case finding is required, for example, to detect a new strain as early as possible after it enters a country (it is probably not possible to keep out such strains [3,4]), highly sensitive case definitions are needed before laboratory testing, recognising that the PPV will be very low.

As noted by the authors, the key distinction between case definitions with higher and lower sensitivity is whether or not fever is required to meet the case definition. The WHO ILI case definition has poor sensitivity (36% for all reported episodes), as do all the other case

definitions except acute respiratory illness (ARI), with sensitivity of 94%. The next most sensitive case definition is the ECDC ILI definition (61% for all episodes). The ARI and ECDC case definitions do not require fever. In the study by Jiang et al., only half of the 36 illness episodes presumed to be caused by influenza A(H1N1)pdm09 were associated with fever. In addition to these 36 participants, a further 62 participants seroconverted but did not report episodes of illness and would not have been captured by any case definition (but may nonetheless shed virus [5]).

The findings from the recent study are consistent with published literature on the prevalence of fever and other symptoms in laboratory-confirmed cases of influenza. Among people with other respiratory symptoms and influenza A(H1N1)pdm09 infection, reported fever prevalence can be as low as 38% for non-pregnant hospitalised adults with community-onset pneumonia or influenza-like symptoms and underlying conditions [6]. For other strains of influenza, as few as 26% of adults with respiratory symptoms have a fever (body temperature $\geq 37.8^{\circ}\text{C}$) at presentation [7]. Where symptoms are not required for influenza testing (for example, when screening), the proportion of people with laboratory-confirmed influenza who have fever (body temperature $\geq 37.8^{\circ}\text{C}$) can be as low as 33% for influenza A(H1N1)pdm09 [8] and even as low as 3% for other strains [9].

Studies that report symptoms in laboratory-confirmed cases of influenza generally report fever at the time of influenza testing and will underestimate the proportion with fever at some time during an illness episode. However, case definitions are applied by clinicians and public health staff when deciding whether to take a specimen for influenza testing, and whether to isolate or quarantine people. When a case definition includes fever, fever at presentation is thus critical for decision-making in practice.

No single case definition will satisfy all situations. For routine surveillance, we suggest that the ECDC case definition probably has the best balance of sensitivity and specificity. On the other hand, case definitions

that do not include fever are necessary when finding almost all cases is required. Among those assessed by Jiang et al., only ARI has sufficiently high sensitivity for this purpose. Careful consideration is required to ensure that influenza or ILI case definitions are fit for purpose.

Conflict of interest

None declared.

Authors' contributions

The authors are equal contributors to all aspects of authorship.

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