Using the internet to estimate influenza vaccine effectiveness

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Body of Text

Influenza virus strains undergo continuous antigenic drift and occasional shifts. Because of ongoing mutation and selection for new strains, influenza vaccines need to be updated annually. Since vaccine development usually takes several months, every year an educated guess is taken well in advance as to which strain will be dominating in the forthcoming season. Despite best efforts by public health officials and vaccine manufacturers, the match between the circulating and vaccine strains is sometimes poor. Hence, every year there is considerable uncertainty as to the efficacy of the vaccine and the effectiveness of the influenza vaccination programme. Yet information on these is essential to help guide future vaccine decisions and to design appropriate immunisation programmes and public health messages. This necessitates annual reassessments of the vaccine and the effectiveness of the programme.

Ideally large scale randomised controlled trials (RCTs) should be undertaken to assess the efficacy of the vaccine, but it is impracticable to conduct them every year and may even be unethical given that many countries recommend the routine use of the vaccine in the elderly and risk groups. For these reasons most data on influenza vaccine effectiveness come from observational studies – usually cohort studies. Again for practical reasons, these are frequently retrospective cohort studies, conducted using routine electronic health records [1-4]. Health outcomes (typically non-specific outcomes such as all-cause mortality or hospitalisation) are compared in the vaccinated and unvaccinated cohorts, usually over the course of a defined season. There are a number of major problems with this method, the most important being selection bias – the vaccinated cohort frequently differing from the unvaccinated, in ways that are difficult to control for by simply comparing routine electronic records [2-5]. These differences are such that the divergence in death rates between the two cohorts appears to persist even when influenza viruses are not circulating [2-4]. Furthermore, even if these difficulties can be properly controlled for (by sensitivity analysis [6], or by stratifying by season [2], for instance) then the methods (being retrospective) cannot provide information about the strain circulating at a given moment. For this, prospective cohort studies could be used. However, such studies, using traditional methods of recruiting individuals (such as through their physicians, or via some form of stratified random sampling) are very expensive and seldom performed.

The internet has permitted a new way to measure the incidence of common ailments in the community [7-10], currently mostly focusing on influenza-like-illness (ILI) as an easily identifiable disease with great public health importance. Such systems recruit participants and remind them (usually by e-mail) to regularly record episodes of illness using simple online surveys. In effect, these form a self-selected cohort, and as the data are recorded (and can be analysed) in real-time, they offer a relatively cheap method for conducting prospective studies. In principle, internet-based surveys can be expanded to very large numbers at little or no additional cost. Moreover, the incidence in self-reported vaccinated individuals can be compared to unvaccinated controls, allowing vaccine effectiveness to be estimated. Indeed, the immediacy of the system allows the relative incidences to be compared in real-time (see figure), thereby giving health authorities a means of estimating the effectiveness of the current vaccination programme. The figure shows the incidence of influenza-like-illness as measured by vaccinated participants and unvaccinated controls matched on age and risk group. The relative incidence of influenza, as recorded by laboratory reports of influenza viruses in Europe, is also shown. It can be seen that there is considerable self-reporting of ILI during the winter months, but there is no consistent difference between the vaccinated and unvaccinated cohorts until late in the season, when influenza viruses are more common. The divergence of incidence in the vaccinated and unvaccinated cohorts coincident with the occurrence of the virus is highly suggestive that what is being measured by the participants is at least in part genuine influenza, and that the vaccine is partially protective against this. Analogous country level results were presented "live" on individual platforms, such as the flusurvey website in the UK (www.flusurvey.org.uk).

Such web-based cohorts suffer from the same problems as other observational designs: controlling for confounders –particularly those that are unmeasured - being the most pertinent and difficult [2-6]. The peculiar nature of the sample may exacerbate some of the problems of representativeness inherent in all epidemiological studies and needs to be addressed as carefully as possible. Typical surveys have a background questionnaire filled out at enrolment, which should be detailed enough to adjust for all known confounders. Indeed, this facility offers an advantage over analysis of routine medical records, which may not consistently contain information on key variables such as smoking or household composition. In principle, the collection and analysis of these cohorts does not differ from any other similar study design, though in practice particular care needs to be taken to control for selection bias.

As currently implemented, these surveys record self-reported illness without laboratory confirmation. ILI is not specific to influenza, as demonstrated by the figure. The less specific an outcome is, the smaller the difference in incidence between the vaccinated and control groups, and the lower the estimate of vaccine effectiveness [4,11]. Thus, one would expect the effectiveness of the vaccine measured using unconfirmed self-reported illness to be less than that measured using more specific techniques [4]. There is no technical reason why self-reported illness cannot be confirmed via self-completed swabs or by asking participants to visit a physician (an approach that has recently been piloted in the Belgian internet-based cohort). If such swabbing schemes become established, it should be possible to estimate the effectiveness of the vaccine at preventing influenza, not just influenza-like-illness. Even so, the current systems provide an estimate of the effectiveness against self-reported illness in the community, which may not be the most specific of measures, but is surely is an important one.

Using the internet provides a convenient mechanism for individuals to report outcomes and behaviours. As such these surveys may offer further benefits to public health officials interested in monitoring the effectiveness of influenza vaccination programmes. Many countries have poor data on vaccine coverage. In particular, the rate of uptake of the vaccine compared with the spread of the infection is a crucial measure of programme success (there is little point vaccinating after the epidemic). Web-based systems are capable of giving this information [11], as self-reported history of influenza vaccine [12] and other health-care usage [13] appears to be accurately recorded. In addition, questions on attitudes to vaccination and disease can be incorporated. These can provide immediate insight into motivations behind vaccination decisions, which can help to monitor and tailor public health messages.

The internet is proving to be a useful adjunct to traditional ways of monitoring the incidence of common diseases [7-10]. Web-based surveys – if well designed – can provide a relatively cheap way to conduct epidemiological studies [11]. Due to the passive nature of recruitment into these surveys, and the requirement that participants have access to the internet, they inevitably suffer from a lack of representativeness. Problems of self-selection occur to some extent in all epidemiological surveys, but are clearly more acute using this sampling frame. However, with increasing access to broadband and availability of smart-phones the issues of representativeness are set to become smaller over time. Coupled with the relative ease with which large sample sizes can be obtained, it seems inevitable that these systems will become ever more common as a means of collecting data on illness in the community. Combined with background information on the participants, this can provide a wealth of information with a variety of applications, of which real-time assessment of vaccine effectiveness is just one obvious one.

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References

[1] Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med. 2007 Oct 4;357(14):1373-81.

[2]Mangtani P, Cumberland P, Hodgson CR, Roberts JA, Cutts FT, Hall AJ. A cohort study of the effectiveness of influenza vaccine in older people, performed using the United Kingdom general practice research database. J Infect Dis. 2004 Jul 1;190(1):1-10.

[3]Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol. 2006 Apr;35(2):337-44.

[4] Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007 Oct;7(10):658-66.

[5]Nichol KL. Challenges in evaluating influenza vaccine effectiveness and the mortality benefits controversy. Vaccine. 2009 Oct 23;27(45):6305-11

[6]Groenwold RH, Nelson DB, Nichol KL, Hoes AW, Hak E. Sensitivity analyses to estimate the potential impact of unmeasured confounding in causal research. Int J Epidemiol. 2010 Feb;39(1):107-17.

[7]Friesema IH, Koppeschaar CE, Donker GA, Dijkstra F, van Noort SP, Smallenburg R, van der Hoek W, van der Sande MA. Internet-based monitoring of influenza-like illness in the general population: experience of five influenza seasons in The Netherlands.Vaccine. 2009 Oct 23;27(45):6353-7.

[8]van Noort SP, Muehlen M, Rebelo de Andrade H, Koppeschaar C, Lima Lourenço JM, Gomes MG.Gripenet: an internet-based system to monitor influenza-like illness uniformly across Europe.Euro Surveill. 2007 Jul 1;12(7):E5-6.

[9] Brooks-Pollock E, Tilston N, Edmunds WJ, Eames KT. Using an online survey of healthcare-seeking behaviour to estimate the magnitude and severity of the 2009 H1N1v influenza epidemic in England. BMC Infect Dis. 2011 Mar 16;11:68.

[10] Tilston NL, Eames KT, Paolotti D, Ealden T, Edmunds WJ. Internet-based surveillance of Influenza-like-illness in the UK during the 2009 H1N1 influenza pandemic.BMC Public Health. 2010 Oct 27;10:650.

[11]Eames KT, Brooks-Pollock E, Paolotti D, Perosa M, Gioannini C, Edmunds WJ. Rapid assessment of influenza vaccine effectiveness: analysis of an internet-based cohort. Epidemiol Infect. 2012 Jul;140(7):1309-15.

[12] Mangtani P, Shah A, Roberts JA. Validation of influenza and pneumococcal vaccine status in adults based on self-report. Epidemiol Infect. 2007 Jan;135(1):139-43.

[13] Palmer L, Johnston SS, Rousculp MD, Chu BC, Nichol KL, Mahadevia PJ.Agreement between Internet-Based Self- and Proxy-Reported Health Care Resource Utilization and Administrative Health Care Claims. Value Health. 2012 May;15(3):458-65.

Figure legend

Comparison of weekly incidence of ILI in two matched cohorts in 7 countries (Belgium, France, Italy, Netherlands, Portugal, Sweden and United Kingdom) collecting data on ILI symptoms from www.influenzanet.eu during the 2011-12 season. Each week, participants are separated by whether they have been vaccinated against influenza (blue curve) or not (red curve), matched by age group and risk factors (underlying illness and living with children). For comparison, combined European sentinel and non-sentinel data on the number of specimens positive for influenza A and B is shown by the green dotted curve (source: European Centre for Disease Prevention and Control http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/epidemiological_data), rescaled so that the area under the curve is the same as in the unvaccinated cohort. The mean weekly number of participants included in the cohorts is approximately 7,500 (half vaccinated, half not).

Figure