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Review

Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis

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ABSTRACT

Introduction: Seasonal influenza affects millions of people globally each year, causing significant morbidity and mortality. However, there remains substantial uncertainty about the attack rate (incidence) of influenza, particularly in unvaccinated individuals.

Methods: We undertook a systematic review of vaccine randomised controlled trials (RCTs) that reported on laboratory-confirmed seasonal influenza in the placebo arm. We calculated the influenza attack rate from included studies as the number of laboratory-confirmed positive seasonal influenza cases in the placebo arm divided by the total number of subjects in this arm. A random effects meta-analysis was conducted to estimate the influenza attack rate among unvaccinated individuals (both symptomatic only as well as symptomatic and asymptomatic combined).

Results: We included 32 RCTs that had a total of 13,329 participants. The pooled estimates for symptomatic influenza were 12.7% (95%CI 8.5%, 18.6%) for children (<18 years), 4.4% (95%CI 3.0%, 6.3%) for adults, and 7.2% (95%CI 4.3%, 12.0%) for older people (65 years and above). The pooled estimates for symptomatic and asymptomatic influenza combined for all influenza were 22.5% (95%CI 9.0%, 46.0%) for children and 10.7% (95%CI 4.5%, 23.2%) for adults. Only one study was identified for symptomatic and asymptomatic combined in older people which had a rate of 8.8% (95%CI 7.0%, 10.8%). There was substantial heterogeneity between studies.

Conclusion: Overall, we found that approximately 1 in 5 unvaccinated children and 1 in 10 unvaccinated adults were estimated to be infected by seasonal influenza annually, with rates of symptomatic influenza roughly half of these estimates. Our findings help to establish the background risk of seasonal influenza infection in unvaccinated individuals.

Contents

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1. Introduction

Influenza is an acute viral infection of the respiratory tract. Influenza can infect individuals of any gender, age and health status, however children and older people are at increased risk of developing severe disease [1]. It is estimated that annually 250,000–500,000 deaths are due to influenza globally [2]. Influenza has previously been estimated to cause symptoms in approximately one quarter of cases [3,4]. While evidence of the level of disease transmission due to asymptomatic cases is varied, they are thought to be an important contributor to influenza spread [5,6]. In temperate climates influenza is largely a seasonal virus and occurs primarily in colder winter months [7]. In tropical and subtropical regions, the seasonality of seasonal influenza is often not as marked with multiple influenza peaks being observed in some cases [8–11].

There is considerable uncertainty and a lack of data to help inform estimates of the annual influenza attack rate. This is illustrated by the World Health Organisation (WHO) seasonal influenza fact sheet which provides an estimate of influenza incidence of 5–10% and 20–30% of adults and children respectively but does not provide supporting evidence [2]. Influenza incidence cannot be obtained from routine surveillance databases due to a lack of routine testing and must be estimated in studies that have a known population size. Many of the studies that meet these criteria (routine testing and a population denominator) are randomized control trials (RCTs) of influenza vaccination [12,13]. However, individually these studies tend to be relatively small in size and usually span only one influenza season and thus cannot on their own provide a comprehensive estimate [14–16].

One systematic review [17] and four meta-analyses [8,18–20] have previously attempted to estimate the influenza attack rate, however each had limitations and/or are now outdated. Turner et al. [8] is the most widely cited source on the topic and estimated a symptomatic attack rate for various age and risk groups in unvaccinated individuals, with a symptomatic attack rate of 6.6% (95%CI 2.9%,12.6%) estimated for adults [8]. Estimating the attack rate in unvaccinated individuals is of particular interest when considering future vaccination programs. For example, economic evaluations require estimates of the influenza incidence in unvaccinated individuals as a baseline to model the impact of future interventions.

The aim of our study was to provide an updated and complete review of available vaccine trial data on seasonal influenza incidence (i.e. the influenza attack rate) among unvaccinated individuals for both symptomatic illness as well as for all infections (symptomatic and asymptomatic infections combined).

2. Methods

This study is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21].

2.1. Search strategy and selection criteria

Three previous Cochrane reviews conducted to examine the efficacy of influenza vaccines in different age groups have comprehensively captured the studies needed for our review until 2009 [22–24]. We have updated these searches to 20 July 2016 (see Appendix I for full search strategy). Included studies were double-blind RCTs among human subjects analysing influenza vaccination that reported on the incidence (or data allowing calculation) of laboratory-confirmed influenza (symptomatic and/or asymptomatic) in a placebo arm. Laboratory-diagnosis was by culture, polymerase chain reaction (PCR), serology (using haemaglutination testing (HAI), with a fourfold rise in antibody titre above baseline being diagnostic), or a combination of these testing methods. Where studies spanned more than one influenza season, we extracted data from the first year only. Subjects were required to be influenza-free at the beginning of the study.

We excluded studies that did not test all symptomatic subjects (or did not test all asymptomatic subjects, where relevant), or where case definitions were not clearly defined, as well as cluster RCTs, non-original articles, phase I or II trials, non-English, unpublished data, modelling studies, and those specifically focused on high risk conditions and/or subgroups. We also excluded studies that only reported on the pandemic H1N1 strain in 2009 in the Southern Hemisphere and/or 2009/2010 in the Northern Hemisphere unless they reported on non-pandemic strains separately, in which case we included the results for the non-pandemic strains. We did not exclude studies in schools or aged care facilities, provided they were not cluster RCTs, as these setting were seen as (at least partially) representative of the individuals in these age group and helpful in establishing incidence in these groups.

2.2. Study selection

MS performed the title, abstract and then full text review. A second independent search and review was performed by LD with discrepancies discussed.

2.3. Data analysis

Data was extracted by MS using a data sheet developed *a priori* (see Appendix II for further details on what data was extracted).

Our primary outcome was the incidence of symptomatic seasonal influenza infection (positive test result) among patients in the placebo arm of the vaccine trials. Our secondary outcome was the incidence of all seasonal influenza infection (symptomatic and asymptomatic combined). In the minority of cases where studies reported multiple results using different laboratory tests for the same individuals, we had the following order of preference: PCR, culture, serology. Although both PCR and culture are highly sensitive and specific for the detection of influenza, it has been suggested that PCR has a greater sensitivity than culture [25,26]. As serology can have variable sensitivity and specificity [25] it was the least favoured test choice.

One author (MS) independently screened trial quality using risk of bias items developed *a priori* from Cochrane guidelines [27]. Items assessed included study duration, blinding, diagnostic test chosen, reporting of time between symptom onset and testing, surveillance and whether intention to treat (ITT) analysis was performed and clearly reported.

We estimated the influenza attack rate by taking the number of laboratory-confirmed cases of seasonal influenza in the placebo arm and dividing this by the total number of people in the placebo arm of the trial. In some instances, the number of cases in the placebo arm had to be derived from other information reported in the study, such as the proportion/percentage of the placebo arm testing positive. To describe study characteristics, we used medians and ranges to summarise continuous measures, and number and percent for categorical measures.

Meta-analysis was conducted when there were 3 or more studies, using a random effects model for proportions, to pool across studies. Influenza estimates were sub-grouped as: "Influenza A and B" which refers to the combined incidence of influenza A and influenza B from studies that reported testing both influenza A and influenza B; "Influenza A" which refers to the incidence in studies that tested only for influenza A; and "Pooled" which refers to pooling the first two groups together to provide an estimate for all seasonal influenza. "Influenza B" was not reported alone in any of the studies included in the analysis and so we do not subgroup

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