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The Duration of Influenza Vaccine Effectiveness: A Systematic Review, Meta-analysis and Meta-regression of Test-Negative Design Case-control Studies

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Running title: Influenza vaccine effectiveness

Summary: The duration of influenza vaccine effectiveness is important for planning vaccination programs. This review found consistent evidence for a decline in effectiveness over a typical temperate winter season, and protection is unlikely to last year-round, as required in tropical regions.

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Abstract

Background. Whether influenza vaccination offers protection for the duration of an influenza season has recently been questioned following analysis of data from test-negative design (TND) case-control studies.

Method. The published literature was systematically reviewed to identify TND studies which estimated change in vaccine effectiveness (VE) with time since vaccination.

Results. Fourteen studies were identified through the literature search as meeting eligibility criteria. Meta-analyses were performed to compare VE 15-90 days after vaccination with 91-180 days. A significant decline in VE was observed for influenza subtype A/H3 (ΔVE -33, 95% CI -57; -12) and type B (ΔVE -19, 95% CI -33; -6). VE declined for influenza subtype A/H1, but this difference was not statistically significant (ΔVE -8, 95% CI -27; 21).

A multivariable mixed-effects meta-regression model indicated ΔVE was associated with the proportion of study participants who were cases and the proportion of vaccinated controls (p<0.05). This could reflect biological effects such as vaccine and circulating strain mismatch or herd immunity respectively, or the reduced power of individual TND studies in the later parts of an influenza outbreak.

Conclusions. Exploration of new influenza vaccination strategies must be a priority for influenza control, particularly in tropical countries with year-round influenza virus activity.
Background

The protection against influenza infection provided by the current methods of vaccination is imperfect. Inactivated influenza vaccines primarily induce an antibody response to the surface haemagglutinin (HA) antigen, and HA antibody titres are typically measured by the haemagglutination inhibition (HI) assay [1]. For vaccine licensure, a HI antibody threshold of \( \geq 1:40 \), is conventionally considering ‘seroprotective’, but confers only approximately 50% protection against infection [2].

Antibody titres decay following their peak at seroconversion 2-4 weeks after vaccination [3]. The rate of this decline is uncertain, and is likely to depend on characteristics of the individual, such as age and co-morbidities, their influenza infection and vaccination history, and the immunogenicity of individual strains. In older adults, a meta-analysis of HI antibody persistence after vaccination suggested titres decline significantly from seroconversion to 180 days after vaccination [4]. By 360 days, titres further declined and were not significantly different from pre-vaccination.

An important question is if this waning immunity also translates into reduced vaccine effectiveness (VE). The duration of VE will help determine the optimal time to vaccinate, as vaccinating too early may substantially reduce protection later in the season if VE wanes too quickly. This issue is of even more relevance in the tropics and sub-tropics where multiple influenza outbreaks may occur every year, while inter-epidemic transmission and year-round influenza activity is frequently described [5]. Vaccination guidelines in the tropics currently recommend annual influenza vaccination, however, these recommendations are based on extrapolating from studies of influenza epidemiology and prospective studies have not been performed to determine if they represent the best vaccination strategy [6]. The implications of this epidemiology for out-of-season travellers from temperate to tropical climates has also not been established [7].

Randomised-clinical trials which assess the duration of influenza vaccine efficacy as the primary endpoint have not been conducted. Similar to antibody titres, recent data from a number of test-
negative design (TND) case-control studies have suggested that following a peak at seroconversion, VE declines significantly [8,9].

The case TND study has become the preferred method for assessing VE in observational studies. With this study design, individuals presenting to a healthcare facility with an influenza-like-illness are prospectively enrolled. Vaccination status is compared between study participants with a confirmed influenza infection (‘test-positive’ cases) versus those whose influenza screen is negative (‘test-negative’ controls). Matching cases and controls in this way reduces the problem inherent in other observational study designs, where differences in health-seeking behaviour between vaccinated and unvaccinated individuals is an important confounding factor [10]. Like any observational study, this methodology has limitations, and these may affect the validity of any observed decline in VE.

We sought to identify all published TND studies which analysed influenza VE by time from vaccination, to provide summary estimates of the magnitude of any change in VE, assess the influence of study characteristics on this change and review the quality of the evidence.
Methods

An abbreviated study protocol is available from the National Institute for Health Research International prospective register of systematic reviews (PROSPERO), registration number CRD42017071890 [11]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting of systematic review was followed [12].

Search strategy and study selection

A search strategy was developed using the PICOST framework:

Population: Individuals presenting with an acute respiratory illness (ARI) who are tested for influenza infection. No restriction is placed on population age, gender or ethnicity, nor on place of residence (e.g. community or long-term care facility) or the presence of particular co-morbidities.

Intervention: Seasonal influenza vaccination in the 12 months preceding study enrolment, of any licensed type (for example live-attenuated, inactivated trivalent or quadrivalent and standard-dose, high-dose or adjuvanted).

Comparison: Odds of vaccination among cases with confirmed influenza infection versus controls with a negative influenza test.

Outcome: Vaccine effectiveness (VE) analysed by time since vaccination, adjusted for measured confounders between cases and controls.

Situation: No restriction is placed on the country in which the study is performed, or the type of healthcare facility (outpatient or inpatient)

Type of Study: Only test-negative design (TND) case-control studies will be included.

A publication date limit of 2005 was chosen to reflect the year when TND methodology was first published [10]. MEDLINE and EMBASE databases were searched to identify relevant literature, using the following search construct, limited to studies indexed as published in English and reported in humans:
1. Title: (Influenza or flu) and vaccin*, AND

2. Any field: (effectiveness or VE), NOT

3. Title: haemophilus or Avian

Reference lists of all included studies were screened. After removal of duplicates, a three-stage screening process was used: reviewing title, then abstract and finally full text where possible. Screening was performed by two independent reviewers (BY and SS), with discrepancies resolved through discussion with a third reviewer (MC).

Data collection

Data was extracted using a standardised template. Data collected included all adjusted VE estimates with 95% confidence intervals, demographics of study participants, and study characteristics.

Verification of entered data was performed by an independent re-collection of data from the source manuscript. Further systematic search for grey or unpublished literature was not performed.

Corresponding authors were contacted for clarification of data where necessary, including VE estimates where only graphical data was available.

Synthesis of Results

Meta-analyses were conducted by influenza subtype A/H1, A/H3 and type B. The reported VE estimate and 95% confidence intervals, adjusted for confounders, were converted to an odds ratio (1-VE/100). The standard error was calculated from the natural log transformed values of the odds ratio (OR) 95% confidence intervals. For pragmatic reasons when using a log scale, a VE estimate of 100 was recorded as 99.5.

Outcome data was grouped for the meta-analysis by best fit to sequential 3-month time periods post-vaccination (15-90, 91-180, 181-270 and 271-360 days). For studies which reported VE as a continuous, rather than categorical variable, midpoint estimates from these time periods were used.

ORs were aggregated by inverse-variance weighting. A random-effects model was used to reflect the
assumption that the effects being estimated in the different studies were not identical. Variability of outcomes between studies was assessed using the heterogeneity statistic $I^2$. No sub-group analyses were planned during protocol development. Possible publication bias was assessed by examination of funnel plots. The GRADE approach was used to evaluate the certainty of evidence for each outcome [13].

The difference in vaccine effectiveness ($\Delta VE$) between time periods was calculated, and the confidence interval for this difference estimated using bootstrapping. Bootstrapped estimates were based on inferring the sample distribution of VEs from each study using the standard error estimated from reported confidence intervals, with 100,000 re-samplings [14]. Median $\Delta VE$ and the 2.5% and 97.5% centiles were recorded as estimates of confidence intervals.

The distribution of $\Delta VE$ was modelled using the normal distribution to estimate a mean and standard deviation. These values were used as the unit of analysis for a mixed-effects meta-analytic regression model of study characteristics, with between study variance estimated using restricted maximum likelihood (REML) estimators. Where available date was incomplete, missing values were omitted, rather than imputing values. Influenza subtype/type were analysed using dummy variables. A multi-variable model of all variables with a p-value <0.1 in the univariate analysis was constructed and refined by backwards elimination. Corrections for multiple testing were not performed.

Meta-analyses were calculated using RevMan v5.3 [15]. All other analyses were performed using R version 3.4.1 and the metafor package [16,17]. Statistical significance was assumed with a 2-sided alpha of 0.05.
Results

Database searches were performed on 17 July 2017. This identified 1614 unique citations for further screening (Figure 1). All studies identified for full text review but subsequently excluded were accessed, and were either not TND studies, or did not include time since vaccination in their analysis.

Study characteristics

A summary of the characteristics of the 14 included studies is shown in Table 1. Reported adjusted vaccine effectiveness (VE) estimates are summarised in Table 2, along with bootstrap estimates of $\Delta$VE.

Most studies (11/14) were conducted in either Europe or the US, with one from Kenya, one from Thailand, and one from Australia. Data covered influenza seasons from 2009 to 2016. Four studies were from the 2011-12 Northern Hemisphere winter, when the decline in VE with time since vaccination was first described. The single-season studies from Europe were conducted as part of the iMOVE (Influenza Monitoring Vaccine Effectiveness in Europe) project, with common study designs and definitions. Some of the cases and controls from these single-season studies, are expected to have been included in the multi-season study by Kissling 2016, though this is a much larger dataset involving additional years and countries. Two of the studies conducted in the Spanish 2011-12 winter have partially over-lapping datasets (Castilla 2013, Jiménez Jorge 2013).

Most studies enrolled participants only from primary care (11/14 studies). The proportion of influenza cases in children and younger adults varied considerably between studies - from 8-72%. One study was conducted only in children aged under 10 years (Katz 2016). Older adults comprised less than 20% of the total sample of influenza cases in all but 2 studies (Jiménez-Jorge 2013, Kissling 2013). The proportion of controls who had received influenza vaccination varied from 11-57%.

Information regarding the type of influenza vaccine administered was generally not available. Studies used similar inclusion criteria to determine the presence of an acute respiratory illness, and all used...
molecular techniques such as polymerase-chain reaction (PCR) as the diagnostic test for influenza infection. All studies excluded influenza cases who were vaccinated within 14 days prior to onset of infection, and most only included subjects who presented within 7 days of symptom onset.

All studies reported a VE which could be mapped to approximately 15-90 days after vaccination, and 91-180 days. Two large, multi-season studies reported VE modelling time from vaccination as a continuous rather than categorical variable. Most of the single-seasons studies did not have sufficient breadth of influenza infections to estimate VE for each seasonal type/subtype. Data was available for A/H3 in 11/14 studies, B in 6/14, and A/H1 in 5/14.

Only 3 studies explored VE more than 180 days following vaccination (Table 3). Two of these studies were conducted in tropical countries with year-round influenza virus activity (Thailand: Levy 2015, Kenya: Katz 2016). In two studies, VE declined as the year progressed, and by year-end, VE was not statistically significant. Katz 2016 reported a largely stable adjusted VE from Days 15-90 to Days 271-360.

**Meta-analysis**

Because of limited VE data more than 180 days after vaccination, meta-analyses and estimates of ΔVE were restricted to comparing 15-90 days and 91-180 days. Forest plots of VE converted to an OR and stratified by time-period and influenza type/subtype, are presented in Figure 2. A significant decline in VE from 15-90 days to 91-180 days was observed for influenza subtype A/H3 (ΔVE -33, 95% CI -57; -12) and type B (ΔVE -19, 95% CI -33; -6). VE declined for influenza subtype A/H1, but this difference was not significant (ΔVE -8 95% CI -27; 21). VE estimates for both time periods were markedly lower for A/H3 compared with B and A/H1 (Table 4).

Heterogeneity as assessed by $I^2$ was generally low (0-24%) apart from A/H3 91-180 days after vaccination ($I^2 = 60\%$) and A/H1 15-90 days after vaccination ($I^2 = 82\%$). Heterogeneity was mainly attributable to high VE estimates by Radin 2016 and Andrews 2014 for the A/H3 and A/H1 meta-
analyses respectively. Excluding either study had little impact on the summary VE estimates (Supplementary material, Appendix 1).

Meta-regression

The distribution of bootstrapped ΔVE samples were negatively skewed, though the normal distribution provided a reasonable fit to derive estimates for a mean and standard deviation (Supplementary material, Appendix 2 and 3).

The univariate meta-regression model identified the proportion of vaccinated controls and percentage of cases as statistically significantly correlated with ΔVE (Table 5). Surprisingly, influenza subtype/type was not significantly associated with ΔVE. Data was complete for all variables except the presence of chronic diseases (three missing data points).

The percentage of recruited study participants identified as influenza cases and percentage of controls which were vaccinated were retained in the multivariable model. A lower proportion of vaccinated controls and higher percentage of cases were associated with larger declines in VE with time since vaccination (i.e. a negative ΔVE).

Publication bias

Due to the small number of studies, funnels plots were only interpretable for influenza A/H3. No evidence of publication bias was found from inspection of the A/H3 91-180 days plot, with studies approximately symmetrically distributed about the OR summary estimate (Supplementary Material, Appendix 4). The plot for A/H3 days 15-90 was similar, except for Radin 2016, which formed an outlier. This study was one of only two for which A/H3 VE was significant from day 91-180, and was previously identified as contributing significant heterogeneity.

GRADE assessment
At baseline, the certainty of evidence derived from a review of TND studies was assessed as low due to their observational nature. With a large effect size, and no serious other issues, the certainty for a decline in influenza A/H3 VE in the first 6 months after vaccination was upgraded to moderate (Table 4). For A/H1 and B, the certainty of $\Delta$VE estimates remained low. Evidence for further decline in VE 6-12 months after vaccination were assessed to be very low due to the limited available data.
Discussion

The review and meta-analysis found consistent evidence of a significant decline in vaccine effectiveness within the first 180 days following influenza vaccination. The decline was observed to be more pronounced for subtype A/H3 and type B as compared with A/H1. The magnitude of the observed decline in VE has important implications for the logistics of influenza vaccination campaigns in temperate and tropical climates.

Evidence from other sources generally corroborate the findings of this review. An RCT comparing an inactivated versus a live-attenuated influenza vaccine in adults aged 18-49 was re-analysed using a time-varying efficacy approach [30]. Immediately following vaccination, efficacy was close to 100%, but declined to approximately 50% after 12 weeks. A TND study performed over the 2008/9 Northern Hemisphere winter season was re-analysed, and found a significantly increased risk for subtype A/H3 infection with time since vaccination in older adults (>75 years) and young children (<2 years) [31]. The adjusted odds for infection increased by 1.3 or 1.2, respectively, per two-week interval. This study was not included in the systematic review, as VE was not calculated.

Antibody persistence following influenza vaccination – the likely corollary to any decline in VE – is not measured in TND studies. As antibodies to influenza vaccination wane faster in older than younger adults, VE would also be expected to decline faster [3]. This was observed in the two studies which recruited a significant proportion of older adults (Castilla 2013, Jiménez-Jorge 2013). Failure to identify older age as a risk factor for decline in VE in most of the studies reviewed, and in our regression model of ΔVE, may reflect a lack of statistical power. As VE in general is lower in older compared with younger adults, the absolute VE decline in older adults will also be numerically smaller [32]. A related question, as yet unstudied, is whether symptomology or the probability of severe disease changes as VE declines [33].

Limited evidence was uncovered in the review to quantitatively estimate how VE changes more than 180 days after vaccination. With the extent of the decline seen in the first six months for influenza
A/H3 and B, sustained year-round protection following vaccination is unlikely. Improved vaccines have the potential for significant public health impact in this region, but have been little studied. For example, vaccines with a higher antigen dose, recombinant antigen, or the inclusion of adjuvants have been developed for older adults and might offer superior year-round vaccine effectiveness to the standard inactivated vaccine [34,35]. However, while these vaccines have better short-term immunogenicity compared with standard inactivated vaccine, little long-term antibody persistence data is available [36–38]. In the studies included in this review, the influence of vaccine type on VE and time since vaccination was not documented.

As an alternative to new vaccines, increasing the frequency of vaccination may improve vaccine effectiveness. A second dose of influenza vaccine, administered at least 4 weeks after the first, is recommended for immunologically naïve young children [39]. Repeat vaccine administration after one to three months in other populations such as immunocompromised adults has serological benefit, though the clinical impact is unknown [40]. Vaccinating every six months in the tropics is attractive due to the simplicity, low cost, and safety profile of the standard dose inactivated vaccine – and reflects the six-monthly update to the recommended vaccine strain composition by the World Health Organization (WHO). The serological outcomes of a six-monthly vaccination strategy in older adults are currently being studied in a clinical trial, with results expected in 2018 [41].

While the observed decline in VE may reflect waning immunity, an alternative explanation is the emergence of influenza strain escape variants mismatched to those included in the vaccine as the season progresses. Several studies assessed the phylogenetics of circulating strains, mainly for A/H3 in the 2011/12 Northern Hemisphere winter. No significant change in the proportion of mismatched viruses as the season progressed was identified, suggesting this was unlikely to explain the apparent decline in vaccine effectiveness entirely. However, the rate of new strains emerging between seasons may explain differences in the VE decline, which is faster for influenza A/H3 strains, as compared with A/H1 and B [42]. Correspondingly, the smaller observed decline in A/H1 VE may reflect the
homogeneity of the A/H1N1 strain (pdm2009) across the period of the study, with repeated vaccination (or infections) boosting strain-specific protection.

Other reasons for the apparent change in VE were explored in the meta-regression. VE change with time since vaccination was negatively correlated with the proportion of influenza cases among study participants, and positively correlated with the proportion of vaccinated controls. This may reflect issues with study power, as VE estimates have a negative skew, which increases as VE approaches zero, and confidence intervals widen. Reflecting this, confidence intervals for VE were almost twice as wide for estimates 91-180 days after vaccination, compared with 15-90 days.

Beyond issues with study power, a higher proportion of vaccinated controls could indicate settings with significant herd immunity effects at the levels of households or even in the community. This potentially protects unvaccinated individuals and thus reduces apparent vaccine effectiveness, and might also protect individuals who had decreased immunity later in the season. As for the higher percentage of cases to controls, this may indicate more influenza virus activity in seasons associated with an imperfect match between circulating and vaccine strains. We postulate that, when an imperfect match occurs, protection earlier in the season might still be mediated by less specific antibodies which would decline rapidly post-vaccination leading to substantially poorer protection later in the season than with a well-matched vaccine.

As observational studies, a number of assumptions are made with the TND design which also limit interpretation of the meta-analysis [43]. For example, TND studies rely on a similar probability of non-influenza infections among vaccinated and unvaccinated individuals. It has been proposed that influenza vaccination may increase the risk of a non-influenza respiratory viral infection resulting in an over-estimate of VE [44]. Rather than a waning of protection against infection, the observed decline in VE, may reflect a waning in this ‘viral interference’. Confounding would also occur if earlier receipt of vaccination before the main influenza season occurred among individuals at higher risk of influenza infection. Further TND studies are unlikely to be able to overcome this confounding.
Other limitations of this systematic review include potentially missed studies, or inaccurate data transcription. Heterogeneity in study methodologies may also limit the reliability of summary estimates for ΔVE. Most significantly in terms of outcome data, we used point estimates of VE from two large studies in the meta-analysis, while the other studies included in the review assessed time since vaccination as a categorical variable with varying cut offs. The effect of partially overlapping datasets was not adjusted for, though exclusion of both Kissling 2016 and Ferdinands 2017 had little impact on summary estimates of VE. Combining TND studies from different seasons, while generally accepted, ignores potentially important differences in influenza strain VE. Data is also not evenly available across the years which may bias findings. Finally, the meta-regression must be interpreted with caution. While ΔVE is a clinically meaningful variable, it is not the primary outcome for included studies, and the reliability of its estimates uncertain.

In conclusion, this study finds evidence to support the assertion that VE against influenza subtype A/H3 and type B declines significantly in the six months following vaccination. Further studies with alternative methodologies would be helpful to confirm this finding. Additional areas to explore include confirming the influence of age on VE decline, and exploring the potential benefits of newer vaccines.
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Conflict of Interest

The authors declare that they do not have a commercial or other association that might pose a conflict of interest

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24. Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-


64:829–838.


