ISRCTN65770516 https://doi.org/10.1186/ISRCTN65770516

Optimizing the time of day of influenza vaccine administration

Submission date	Recruitment status	[X] Prospectively registered
24/04/2024	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
15/07/2024	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
12/05/2025	Other	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
There is increasing evidence that the immune response to vaccination is influenced by the time of day at which the vaccine is administered. This suggests that there could be an optimal time for vaccine administration, at which protection against pathogens is most effective. In a literature review, we found that morning influenza vaccination yields higher antibody titers compared to afternoon vaccination. Evidence from the only two available randomized controlled trials (RCTs) was combined in a meta-analysis, which revealed that morning vaccination only induced a significantly stronger antibody response in participants aged 65 years and older.

In these two RCTs, antibody responses to the influenza vaccine strains were compared between two groups; participants vaccinated in the morning (09:00-11:00) and in the afternoon (15:00-17:00). Deducing the optimal time for influenza vaccine administration based solely on these comparisons is challenging. Considering an observational study suggested that the optimal administration time might be between 11:00 and 13:00, it would be worthwhile to compare vaccine responses at additional timepoints throughout the day. Furthermore, there are currently no studies that investigated the effect of vaccination timing on the T cell response. Since T cells are important to vaccine-induced immunity to respiratory viruses such as influenza and protection against disease development, gaining new insights in the effect of timing of vaccine administration on the T cell response will be valuable.

Therefore, the aim of our study is to assess the effect of the time of day of influenza vaccine administration on both humoral and cellular responses in older adults vaccinated between 09:00-17:00, to determine whether there is an optimal time for administration of the influenza vaccine, and to gain a better understanding of the mechanisms underlying these time-of-day effects. We focus on influenza vaccination, due to the high disease burden of influenza and its suboptimal effectiveness in older adults, who experience the highest influenza-associated rate of hospitalization and mortality. Optimizing the time of vaccine administration could offer a safe and cost-effective strategy to boost vaccine effectiveness in older adults and might thus reduce the burden of influenza.

Who can participate?
Volunteers aged 60-85 years, who are eligible for the annual influenza vaccine (n = 440).

What does the study involve?
First visit / baseline visit = T0
Second visit, one month after baseline = T1
Individuals aged 60-85 years will be recruited for participation in the Chrono-Vax trial. All participants (n = 440) will be randomly assigned to a timeslot of e.g. 40 minutes between 09:00 and 17:00 to receive the seasonal quadrivalent influenza vaccine (QIV) (season 2024/2025), at T0. If individuals born between 01-01-1961 and 01-06-1964 wish to receive the pneumococcal polysaccharide vaccine (PPV23), that is offered to this age category in 2024, this vaccine will also be administered at that randomized timeslot. A baseline questionnaire on demographics and lifestyle (T0) will be completed, body weight and length will be measured (for Body Mass Index, at T0), and blood will be collected via venipuncture (T0, T1). The participants are asked to monitor influenza-like illness (ILI) symptoms by filling out a diary when experiencing these symptoms from baseline until the end of follow-up (six months post-vaccination). Participants will receive instructions to perform a rapid diagnostic self-test (for influenza, SARS-CoV-2 and Respiratory Syncytial Virus combined) when they experience any ILI symptoms to assess which pathogen is involved in the symptoms, which will be recorded in the diary as well. A subgroup of the participants (n = 60) will wear an activity monitor (MotionWatch) for five consecutive days following vaccination to objectively measure sleep duration. Another subgroup (n = 22) will receive melatonin (1 mg) as a tablet orally prior to administration of the QIV.

What are the possible benefits and risks of participating?
Receiving the influenza vaccine is not considered a benefit for participating in this trial, as the vaccine could also be obtained through the Nationaal Programma Grieppreventie. Our primary intervention involves randomizing the time at which the participants receive the influenza vaccine, which has no associated risks. Common side effects, such as headache, fatigue, sore muscles, and local injection site reactions, are often mild and short-lived. Participants will undergo blood collection, complete a questionnaire, keep a diary (only when experiencing ILI symptoms), and may wear a MotionWatch (n = 60) to measure sleep duration, all with minimal burden. A subgroup of the participants (n = 22) will ingest a 1 mg melatonin tablet orally immediately before vaccine administration, which might cause some drowsiness during the day. Overall, the potential risks of participating in this trial are minimal. The participants will be compensated accordingly to the burden of participation.

Where is the study run from?
National Institute for Public Health and the Environment (RIVM) (Netherlands)

When is the study starting and how long is it expected to run for?
December 2023 to May 2025

Who is funding the study?
Dutch Research Council (NWO) (Netherlands)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Clinical Trials Information System (CTIS)
2024-513558-30-00

Protocol serial number
IIV-654

Study information

Scientific Title
Optimizing the time of day of influenza vaccine administration in adults aged 60-85 years: A randomized controlled trial

Acronym
Chrono-Vax

Study objectives
The administration of influenza vaccines in the morning elicits stronger influenza-specific antibody and T cell responses compared to afternoon administration in adults aged 60-85 years.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 15/08/2024, NedMec (Heidelberglaan 100, Utrecht, 3584 CX, Netherlands; +31 088 75 56 376; metc@nedmec.nl), ref: 2024-513558-30-00

Primary study design
Interventional

Study design
Nonblinded randomized controlled trial

Study type(s)
Other, Efficacy

Health condition(s) or problem(s) studied
Influenza vaccination

Interventions
All participants will be administered the quadrivalent influenza vaccine (QIV) for the 2024/2025 season. QIV-administration will take place at a randomized time between 09:00 and 17:00 at T0. Optionally, participants aged 60-63 years will receive the 23-valent pneumococcal polysaccharide vaccine (PPV23; Pneumovax-23) together with the influenza vaccine at T0. Both the QIV and Pneumovax-23 will be administered as a single 0.5 mL intramuscular injection. Blood will be collected via venipuncture during the baseline visit (T0) and 28 days (+/- 3 days) (T1) after vaccination. A subgroup of the participants (n = 60) will wear an activity monitor (MotionWatch) for five consecutive days following vaccination. Another subgroup (n = 22) will receive melatonin (1 mg) as a tablet orally prior to administration of the QIV, and 22 age-matched participants of the overarching trial will be used as controls.

The primary intervention of the trial is randomizing the time of day at which the participants receive their vaccination. Participants in the trial will be randomly assigned to a 40-minute vaccination timeslot throughout the day (09:00-17:00). Each timeslot will have a randomized order of the following four preferences in terms of sex and age; (I) men younger than the expected median age, (II) men older than the expected median age, (III) women younger than the expected median age, and (IV) women older than the expected median age. Based on these preferences, the participants will be allocated a randomized 40-minute timeslot as their designated appointment to receive the influenza (and pneumococcal) vaccine, while stratifying on sex and age. This randomization method allows us to randomly assign the participants a vaccination time, when it is still unknown how large the strata based on sex and age will be. Furthermore, it ensures an even distribution of vaccination timeslots within each stratum, and we can take participants' preferences for certain days and study groups into account. The timeslot for the T1 visit will be the same.
The nature of this intervention does not allow for blinding. For the aforementioned randomization method, a randomization sequence will be generated using the software environment for statistical computing: R, version 4.3.0 (R Core Team, Vienna, Austria). This sequence will be created by a statistician. To minimize potential bias, the randomization method will be set up independently by the statistician and will not be influenced by individuals directly involved in participant enrolment and the day-to-day study activities.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
The registered quadrivalent influenza vaccine (QIV) season 2024/2025; The registered 23-valent pneumococcal polysaccharide vaccine (PPV23; Pneumovax-23); Melatonin 1 mg tablet

Primary outcome(s)
The increase in influenza vaccine strain-specific serum antibody titers from pre-vaccination (T0) to 28 days (+/- 3 days) post-vaccination (T1) as measured by hemagglutination inhibition (HI) assay.

Key secondary outcome(s)
1. The increase in influenza-specific T cell responses in peripheral blood mononuclear cells (PBMCs) from pre-vaccination (T0) to 28 days (+/- 3 days) post-vaccination (T1) as measured by ELISpot.
2. Chronotype, assessed via the micro-Munich Chronotype Questionnaire (μMCTQ) at baseline
3. The incidence of influenza virus infection, as determined by rapid diagnostic self-tests, and self-reported ILI symptoms up to six months of follow-up

Completion date
01/05/2025

Eligibility

Key inclusion criteria
1. Aged 60-85 years at the time of inclusion.
2. Willing and able to come to the vaccination location at a randomly assigned timeslot.
3. Available for the follow-up period of 6 months.
4. Have provided written informed consent.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
60 Years

Upper age limit
85 Years

Sex
All

Total final enrolment
280

Key exclusion criteria
1. Known or suspected allergy to any of the vaccine components or having experienced a previous severe adverse reaction to any vaccine.
2. Present evidence of serious diseases demanding either regular use of oral immunosuppressive medical treatment, like corticosteroids, three months prior to study enrolment, or demanding acute use of high dose oral immunosuppressives two weeks prior study to study enrolment.
3. Receipt of an organ- or bone marrow transplant.
4. Receipt of chemotherapy in the previous year.
5. Receipt of blood products or immunoglobulins, within 3 months before study entry.
6. Known or suspected immunodeficiency, auto-immune disease, any type of cancer.

7. Known to be positive for human immunodeficiency virus, and/or hepatitis C virus and/or hepatitis B virus.
8. Receipt of any vaccine(s), including the COVID-19 vaccine, less than two weeks prior to or within one month after baseline (T0).
9. Receipt of influenza 2024/2025-season vaccine prior to or within one month after T0.

Date of first enrolment
29/07/2024

Date of final enrolment
01/11/2024

Locations

Countries of recruitment
Netherlands

Study participating centre
National Institute for Public Health and the Environment (RIVM)
Antonie van Leeuwenhoeklaan 9
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3721 MA

Sponsor information

Organisation
National Institute for Public Health and the Environment

ROR
https://ror.org/01cesdt21

Funder(s)

Funder type
Government

Funder Name
Nederlandse Organisatie voor Wetenschappelijk Onderzoek

Alternative Name(s)

Netherlands Organisation for Scientific Research, Dutch National Scientific Foundation, Dutch National Science Foundation, Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek), NWO:Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), Dutch Research Council, The Dutch Research Council (NWO), Dutch Research Council, Netherlands, NWO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in RIVMdata, a non-publicly available data repository. Storing the data in RIVMdata allows us to publish the metadata on data.overheid.nl (external sharing). This way other researchers know that the data exists and if they are interested in viewing the data, they can ask us.

IPD sharing plan summary
Stored in non-publicly available repository, Available on request