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Long-term cellular memory immunity against Bordetella pertussis and other components of the DTP-IPV-Hib vaccine in Dutch children: comparison of a whole cell vaccine (WCV) with an acellular vaccine (ACV)

Submission date	Recruitment status	[_] Prospectively registered
29/04/2008	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
07/11/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
04/07/2019	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mrs Lotte Hendrikx

Contact details
Antoni van Leeuwenhoeklaan 9
Postbak 22
Bilthoven
Netherlands
3720 BA
+31 (0)30 274 3944
Lotte.Hendrikx@rivm.nl

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
LTR137

Study information

Scientific Title
Long-term cellular memory immunity against Bordetella pertussis and other components of the DTP-IPV-Hib vaccine in Dutch children: comparison of a whole cell vaccine (WCV) with an acellular vaccine (ACV) - observational study

Study objectives
Whooping cough is a respiratory disease, caused by Bordetella pertussis. Whooping cough is a serious disease in the young, vulnerable infant. Older children and adults are the main source of infection. Since 1996 the incidence of whooping cough is increasing in the Netherlands. Since the acellular vaccine (ACV) against whooping cough (pertussis) was introduced in the Netherlands in 2005 and qualitative differences in infant immunity to ACV and whole cell vaccine (WCV) have been described, cellular immunity and memory against pertussis need to be addressed. Both vaccines are given at an age when the immune system is not yet fully developed and the (long term) effects of this major change in the vaccination programme are largely unknown. This study aims to investigate the effects of the switch from WCV to ACV on the long-term protective immunity against pertussis and on the development of the immune system. Furthermore, the influence on the TH1/TH2 balance differs between the cellular and acellular pertussis vaccinations and will be further investigated after booster vaccination at 4 years with ACV.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Medical Ethics Committee, Almere (Medische Ethische Toestingscommissie [METC] te Almere). Date of approval: 03/04/2006 (ref: R06-025)

Study design
Observational cohort multicentre study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Other

Study type(s)
Prevention

Participant information sheet

Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Whooping cough/ Bordetella pertussis infection

Interventions
This is an observational, cohort study. Recruitment will be carried out in two stages.

Populations of children at different ages who already had received four vaccinations at 2, 3, 4 and 11 months with the whole cell vaccine DTPwcv-IPV-(Hib) were recruited in 2006 as follows:

3 years old: 2 year after the forth priming vaccination at 11 months
4 years old: before the booster vaccination with ACV
4 years old: 10 (+/-1 day) days after the booster vaccination with ACV (Triaxis®)
4 years old: 28 (+/-3 days) days after the booster vaccination with ACV (Triaxis®)
4 years old: 28 (+/-3 days) days after the booster vaccination with ACV (Infanrix®-IPV)
6 years old: 2 years after the booster vaccination with ACV
9 years old: 5 years after the booster vaccination with ACV

One blood sample was taken, and questionnaires (including questions concerning clinical manifestations of allergic reactions) were carried out.

For comparison, the same age groups of children (but different children from the previous recruitment) who already had received four vaccinations at 2, 3, 4 and 11 months with the acellular vaccine DTPacv-IPV-(Hib) (Infanrix®-IPV) will be recruited from 2008 till 2015.

B- and T-cells will be isolated and enzyme-linked immunosorbent spots (ELIspots) will be carried out. In a multiple immuno beads assay, the antibody titres will be measured.

Intervention Type
Biological/Vaccine

Phase
Not Specified

Primary outcome measure
B cell and T cell immune responses:
Peripheral blood mononuclear cells (PBMC's) will be isolated from the blood samples. PBMC's will be divided in purified B cell populations and T cell populations. B cells will be cultured and memory B cells will be polyclonal stimulated. After 5 days stimulation, B cell memory responses will be measured against the various proteins of B pertussis (filamentous hemagglutinin adhesin [FHA], pertactin [PRN], pertussis toxin [PT], fimbriae [Fim], lipopolysaccharide [LPS]) by ELIspot assays and enzyme-linked immunosorbent assay (ELISA)/Luminex® of the culture supernatants.

T cells will be stimulated with the various proteins of B. pertussis and at 24 hours and 5 days of culture, cells and supernatants will be harvested. Memory T cell responses will be measured by IFN-y and/or IL2 ELIspot assays. TH1/TH2 ratios will be measured by analysing cytokines in the culture supernatants by Luminex® bead protein assay or ELISA.

All data collection will be completed by the end of 2010.

Secondary outcome measures
Blood samples will be separated in PBMC's and plasma samples. The plasma samples will be used to measure antibody responses against the various proteins of B. pertussis as well as against the other proteins of the DKT-IPV-HIB vaccine.

Plasma parameter assays:
1. Pertussis (PT, PRN, FHA, FIM2 and FIM3): IgG antibody titer is measured in an ELISA/Luminex® with two-fold serial dilution series in duplicate using FDA reference serum as standard (EU/ml)
2. Diphtheria, tetanus: IgG antibody titer is measured in a ToBI-ELSA/Luminex® with twofold serial dilution series in duplicate using the national reference serum (IU/ml) as standard which is calibrated on the World Health Organization (WHO) standard
3. Haemophilus influenzae type b (Hib): IgG antibody titer is measured in an ELISA/Luminex® with two-fold serial dilution series in duplicate using CBER-FDA reference serum as standard (µg /ml)
4. Polio: total Ig is measured in a neutralisation assay on Vero cells with two-fold serial dilution series in duplicate using the WHO reference serum as standard
5. To monitor the effect of WCV or ACV on TH2 mediated disease manifestations, total IgE levels and some components of the DTP-IPV-Hib vaccine (PT and tetanus) will be measured in the plasma
6. Mucosal IgA antibodies will be measured in the plasmas

All data collection will be completed by the end of 2010.

Overall study start date
01/09/2006

Completion date
18/12/2007

Eligibility

Key inclusion criteria
1. Both male and female children, aged 3 to 9 years old
2. Infants in good general health (eligible) who have been vaccinated according to the Dutch national vaccination programme
3. Provision of written informed consent by both parents and legal representatives

Participant type(s)
Patient

Age group
Child

Lower age limit

3 Years

Upper age limit
9 Years

Sex
Both

Target number of participants
420

Total final enrolment
338

Key exclusion criteria
1. Present evidence of serious disease(s) demanding immunosuppressive medical treatment, such as corticosteroids, that might interfere with the results of the study within 3 months
2. Any known primary or secondary immunodeficiency
3. Vaccination with any other vaccine than those used in the National Immunisation Programme (Rijks Vaccinatie Programma [RVP]) within a month before the blood sampling

Date of first enrolment
01/09/2006

Date of final enrolment
18/12/2007

Locations

Countries of recruitment
Netherlands

Study participating centre
Antoni van Leeuwenhoeklaan 9
Bilthoven
Netherlands
3720 BA

Sponsor information

Organisation
National Institute for Public Health and the Environment (RIVM) (The Netherlands)

Sponsor details

Antoni van Leeuwenhoeklaan 9
Bilthoven
Netherlands
3720 BA

Sponsor type
Government

Website
http://www.rivm.nl/en/

ROR
https://ror.org/01cesdt21

Funder(s)

Funder type
Government

Funder Name
National Institute for Public Health and the Environment (RIVM) (The Netherlands)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2013	04/07/2019	Yes	No