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Chrono-optimizing vaccine administration: A systematic review

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 January 2025 and was last updated on 17 January 2025.

INTRODUCTION

Review question / Objective This systematic review aims to provide a comprehensive overview of the current evidence from observational and experimental studies that compare vaccine responses based on the timing of administration throughout the day. The objective is to assess the overall impact of vaccination timing on immune responses and identify key areas for further research to better understand how vaccine administration timing affects immunogenicity and its potential role in optimizing vaccination programs.

Rationale Increasing evidence indicates that the strength of immune responses may be influenced by the time of day at which vaccines are administered. Although the underlying mechanisms are not well understood, the circadian rhythms in cytokine production, antigen presentation and the activity of both innate and adaptive immune cells likely contribute to this time-of-day effect. Aligning the time of vaccine administration with these oscillations in the immune system could improve immune responses, and could potentially increase vaccine effectiveness. Therefore, optimizing vaccination timing might offer a low-risk, low-cost approach to improve vaccine-induced protection against infectious diseases.

Condition being studied The condition being studied is the effect of the time of day at which a vaccine is administered on immune responses. Studies were included that compare immune responses, such as antibody and T cell responses, between participants vaccinated at different times

of the day. This systematic review encompasses vaccines targeting any infectious disease.

METHODS

Participant or population The review will address participants of all ages and health statuses who have received vaccines targeting any infectious disease.

Intervention The intervention being evaluated in this review is the timing of vaccine administration throughout the day. Specifically, we will examine the impact of administering vaccines at different times of the day (morning, afternoon, evening, etc.) on vaccine responses.

Comparator The immune responses will be compared between participants who received the same vaccine at different times of the day.

Study designs to be included This systematic review will include both observational studies and randomized clinical trials.

Eligibility criteria Studies qualified for inclusion if they (I) measured antigen-specific antibody or T-cell responses following vaccination, and (II) if these immune responses were compared between participants vaccinated at different timepoints during the day. Studies were excluded if they (I) did not provide sufficient data on the timing of vaccination or (II) involved non-human subjects.

Information sources A systematic literature search was performed in the Embase and Medline databases to identify relevant studies.
To quantify the effect size of vaccination timing on antibody responses (in the form of a meta-analysis), data were obtained from published supplementary materials and by directly contacting the study authors.

Main outcome(s) The primary outcome of the meta-analysis was the pooled standardized mean difference (SMD) in antibody titers one month post vaccination between morning and afternoon vaccine administrations.

Additional outcome(s) Secondary outcomes included the potential modifying effects of age and sex on the relationship between vaccination timing and the antibody response.

Quality assessment / Risk of bias analysis The risk of bias of the included studies was critically appraised by two assessors using Cochrane's Risk of Bias tool 2 (RoB2) for (cluster-)RCTs, and the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool for observational studies. A third assessor was consulted in case of disagreements to reach a final judgement.

Strategy of data synthesis A three-level random-effects model was used to obtain a pooled effect estimate with confidence intervals for the difference in the antibody response between morning and afternoon vaccination. This model corrected for the correlation between the multiple effect sizes within each study. A forest plot was created using the model output to visualize the results of the meta-analysis.

Subgroup analysis Subgroup analyses were conducted based on sex, age group, and vaccine strain to explore potential sources of heterogeneity and assess whether these variables moderated the relationship between vaccination timing and the antibody response. These subgroups were pre-specified based on prior evidence suggesting that these variables could influence vaccine responses.

Sensitivity analysis Not applicable.

Language restriction No.

Country(ies) involved The Netherlands.

Keywords Influenza; COVID-19; Vaccination timing; Vaccine response; Vaccine effectiveness; Chronobiology.

Contributions of each author
Author 1 - Koen Vink - KV contributed to the study's design, conducted the literature search, screened records, selected studies, assessed the risk of bias in the included studies, extracted data, and performed the analyses. KV also drafted the manuscript with guidance from JW.
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Author 2 - Johannes Kusters - JK helped with the literature search, record screening, study selection, and the assessment of bias in the included studies. JK also provided feedback on the manuscript.
Author 3 - Jacco Wallinga - JW co-conceptualized the study, helped with the assessment of bias in the included studies, provided supervision to KV, and reviewed the manuscript, offering feedback and guidance.