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Review

Do antibody responses to the influenza vaccine persist year-round in the elderly? A systematic review and meta-analysis

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ABSTRACT

Introduction: The influenza vaccine is less immunogenic in older than younger adults, and the duration of protection is unclear. Determining if protection persists beyond a typical seasonal epidemic is important for climates where influenza virus activity is year-round.

Methods: A systematic review protocol was developed and registered with PROSPERO [CRD42015023847]. Electronic databases were searched systematically for studies reporting haemagglutination-inhibition (HI) titres 180–360 days following vaccination with inactivated trivalent seasonal influenza vaccine, in adults aged ⩾65 years. Geometric mean titre (GMT) and seroprotection (HI titre ⩾1:40) at each time point was extracted. A Bayesian model was developed of titre trajectories from pre-vaccination to Day 360. In the meta-analysis, studies were aggregated using a random-effects model to compare pre-vaccination with post-vaccination HI titres at Day 21–42 ('seroconversion'), Day 180 and Day 360. Potential sources of bias were systematically assessed, and heterogeneity explored.

Results: 2864 articles were identified in the literature search, of which nineteen met study inclusion/exclusion criteria. Sixteen studies contained analysable data from 2565 subjects. In the Bayesian model, the proportion of subjects seroprotected increased from 41–51% pre-vaccination to 75–78% at seroconversion. Seroprotection subsequently fell below 60% for all serotypes by Day 360: A/H1 42% (95% CI 38–46), A/H3 59% (54–63), B 47% (42–52). The Bayesian model of GMT trajectories revealed a similar pattern. By Day 360, titres were similar to pre-vaccination levels. In the meta-analysis, no significant difference in proportion of subjects seroprotected, 0 (−0.11, 0.11) or in $\log_2$GMT 0.30 (−0.02, 0.63) was identified by Day 360 compared with pre-vaccination. The quality of this evidence was limited to moderate on account of significant participant dropout.

Conclusions: The review found consistent evidence that HI antibody responses following influenza vaccination do not reliably persist year-round in older adults. Alternative vaccination strategies could provide clinical benefits in regions where year-round protection is important.

Contents

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1. Introduction

Influenza is a common viral respiratory infection, which worldwide causes substantial morbidity and mortality, particularly at extremes of age [1,2]. Influenza vaccination is the primary tool available for disease control but immune responses to vaccination are reduced in the elderly compared with younger, healthy adults [3]. Persistence of vaccine-induced immunity over periods longer than a typical winter season have not been widely investigated, but similar to short term responses a reduced duration of persistence and hence protection against infection may be expected [4].

The primary immune response to the standard inactivated influenza vaccine is strain-specific antibody to surface haemagglutinin (HA) [5]. These antibodies mediate protection against infection by interfering with virus binding to host-cell receptors, and are measured with standardised Haemagglutination-Inhibition (HI) Assays [6]. Currently, age specific immunogenicity criteria based on the HI titre are used by the regulatory committees of the European Medicines Agency (EMA) and Federal Drug administration (FDA) [7]. For example, a HI titre of $\geqslant$1:40 is conventionally considered 'seroprotection', and more than 70% of younger adults, or 60% of older adults must reach this threshold for licensing.

A literature review published in 2008 studied antibody persistence in the elderly (>60 years) [8]. Up to 16 weeks post-vaccination the authors did not find evidence for substantial waning of seroprotection. This review was primarily qualitative and did not attempt to apply statistical methods to reported outcomes. Beyond this review, antibody persistence in the elderly has not been systematically assessed and a number of new studies providing data on antibody persistence have since been published.

Waning of vaccine effectiveness over the course of a winter season has been reported from a number of surveillance studies in Europe and Australia [9–11]. For example, in a study in Spain, vaccine effectiveness declined from 61% in the first 100 days after vaccination to 42% between days 100–119, and no protection after 120 days. This decline in effectiveness was most significant in the elderly aged over 65 years. These studies used the test-negative case-control design, and so do not include accompanying serological data. It is not clear to what extent this decline in effectiveness reflects loss of vaccine-induced immune responses, or reduced vaccine-strain matching from antigenic drift in circulating strains.

Limited data is available from studies of antibody persistence after influenza infection. An observational study monitored titre trajectories in subjects who were assessed to be infected with A/H1N1 during the 2009 pandemic (seroconversion without vaccination) [12]. In 71% haemagglutination-inhibition (HI) antibody titres were $\geqslant$1:40 immediately after the epidemic peak. This declined to 25% of subjects at 6 months, and only 14% at 1 year after the pandemic. In a sub-group analysis of the small number of elderly subjects in the cohort, the rate of antibody decline was significantly faster.

The duration of protection following vaccination is of particular public health importance in countries which report more than a single annual influenza season. Biannual epidemics, triannual epidemics and year round virus activity are described in tropical countries, from Indonesia and Malaysia to Peru and Mexico [13,14]. Despite the difference in seasonality, the burden of disease from influenza in countries with tropical, sub-tropical and temperate climates has been reported to be similar [15]. The implication of this differing epidemiology for vaccination schedules is yet to be understood. For example, recommendations for influenza vaccine timing from the World Health Organization (WHO) are based the pattern of influenza virus activity rather than prospective studies of year-round vaccine effectiveness [16,17].

With year-round influenza virus activity in the tropics, year-round seroprotection is expected to be beneficial, but is least likely to be attained in populations such as the elderly with impaired immune responses. This study is a systematic review and meta-analysis of the available evidence for year-round persistence of vaccine-induced antibody following trivalent, inactivated, seasonal influenza vaccination in the elderly.

2. Materials and methods

An abbreviated study protocol is available from the National Institute for Health Research International Prospective Register of Systemic Reviews (PROSPERO), registration number CRD42015023847 [18]. The Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) checklist for reporting of systematic review was also followed [19].

2.1. Search strategy and study selection

A search strategy was developed using the PICOST framework. Study inclusion and exclusion criteria are presented in Table 1.

Population: Elderly $\geqslant$65 years
Intervention: Trivalent inactivated seasonal influenza vaccination administered by intra-muscular injection
Comparison: No comparative group (e.g. healthy younger adults) will be included. HI antibody responses at selected time points will be compared with the pre-vaccination results.
Outcome: HI geometric mean titre (GMT) from 180 to 360 days after vaccination and proportion with GMTs $\geqslant$ 1:40 per Centre for Biologics Evaluation and Research (CBER) criteria [20]
Situation: For immunologic studies, the country in which the study is performed is not important