

Evidence and policy for influenza control

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This edition of the journal includes two studies related to the control of influenza, one on neuraminidase inhibitor (NI) resistance [1] and the other on the effectiveness of trivalent influenza vaccine in the United Kingdom in 2012/13 [2]. Neuraminidase inhibitors (NIs) are the mainstay in influenza treatment and vaccination is the mainstay of prevention. It is thus important to monitor the effectiveness of both interventions over time. The current NI study demonstrates that mutations which may have had clinical significance for previously circulating seasonal influenza A(H1N1) viruses may not be clinically significant for influenza A(H1N1) pdm09 viruses, highlighting the importance of continued monitoring of NI resistance. Of equal importance is the continued monitoring of NI effectiveness [3].

Influenza is a common disease with the annual risk of influenza virus infection exceeding 20% in some years [4,5]. However the great majority of influenza virus infections do not present as the classical triad of fever, cough and fatigue [6-8], and a substantial proportion of infections, perhaps even more than half, are asymptomatic [4,5]. Even symptomatic illnesses are generally self-limiting. However a small proportion of persons with influenza virus infections will require admission to hospital, intensive care and a smaller proportion will die [9]. These outcomes are uncommon and are influenced by age, with increased risk at the two extremes of life, and the presence of co-morbidities [10]. For instance, unadjusted annual risk estimates of laboratory-confirmed influenza hospitalisation in hospitals from the Emerging Infections Program in the United States between 2005 and 2011 ranged from 20 to 72 per 100,000 for children up to the age of four years, from 16 to 76 per 100,000 for adults aged at least 65 years, but only from 5 to 14 per 100,000 for adults aged 20 to 64 years, although higher in the first year after influenza A(H1N1)pdm09 emerged [11]. About 10–30% of people hospitalised with influenza will require intensive care [12-14], and about 3–10% of patients hospitalised with laboratory confirmed influenza will die [13-15].

Because serious outcomes are relatively rare, randomised controlled trials (RCTs) in ambulatory settings for the treatment of influenza with NIs or the prevention of influenza by vaccination have not been designed with sufficient power to examine these outcomes. RCTs of antiviral drugs [16] and vaccines [17] and have shown efficacy against suspected and laboratory-confirmed influenza acquired and managed in the community but there are no RCTs investigating outcomes of hospitalisation or death due to laboratory-confirmed influenza.

It is generally acknowledged that when outcomes are rare, the RCT is not necessarily the study design of choice. The classic case–control study, in which cases and controls are ascertained retrospectively, has often been the preferred alternative design. A variation of the classic design has become increasingly popular for studying vaccine effectiveness (VE) against specific outcomes. In what is referred to as the case–test–negative design, patients with respiratory symptoms are ascertained prospectively, and vaccine coverage is compared between those who test positive and those who test negative for influenza, adjusting for potential confounders [18]. The second study of influenza in this issue of the *Eurosurveillance* uses the case–test–negative design in pooled community-based studies from the United Kingdom to estimate influenza VE against medically-attended respiratory disease confirmed as influenza. It reports point estimates of 73%, 26% and 51% against influenza A(H1N1), A(H3N2) and B, respectively [2]. These results confirm a number of other findings of low VE against influenza A(H3N2) in recent years [19-21], attributed to mismatch between the vaccine and circulating strains [19]. They also highlight the importance of monitoring not only the antigenic match, as determined by serological assays, but also the genetic relatedness of circulating and vaccine viruses.

The case–test–negative design is also being increasingly used for studies of hospitalised patients, using PCR-confirmed influenza as an outcome. These studies suggest that inactivated influenza vaccines decrease the risk of hospital admission for laboratory-confirmed influenza by about half [22,23], although lower

estimates have been reported for the protection against influenza A(H₃N₂) in the elderly [24] and higher estimates for protection against influenza A(H₁N₁)pdm09 [25]. A 50% decrease in risk is similar to effectiveness estimates from community observational studies using the same design [26,27], and efficacy estimates from meta-analyses of community-based trials [17].

For information on the effectiveness of NIs among hospitalised patients, we likewise need to rely on observational studies. A recent review critically examined published cohort studies assessing oseltamivir treatment for laboratory-confirmed influenza and found evidence suggesting protection against mortality in four studies, all of which were judged by the review to be of reasonable quality, and between which there was no statistical heterogeneity [28].

Even the best designed observational studies may be subject to residual bias, suggesting the need for RCTs. However RCTs of NIs in outpatients with increased risk of complications, and in patients hospitalised soon after onset of symptoms may no longer be feasible because oseltamivir is the accepted front-line treatment in groups of patients with suspected or confirmed influenza [29-31] and such trials may no longer be granted ethical approval. The same argument applies to influenza vaccination for people aged 65 years and over. For these reasons, better quality data are unlikely to be derived from RCTs, so that observational studies might do well to follow published quality guidelines in an effort to improve VE estimates [32].

Doubt has been cast on the efficacy of influenza vaccines against serious outcomes in the elderly because of the absence of trial data [33]. Similar discussions are occurring about the efficacy of anti-viral medication [3,16]. At the same time, it is being increasingly recognised that influenza infection in the community is common and that infections are associated with a wide clinical spectrum, but the serious consequences of infection are generally uncommon, and often rare, in healthy young people [5]. Improved policies for the control of influenza virus infection should acknowledge the wide clinical spectrum resulting from infection, so that prevention or treatment of serious outcomes will be attempted when serious outcomes are more likely. Such policies should use data from observational studies where trial data are absent.

Conflict of interest

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