Vaccine 32 (2014) 6884–6901

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Are influenza-associated morbidity and mortality estimates for those ≥65 in statistical databases accurate, and an appropriate test of influenza vaccine effectiveness?

Roger E. Thomas*

Department of Family Medicine, University of Calgary, Health Sciences Centre, 3330 Hospital Drive NW, Calgary, AB, Canada T2N 4N1

ARTICLE INFO

Article history:
Received 5 January 2014
Received in revised form 14 July 2014
Accepted 27 August 2014
Available online 27 October 2014

Keywords:
Influenza
Morbidity and mortality
Influenza vaccine effectiveness
Statistical models
Databases
RCTs

ABSTRACT

Purposes: To assess the accuracy of estimates using statistical databases of influenza-associated morbidity and mortality, and precisely measure influenza vaccine effectiveness.
Principal results: Laboratory testing of influenza is incomplete. Death certificates under-report influenza. Statistical database models are used as an alternative to randomised controlled trials (RCTs) to assess influenza vaccine effectiveness. Evidence of the accuracy of influenza morbidity and mortality estimates was sought from: (1) Studies comparing statistical models. For four studies Poisson and ARIMA models produced higher estimates than Serfling, and Serfling higher than GLM. Which model is more accurate is unknown. (2) Studies controlling confounders. Fourteen studies mostly controlled one confounder (one controlled comorbidities), and limited control of confounders limits accuracy.
Evidence for vaccine effectiveness was sought from: (1) Studies of regions with increasing vaccination rates. Of five studies two controlled for confounders and one found a positive vaccination effect. Three studies did not control confounders and two found no effect of vaccination. (2) Studies controlling multiple confounders. Of thirteen studies only two found a positive vaccine effect and no mortality differences between vaccinees and non-vaccinees in non-influenza seasons, showing confounders were controlled.

Key problems are insufficient testing for influenza, using influenza-like illness, heterogeneity of seasonal and pandemic influenza, population aging, and incomplete confounder control (co-morbidities, frailty, vaccination history) and failure to demonstrate control of confounders by proving no mortality differences between vaccinees and non-vaccinees in non-influenza seasons.
Major conclusions: Improving model accuracy requires proof of no mortality differences in pre-influenza periods between the vaccinated and non-vaccinated groups, and reduction in influenza morbidity and mortality in seasons with a good vaccine match, more virulent strains, in the younger elderly with less immune senescence, and specific outcomes (laboratory-confirmed outcomes, pneumonia deaths).

Proving influenza vaccine effectiveness requires appropriately powered RCTs, testing participants with RT-PCR tests, and comprehensively monitoring morbidity and mortality.

1. Introduction

Outcome measures in reviews of influenza vaccine usually include laboratory proof of influenza, respiratory and cardiovascular illness attributed to influenza, hospitalisation for influenza or pneumonia, death from influenza or pneumonia/influenza, influenza-like illness (ILI), ILI consultations, and all-cause mortality.

Influenza trends are estimated by statistical modelling of databases and are used as an alternative to RCTs to ascertain vaccine effectiveness but problems are:

> "To estimate the numbers of deaths attributable to seasonal and pandemic influenza is difficult, as influenza infections generally are not laboratory confirmed, are not often recognized and mostly not specified on hospital discharge forms or death certificates. Additionally many influenza associated deaths occur weeks after the initial infection from secondary complications or from exacerbations of chronic illnesses and in both cases influenza viruses are no longer detectable. ... the influenza virus may predispose to ... bacterial super infections and cardiovascular complications...The inability of diagnoses on death

* Corresponding author at: Department of Family Medicine, Faculty of Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, AB, Canada T2M1M1. Tel.: +1 403 220 0157; fax: +1 403 270 4329.
E-mail address: rthomas@ucalgary.ca

http://dx.doi.org/10.1016/j.vaccine.2014.08.090
0264-410X/

certificates to give a reliable and consistent account of the burden of death due to influenza has been understood for many decades and this understanding led to the development of statistical models to estimate influenza associated deaths" [1].

The purpose of this review is to assess whether estimates of influenza-associated morbidity and mortality are accurate, and are an appropriate test of influenza vaccine effectiveness.

2. Material and methods

Medline, Embase and Cochrane reviews were searched from inception to 28 December 2013 using "influenza" and ("death" or "mortality") with no language limitations. Relevant citations were also followed up with the Pub Med single citation search utility. A final search was performed on 1 July 2014 with "influenza" and ("death" or "mortality)" and ("model" or "statistic")

3. Results

3.1. Search

In total, 8740 abstracts/titles were retrieved (Medline: 897, Embase: 7721, Cochrane reviews: 122); 1487 entries were duplicates. Of the remaining 7253 entries, 278 were read in full-text. All relevant abstracts were read in full-text and followed up in Pub Med with the single citation search. A final search on 1 July 2014 identified 266 in Medline, 991 in Embase and 117 in the Cochrane database, yielding 4 additional articles.

3.2. Completeness of death certificates and laboratory reports

Death certificates markedly under-record influenza, especially older people with co-morbidities. In England and Wales 2005–8, 131 death certificates were coded influenza yet models estimated 12,700 premature deaths [2]. Autopsy rates are low: only 14% of Western Australian deaths received a coroner's autopsy: 22% had unknown or suspected infectious causes of death, of these 8.3% had a respiratory virus (0–9 years 28%), 3% influenza and 2% RSV [3]. Laboratory testing also underestimates influenza deaths as physicians test few cases. During the Danish 2009 pandemic regression models estimated deaths ten times higher than laboratory-confirmed influenza [4].

3.3. Influenza in nursing homes

Nursing homes are appropriate to assess vaccine effectiveness but there are few prospective studies with comprehensive laboratory testing. In 578 French nursing homes (44,869 residents ≥65; 93.4% received influenza, 13% pneumococcal vaccine) patients were assessed for infection by questionnaire and clinical examination [5]. The annual infection rate was 11.23% (95%CI 10.50, 11.97), with 4.60% (4.04, 5.54) classified definite; probable pneumonia 0.89% (0.69, 1.04) and definite 0.39% (0.32, 0.52); and probable upper + lower respiratory tract infections 3.34% (2.88, 3.87) and definite 1.31% (1.09, 1.68) [6]. A study of 98 French long-term care institutions 2004–5 (8041 patients; 93% residents received influenza vaccine, 35% staff) found 64% of residents exposed to ILI but only 3.5% tested for influenza. ILI-exposed patients had slightly higher hospitalisation risks (9.2% vs. 7.4%; RR 1.24; 1.05, 1.47) and all-cause mortality (5.8% vs. 4.3%; RR 1.36; 1.10, 1.70) [7]. Neither study assessed influenza vaccination. Because few prospective studies assess all patients for respiratory illness, collect virological data and assess all patient outcomes, statistical models assess influenza-attributed morbidity and mortality. Evidence was sought from two sources for influenza morbidity and mortality: studies comparing different statistical models, and models controlling for confounders. For vaccine effectiveness evidence was also sought from two sources: studies of the same region with low and higher rates of influenza vaccination (usually a policy change), and studies controlling for multiple confounders.

3.4. Do Serfling, GLM, Poisson and ARIMA models provide similar influenza mortality estimates?

Farr's Serfling model subtracted deaths in London during a winter with little influenza from an epidemic winter [8]. Four studies comparing different models were identified (Table 1). Studies of single models are widely reported in the literature and not commented on here. Lemaitre for France 1969–2010 compared Serfling and Poisson models only for the A/H1N1 2009–10 pandemic. For those >65 years-of-age estimates differed substantially. For pneumonia and influenza excess deaths the Poisson model estimated 3.5 (95%CI 1.2, 5.6)/100,000 and the Serfling 1.8 (−0.16, 3.7) and for respiratory excess deaths 4.1 (−0.94, 8.9) and 3.2 (−1.1, 7.8), respectively. Estimates were in the opposite direction with wide 95%CIs for cardio-respiratory −3.1 (−18, 11) and 7.4 (−4.6, 19), and all-cause deaths −6.59 (−41, 27) and 22 (−1.9, 45) [9]. López-Cuadrado found for Spain 1999–2005 that the Serfling model's estimates were higher than the GLM model (which assumed influenza deaths in any week were proportional to isolates). The Serfling model for those >64 years-of-age estimated a higher influenza and pneumonia excess annual death rate (15.25/100,000; 6413 deaths) than the GLM model (6/100,000; 2473 deaths); and also a higher all-cause annual death rate (164.1/100,000; 68,977 deaths) than the GLM model (57.05/100,000; 23,560 deaths). López-Cuadrado explained the differences by the GLM model assuming deaths/week due to influenza are directly proportional to viral laboratory detections, and the Poisson log-link models exponentially increase deaths with the number of isolates [10]. Newall for Australia 1997–2004 found the Poisson model consistently estimated higher death rates for respiratory, circulatory and all-cause mortality than the Serfling model. For those 75–84 the Serfling model estimated respiratory deaths at 31.18/100,000 and the Poisson model 50.63, circulatory deaths as 52.93/100,000 (Poisson 63.80), and all-cause deaths as 87.92/100,000 (Poisson 138.06). Newall attributed the difference to fewer influenza months in the Serfling model [11]. Thompson for the US 1972–2003 for those ≥65 years-of-age found the Serfling model estimated annual influenza-associated deaths as 20,161 (95%CI 14,907 to 25,415), the Serfling-Poisson model 22,790 (95%CI 17,565 to 28,033) and the ARIMA model 24,856 (95%CI 19,576 to 30,136). The rate-difference model estimated the peri-season lasted an average of 7.4 epidemic weeks (involving 19,954 excess deaths) and the summer season experienced 36,430 excess deaths. Thompson's Poisson model using virological data produces estimates between Serfling and ARIMA models which do not [12]. Thompson commented that: "A strength of the Serfling least squares regression model is that it provides estimates of influenza-associated deaths without the need for influenza virus surveillance data" [12]. This approach vitiates a key step in medicine of obtaining pathological data for confirmation. Thompson noted that: "Disadvantages of Poisson models as used by CDC include requirements for consistent, robust weekly viral surveillance data and for at least 5 years of mortality data before stable estimates . . .can be made." and "The ARIMA method . . . suffers from some of the same weaknesses . . .including defining influenza seasons solely by the use of statistical models" [12]. For children 1–23 months a prospective study of virus-attributable hospitalisations was compared with estimates by six models (Serfling, peri-season differences, Poisson regression with log-link, negative binomial regression with identity link, and Box–Jenkins transfer function). No model provided accurate or consistent estimates. The authors concluded the problems