INPLASY

Immunogenicity as a Predictor of Influenza Vaccine Efficacy

INPLASY202570064
doi: 10.37766/inplasy2025.7.0064
Received: 16 July 2025
Published: 16 July 2025

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ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202570064

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 July 2025 and was last updated on 16 July 2025.

INTRODUCTION

Review question / Objective Can the efficacy of the flu vaccine be predicted by HAI titer levels?

Rationale Influenza represents a significant burden in global public health and vaccination is the most effective strategy to reduce it. The large investment in vaccination programs and the need for adjustments in vaccine serotypes are important reasons for evaluating influenza vaccines efficacy every year. Establishing a relationship between immunogenicity data and efficacy is also crucial for predicting the efficacy of a vaccine during its development. The antibody response measurement is one of the most common methods for evaluating immunogenicity, particularly in vaccines and biologics. This systematic review aims to examine the relationship between immunological factors—specifically hemagglutination inhibition (HAI) antibody titers—and the efficacy of the influenza vaccine. The objective is to assess whether the threshold values proposed by Hobson et al. in the 1970s remain valid today and to explore potential new immunological markers or therapeutic targets that could enhance vaccine efficacy.

Condition being studied The primary outcome of interest is the efficacy of the influenza vaccine, assessed by the presence or absence of laboratory-confirmed influenza infection.

METHODS

Search strategy We used the Scopus and Pubmed scientific article databases using the following search string: TITLE-ABS-KEY (((flu OR influenza OR influenzavirus) AND (HAI OR NAI) AND (RCT OR clinical trial OR controlled trial OR efficacy))).

Participant or population Human population.

Intervention Administration of the seasonal influenza vaccine. Individuals are considered

vaccinated only after 14 days have passed since the administration of the influenza vaccine.

Comparator Individuals not vaccinated against influenza during the ongoing vaccination campaign serve as the comparison group.

Study designs to be included Randomised clinical trials (RCT).

Eligibility criteria
Studies were included if they met the following criteria:
i) they reported immunogenicity data including HAI titres;
ii) were randomised clinical trials (RCTs);
iii) assessed the association between HAI levels and efficacy against infection,
iv) including studies in which data were available only in graphical form;
v) were published in English.
No restriction on publication date was used, given the limited number of relevant studies.

Information sources Eletronic databases: Pubmed and Scopus.

Main outcome(s) The measure of stress and protection against influenza infection associated with the level of HAI titers. Vaccine performance is determined by vaccine efficacy (VE), that is equal to VE=(1-RR)×100 where RR is the relative risk, which is given by the proportion of infections among the vaccinated over the proportion of infections among the unvaccinated. The estimate of the vaccine efficacy was extracted for each observed titer level. When it was not reported, efficacy was calculated by using the proportion of infections among the vaccinated at each titer level as the numerator and the proportion of infections among all the unvaccinated as the denominator of the RR formula.

Data management Two authors of this review independently assessed the study eligibility by screening the title and abstract. All selected articles from this initial screening were further reviewed for inclusion through full text assessment. The information from all selected papers was independently extracted into a form that included: study design, participants, sample size, description of intervention, outcomes, and quality assessment indicators.

Quality assessment / Risk of bias analysis Two authors independently assessed the included studies for risk of bias using validated critical appraisal tools. Inconsistencies were resolved by a third reviewer.
The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used for RCT.

Strategy of data synthesis Software WebPlotDigitizer was used to digitise plots when analytical data was not available.
Models for associating vaccine efficacy with HAI titers were derived through a meta-regression approach. Polynomial (linear, quadratic and cubic), exponential, logarithmic and a generalized additive using cubic regression splines with 4 knots, models were tested. The weight of each observation was given by the sample size divided by the number of reported VE estimates of each study. When VE estimates were not reported the weight is calculated by: (number of vaccinated for a level of titers/ total number of vaccinated) x Sample size. The best model was selected using the BIC criteria.
For each strain of influenza virus, type of vaccine a model was fitted. The different models were also applied to the specific population of children, in addition to testing all the information gathered.
The selected models were used to calculate an estimate of the efficacy for a HAI titers level of 1:30, 1:40 and 1:50. The quality of the model fit was evaluated using the coefficient of determination r^2. Data analysis was conducted in R software, including splines and mgcv package.

Subgroup analysis Subgroup analyses was performed to evaluate vaccine efficacy according to vaccine type, influenza strain, and age group.

Sensitivity analysis Sensitivity analyses were planned for studies with a high risk of bias. However, these analyses were not conducted, as no studies meeting the criteria for high risk of bias were identified.

Language restriction Only articles in english.

Country(ies) involved Portugal.

Other relevant information Although the systematic review had already been completed at the time of this registration, we chose to retrospectively register the protocol on INPLASY to promote transparency, strengthen methodological reproducibility, and allow for critical appraisal of our review process. The study was conducted according to a predefined methodology aligned with the PRISMA guidelines. No changes were made to the research question, inclusion criteria, or analytical methods after the review was completed.

Keywords Influenza, Influenza vaccine, efficacy, immunogenicity.

Contributions of each author

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