Characterization of immune mechanisms in measles and other infectious diseases

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON22598

Source
NTR

Brief title
Imm-f@ct

Health condition

Measles virus (MV)
Bordetella pertussis (Bp)
Streptococcus pneumonia (Sp)
Mumps virus (MuV)
Influenza A virus (IAV)
Neisseria meningitidis B (MenB)
Respiratory Syncytial Virus (RSV)

Sponsors and support

Primary sponsor: RIVM
Source(s) of monetary or material Support: Ministry of Health, Welfare and Sport (VWS)

Intervention

Outcome measures

Primary outcome

Study parameters will be the i) level, ii) functionality, iii) specificity, iv) crossreactivity and v) waning of pathogen specific immune responses. This will be ascertained by testing peripheral blood samples of cases and uninfected controls against various types of antigens. This will be done according to advancing knowledge using dedicated immuno-assays. These will be a) proliferation assays, b) cytokine release spot assays (T cell ELISPOT), c) flowbased and mass cytometry (CyTOF)-based single cell-based assays, d) flowbased MHC-peptide multimer analysis, e) whole blood assays, and f) antibody secretion spot assays (B cell ELISPOT), for evaluation of cellular responses; and g) multiplex immuno- assays (cytokines, antibodies) and h) micro array based immuno-assays (antibodies, cytokines, chemokines), i) functional antibody assays, j) Vh repertoire analysis for characterization of soluble markers in plasma, saliva, or culture supernatants and k) assays to measure gene expression and epigenetic regulation both of adaptive and innate immune cells during the specific immune response.

Secondary outcome

For each infection and age group: age at first day of disease, age at diagnosis (in years, or months and years if relevant, calculated from date of birth, first day of disease etcetera) as well as intervals, i.e. number of days between first day of disease/age at diagnose and home visits; gender; use of antibiotics last 3 months; chronic diseases; other disorders relevant for results of study; infectious diseases in past 5 years, including whether it was lab confirmed; presence or absence of clinical symptoms during the infectious disease under study; medication relevant for results of study; type of strain that caused the infectious disease under study; vaccination status.

Study description

Background summary

Rationale: In addition to the presence of antibodies, cell mediated immunity (CMI) plays an important role in the protection against viruses and bacterial pathogens. In general, humoral immune responses prevent infection by killing the microorganism, whereas CMI prevents disease. Both responses are required for protection against infectious diseases.
CMI involves multiple T lymphocyte (T-cell) populations of the adaptive immune system, with unique antigen specificities and functions such as CD8+ cytotoxic T-cells and CD4+ helper T-cells, also involved in helping antibody production. Both humoral and CMI mechanisms of the adaptive immune response can be acquired through natural infection or exposure to components of pathogens by vaccination. Not only direct effector mechanisms are then primed but also base levels of memory cells recalling specific antigens. These memory cells are there to rapidly and more effectively respond to renewed encounters with the pathogen, which is the mechanism behind vaccination. However, after an initial sharp rise of these responses post-encounter, a period of gradual waning follows. Studying characteristics of disease specific serological and CMI mechanisms in cases versus healthy controls of various age groups in early and late phase after infection is important to unravel life-spanning hallmarks of protection and waning immunity. In cases with a vaccination history, the type of

humoral response may for example allow to distinguish between primary and secondary immune (vaccine) failure. These kinds of studies provide important information for future vaccination strategies and offer the opportunity to asses shared or unique immune responses after natural infection or vaccination, as well as to compare immune responses after infection with different viruses and pathogens.
Objective: The main objective is to assess hallmarks of protective and waning immunity to vaccine preventable and non-preventable viral and bacterial diseases in cases of various age groups and age-matched healthy controls. Secondary objectives are 1) to assess the proportion of cases that are due to primary or to secondary vaccine failure (in the case of measles and mumps), in order to determine if waning immunity is responsible for infection amongst those vaccinated and if additional steps need to be undertaken to prevent the risk of additional cases occurring amongst the vaccinated Dutch population; 2) to identify biomarkers of specific T-cell and B-cell responses for the evaluation of the breadth of the humoral and CMI response immediately, and longitudinally after infection; 3) to compare T-cell and B-cell responses after natural infection with vaccine-induced responses; 4) to relate magnitude, quality and dominance of pathogen specific T-cell responses to the quality of concomitant B-cell responses; 5) to compare T-cell and B-cell responses after natural infection between age-groups; 6) to compare the quality and quantity of humoral responses in serum and saliva; 7) to compare T-cell and B-cell responses after natural infection between different microorganisms; and 8) to assess the level of waning immunity over time, both within-host and cross-sectional.
Study design: Controlled observational, non-therapeutic trial
Study population: Laboratory confirmed infectious disease cases and age-matched controls. Depending on the specific infectious disease of the case, cases and controls can be either vaccinated or unvaccinated. Measles was our first disease of interest, due to the outbreak of Measles in 2013. Vaccine failure results in an elevated number of pertussis infections in the last years, the efforts to assess hallmarks of protective and waning immunity are intensified. Therefore, additional cases will be included (in a separate group) for Bordetella pertussis. In addition, we aim to include cases infected with Neisseria meningitidis serogroup B Streptococcus pneumoniae, Mumps Virus, Influenza A Virus and Respiratory Syncytial Virus for immunological evaluation to investigate more divergent mechanisms of protective and waning immunity, and to identify general as well as pathogen specific mechanisms of protection.

Study objective

To provide important information for future vaccination strategies and offer the opportunity to asses shared or unique immune responses after natural infection or vaccination, as well as to compare immune responses after infection with different viruses and pathogens.

Study design

Within 3 months of diagnosis of disease, around 9/12 months after diagnosis (depending on the group), around 18 months after diagnosis, around 36 months after diagnosis. Control group, only one time point.

Intervention

Not applicable

Contacts

Public
RIVM
Alienke Wijmenga-Monsuur

NA
Scientific
RIVM
Alienke Wijmenga-Monsuur

NA

Eligibility criteria

Inclusion criteria

For cases entering the study at time point 1:
In order to be eligible to enter the study at time point 1, the following criteria must be met:
• A case has a symptomatic viral/bacterial infection that is laboratory confirmed, and the time point of inclusion is within 3 months after diagnosis (‘acute phase’)
• Willing to adhere to the protocol and perform all planned visits and sample collections
• Having given written informed consent themselves and/or through parents or legal representatives

For cases first entering the study at time point 2:
In order to be eligible to enter the study at time point 2, the following criteria must be met:
• A case has had a symptomatic viral/bacterial infection that is laboratory confirmed, and the time point of inclusion is around 9 months (± 1 month) after diagnosis
• A case does not enter the Periscope pertussis group
• Is willing to adhere to the protocol and perform all further planned visits and sample collections
• Has given written informed consent him/herself and/or through parents or legal representatives

For cases first entering the study at time point 3:
In order to be eligible to enter the study at time point 3, the following criteria must be met:

• A case has had a symptomatic viral/bacterial infection that is laboratory confirmed, and the time point of inclusion is around 18 months (± 2 months) after diagnosis
• A case does not enter the Periscope pertussis group
• Is willing to adhere to the protocol and perform the further planned visit and sample collection
• Has given written informed consent him/herself and/or through parents or legal representatives

For cases first entering the study at time point 4:
In order to be eligible to enter the study at time point 4, the following criteria must be met:
• A case has had a viral/bacterial infection that is laboratory confirmed, and the time point of inclusion is around 36 months (± 3 months) after diagnosis
• A case does not enter the Periscope pertussis group
• Is willing to adhere to the protocol
• Has given written informed consent him/herself and/or through parents or legal representatives

For age-matched controls:
• Negative clinical history and absence of a serological response against at least one of the panel of pathogens of interest for this study in the past 12 months.
• Having given written informed consent themselves and/or through parents or legal representatives
• Having been vaccinated, if applicable according to birth cohort, against measles, Bordetella pertussis, Streptococcus pneumoniae and/or mumps

Exclusion criteria

Any of the following criteria will exclude a volunteer from participation, at the entry into the study:
• Be or have been under immunosuppressive medical treatment, like cytostatics and prednisolons that might interfere with the results of the study, within the previous 3 months. In exemption to this criterion, short-term (≤15 days), systemic immunosuppressive medication is permitted in case this medication is used to treat infections.
• Have any known primary or secondary immunodeficiency;
• Have a bleeding disorder or be under treatment with anticoagulants. In case of use of anti-coagulants, adult volunteers can be included if no spontaneous bleedings occurred in the month prior to venipuncture, if the dose of medication is stable (no changes in the month prior to venipuncture) and/or INR testing is performed at ≤ 2 times a month, and if the INR value is below 3.5 (based on the information provided by the volunteer)
A control is not eligible when he/she reports to
• Have developed clinical symptoms of a virus or pathogen infection in the very short period of time between the identification as a control and the date of the home visit.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-05-2014
Enrollment:	419
Type:	Actual

IPD sharing statement

Plan to share IPD: No

Plan description
IPD will not be shared. Biobank with materials that will be used in the coming years for research. Group sizes are small and disease information too specific, which makes sharing of individual participant data too vulnerable for identification.

Ethics review

Positive opinion

Date:	06-10-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 47081
Bron: ToetsingOnline

Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL9775
CCMO	NL46795.094.13
OMON	NL-OMON47081

Study results

Summary results
Publications using study material (untill 12-04-2022)

Kaaijk P, Pimentel VO, Emmelot ME, Poelen M, Cevirgel A, Schepp RM, den Hartog G, Reukers DFM, Beckers L, van Beek J, van Els CACM, Meijer A, Rots NY, de Wit J. Children and Adults With Mild COVID-19: Dynamics of the Memory T Cell Response up to 10 Months. Front Immunol. 2022 Feb 7;13:817876. doi: 10.3389/fimmu.2022.817876. PMID: 35197982; PMCID: PMC8858984.

Lambert Eleonora E., van Twillert Inonge, Beckers Lisa, Poelen Martien C. M., Han Wanda G. H., Pieren Daan K. J., van Els Cécile A. C. M. Reduced Bordetella pertussis-specific CD4+ T-Cell Responses at Older Age. 2022. Frontiers in Aging. Aging and the immune system. Doi: 10.3389/fragi.2021.737870. ISSN=2673-6217 https://www.frontiersin.org/article/10.3389/fragi.2021.737870. https://doi.org/10.3389/fragi.2021.

Lanfermeijer J, Nühn MM, Emmelot ME, Poelen MCM, van Els CACM, Borghans JAM, van Baarle D, Kaaijk P, de Wit J. Longitudinal Characterization of the Mumps-Specific HLA-A2 Restricted T-Cell Response after Mumps Virus Infection. Vaccines (Basel). 2021 Dec 3;9(12):1431. doi: 10.3390/vaccines9121431. PMID: 34960178; PMCID: PMC8707000.

Lesne E, Cavell BE, Freire-Martin I, Persaud R, Alexander F, Taylor S, Matheson M, van Els CACM, Gorringe A. Acellular Pertussis Vaccines Induce Anti-pertactin Bactericidal Antibodies Which Drives the Emergence of Pertactin-Negative Strains. Front Microbiol. 2020 Aug 27;11:2108. doi: 10.3389/fmicb.2020.02108. PMID: 32983069; PMCID: PMC7481377.

de Wit J, Emmelot ME, Poelen M, van Binnendijk R, van der Lee S, van Baarle D, Han WGH, van Els CACM, Kaaijk P. Mumps infection but not childhood vaccination induces persistent

polyfunctional CD8+ T-cell memory. J Allergy Clin Immunol. 2018 May;141(5):1908-1911.e12. doi: 10.1016/j.jaci.2017.11.047