# Editorial

## Mistaken identity: seasonal influenza versus influenza-like illness

Readers of *Clinical Evidence* who are interested in influenza will have been struck by the disparity between policy recommendations and the clinical evidence of the performance of inactivated influenza vaccines.[1][2] For example, there are few RCTs assessing the effectiveness of inactivated vaccines in children and the elderly. Only five RCTs have been carried out in elderly people, of which only one was carried out in the past 2 decades using vaccines available today.[3] Although the evidence is more robust in healthy adults, and partly supports the use of vaccines, this is the population who are universally considered to need them least.[1][2]

The reasons for the contradictions between policy and evidence, and the dearth of corroborating evidence on vaccine performance, are complex and include: the relative rarity of influenza; the current confusion between influenza-like illness and influenza (a simplistic aetiopathogenic model hide-bound by Henle-Koch's postulates of one germ, one disease, one solution); the inability of vaccines to protect populations from an ever-mutating agent; and the difficulty of conducting meaningful prospective studies to assess vaccine efficacy. In addition, the powerful image of influenza depicted by the media is not proportional to the actual threat. The "monster at your door" fame of influenza helps to create preventive expectations that are unachievable with today's technology and with only partial reading of the evidence. For example, we know that in the past 2 decades influenza vaccine studies have risen in prominence in the scientific media, possibly as a result of pharmaceutical sponsorship and the need of larger journals to boost their revenue by selling bulk reprints and subscriptions to offset the decline in print-based returns.[4][5] This rise in prominence is, however, in contrast to the threat from influenza. In the US, the influenza-related mortality rate of the past 20 years has not increased, but plateaued.

Here, I examine the evidence for and the impact of the first two factors listed above — the incidence of influenza, and the masking of its rarity by the systematic failure to distinguish between influenza (a disease) and influenza-like illness (a syndrome, caused also in minor part by influenza viruses).

The causal relationship between the two is scarcely investigated and is frequently overlooked, perhaps because of technical difficulties in quantifying the incidence of "seasonal" influenza and its complications. I must confess that I realised the importance of incidence only after having carried out scores of Cochrane reviews and updates on influenza vaccines and antivirals. I started from the end (the interventions) instead of concentrating on the beginning (the epidemiology of influenza and the other respiratory viruses).

The incidence statistic for influenza, which is often taken for granted, is estimated from virological testing of symptomatic people (so-called viral circulation). What is often poorly understood is that the patient presenting to a physician typically has a syndrome (influenza-like illness, or ILI) that can be caused by various agents. Only a proportion of these syndromes is caused by influenza A and B viruses, but differential diagnosis on clinical grounds alone is not possible.[6][7] Google's near real-time instrument, Flu Trends, provides an excellent example of the confusion generated from following the inaccurate equation "influenza = ILI".[7] Users of Flu Trends think they are following the spread of influenza, while in reality the site depicts the spread of ILI.

To determine (not estimate) the incidence of influenza at any one time, virological testing of a truly random sample of people with ILI is needed. At the same time, testing for all other major causal agents should be carried out, but this is not typically done. In addition, it is not known, or cannot be estimated accurately, how many people have ILI at a given time, which further complicates calculation of incidence. The consequence of this is biased estimates of incidence, where attention is focused on testing for influenza viruses in non-randomly identified people with ILI. Ignorance of the presence of other causal agents has made us blind to the complex ecology of respiratory viruses. How can systematic reviews obviate such tunnel vision?

At present, the only method of determining influenza incidence with a high level of accuracy is to use the control arms of influenza vaccines and antiviral studies. From these, reliable denominators (i.e., number of people with ILI) and numerators (i.e., number of people with influenza and its complications) can be calculated. This is simpler than it sounds. The Cochrane Vaccines Field group has a database of all identifiable studies from 1948 to 2007 that assess the effectiveness of inactivated influenza vaccines and report clinical outcomes (as opposed to surrogate outcomes, such as antibody responses). These are the studies that populate our Cochrane reviews and their updates. The database also comprises studies excluded from the reviews, provided they are comparative and report clinical outcomes. Data available in these studies are collected during the active follow-up of formal studies (often prospectively), in which participant controls with ILI are typically tested (figure 1). As such, they are the optimum data available on influenza incidence. However, high loss to follow-up detracts from the reliability of the data. The data depicted in figure 1 come from the control arms of 95 vaccine comparative studies published between 1965 and 2005 that report, between them, several million observations on incidence.

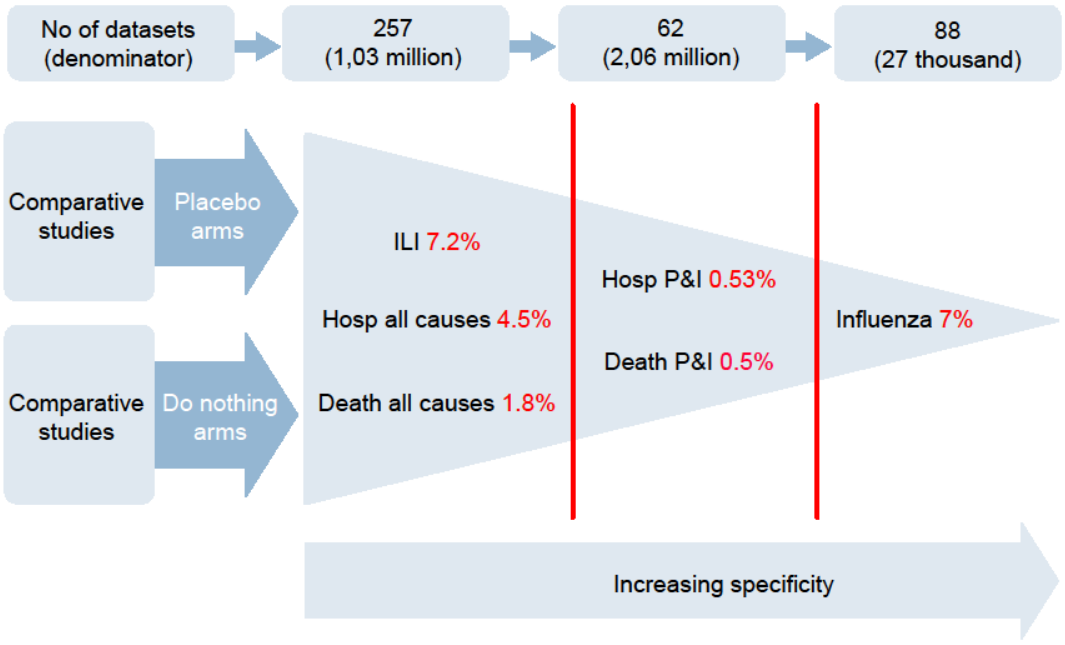


**Figure 1.** Graphic representation of funnel data in the general population. ILI, influenza-like illness; P&I, pneumonia and influenza (includes ICD 9 codes 480–488).

The availability of a considerable body of data, as figure 1 illustrates, does not always generate a strong evidence base on which to judge efficacy. In the case of inactivated influenza vaccines, the key issue in interpreting the data is over-reliance on non-specific outcomes, such as death from all causes, which may have little to do with influenza-related death. Studies with such non-specific outcomes have been purported to show the effectiveness of influenza vaccines, but actually they only introduce confounding. The funnel in figure 1 exemplifies the richness of data on non-specific outcomes, and the paucity of data on laboratory confirmed influenza A or B. However, this is only part of the story, as data from control arms of comparative vaccine studies seldom look for other viral agents among the samples. Control arms show what is certainly influenza (as is their objective), but do not identify other agents. One of the subliminal effects of this is that observers focus exclusively on one agent, ignoring the rest.

In addition, the data allow a best guess as to how prevalent influenza is, but not its complications. Based on studies in the Cochrane database, incidence of influenza is estimated at around 7%. However, the control arms of the 95 studies identified evaluate people with ILI. Therefore, 7% is not the absolute incidence of influenza in the general population, but is rather the portion of ILI that is caused by influenza, making the incidence of influenza itself in the general population much smaller (approximately 0.5%). Studies of influenza vaccines do not serve well for apportioning slices of the ILI "pie" to non-influenza agents, as they seek only influenza. To do this, we must turn to pie studies, which are a systematic assembling of data from the few studies that followed a defined population, and swabbed ILI symptomatic people for all major agents.

A brief review of pie studies published in the past decade and available in the Cochrane database paints a remarkably similar picture to that of control arms, with an incidence of influenza of 0.5% to 1% of ILIs. Figure 2 shows how the systematically assembled evidence from control arms fits with that from pie studies. Surprisingly, most ILIs cannot be attributed to a specific causal agent. Although many other conclusions can be drawn from observations of pie slices, our aim here is to discuss why influenza inactivated vaccine performance is poor, and why most studies rely on non-specific outcomes, such as death from all causes, and hospitalisations for pneumonia and influenza (which are not usually based on virological testing). One possible answer is that seasonal influenza is a relatively rare and benign condition, with an incidence not exceeding 1% in the general population during autumn and winter months.

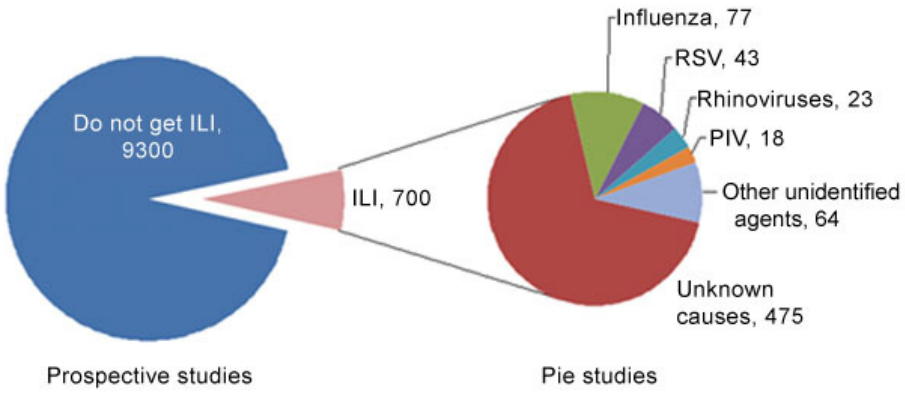


**Figure 2.** Incidence of influenza-like illnesses (ILI) per 10,000 people (calculated from prospective studies), with breakdown by agent, based on information in pie studies.

Vaccine effectiveness (expressed as a percentage) is calculated by subtracting the ratio of incidence in vaccinated and unvaccinated populations from 1. Therefore, if the incidence in the unvaccinated population is low, then the ratio will be close to 1 and effectiveness will be low. So, vaccines seem to be less effective in illnesses with low incidence. A systematic approach to best evidence completes the picture, and explains what is observed in trials and other comparative studies. In summary, evidence presented here points to influenza being a relatively rare cause of ILI and a relatively rare disease. It follows that vaccines may not be appropriate preventive interventions for either influenza or ILI.

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