Immunogenicity of HPV-vaccination in a reduced-dose schedule

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- To study the kinetics of the vaccine-induced antibody response against HPV16/18 after a two-dose schedule by measuring these antibody responses at approximately 7, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months following the first dose of HPV-...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON53042

Source
ToetsingOnline

Brief title
HPV-2/1D

Condition

- Viral infectious disorders

Synonym
cervical cancer, HPV

Research involving
Human

Sponsors and support

Primary sponsor: RIVM
Source(s) of monetary or material Support: Ministerie van VWS

Intervention

Keyword: Cervarix, HPV, Immunogenicity, Two Doses

Outcome measures

Primary outcome

- Type specific antibody levels against HPV types 16 and 18,in serum following the two-dose schedule and whether these levels remain above plateau for HPV-16/-18 up to 24 months after the first dose

- Kinetics of type specific antibody levels against HPV types 16 and 18 in serum following the two-dose schedule up to 120 months after the first dose

- Whether the two-dose schedule is non-inferior for HPV 16 and HPV 18 to the three-dose schedule up to approximately 7.5 years after the first dose

- To study HPV-16/-18 antibody responses after a one-dose schedule at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years following vaccination.

- To study the kinetics of the antibody response against HPV types 16 and 18 at approximately 7, 12, 24, and 36 months after the first dose of HPV vaccination in a two-dose schedule among boys.

- To study whether the antibody response against HPV types 16 and 18 after HPV vaccination in a two-dose schedule among boys vaccinated at 9-10 years of age is non-inferior to that of a two-dose schedule among girls vaccinated at 12-13 years of age approximately 7, 12, 24, and 36 months after the first dose.

Secondary outcome

- Avidity of HPV types 16 and 18 specific IgG antibodies in serum following the two-dose schedule up to 120 months after the first dose

- A comparison of the avidity of HPV-16/-18 specific IgG antibodies following a

three or two dose schedule up to 7.5 years after the first dose.

- Explorative: Functionality of antibodies against HPV types 16 and 18 in serum (PBNA) following the two-dose schedule up to 60 months after the first dose

- Whether the level of antibodies against HPV 16/18 after a two-dose schedule remains above plateau in a cross-sectional design up to approximately 7.5 years after the first dose

- Type specific antibody levels against HPV 31/33/45/52/58 in serum measured at 7, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months following the two-dose vaccination schedule

- Differences in type specific antibody levels against possible cross-protection types HPV 31 and 45 in serum measured up to 7.5 years after the first dose in both vaccinated in a two dose schedule and vaccinated in a three dose schedule.

- The kinetics of the antibody response against HPV types 31/33/45/52/58 at approximately 7, 12, 24, and 36 months after the first dose of HPV vaccination in a two-dose schedule among boys.

- To compare the antibody response against HPV types 31/33/45/52/58 after HPV vaccination in a two-dose schedule among 9-10 year old boys compared to a two-dose schedule among 12-13 year old girls at approximately 7, 12, 24, and 36 months after the first dose.

- Cellular immunity represented by the number of HPV-specific B-cells.

- Whether HPV-16/-18 antibody responses after a one-dose schedule are non-inferior compared to a two-dose schedule, at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years following vaccination.

- A comparison of the avidity of antibodies against HPV-16/-18 after a one-dose schedule with the avidity after a two-dose schedule, at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years after vaccination.

- Possible differences in antibody responses after a one-dose schedule for HPV-31 and -45 for which cross-protection has been described, and other types if possible, at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years after vaccination.

- Vaccine-induced cellular immunity at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years after a one-dose schedule.

- Explorative: Functionality of antibodies against HPV types 16 and 18 in serum (PBNA) following a one-dose schedule.

- Exploratory: avidity of antibody response against HPV types 16 and 18 at approximately 7, 12, 24, and 36 months after the first dose of HPV vaccination in a two-dose schedule among boys.

- Exploratory: avidity of antibody response against HPV types 16 and 18 after HPV vaccination in a two-dose schedule among 9-10 year old boys compared to a two-dose schedule among 12-13 year old girls at approximately 17, 12, 24, and 36 months after the first dose.

Study description

Background summary

In December 2013, the European Medicines Agency (EMA) approved a two-dose schedule for the bivalent vaccine for girls 9 to 14 years of age. Following this approval and the registration, the Minister of Health decided in January 2014 that the Netherlands would directly change their HPV vaccination schedule.

From that moment, girls up to 14 years of age will be vaccinated by the use of a two-dose schedule, at month 0 and 6. The change from three- to two-dose schedule asks for monitoring of the kinetics over time and quality of vaccine induced immunity after a two-dose schedule. Furthermore, some girls only received one dose of the HPV vaccine. Monitoring of the immunity in these girls is important. From 2022 onwards, boys will also be invited for a two-dose schedule. In addition, the age has been lowered to 9/10 years. Monitoring the immunogenicity of the HPV vaccine after two doses among 9-10 year old boys in the Netherlands is important to monitor the effects of HPV vaccination.

Study objective

- To study the kinetics of the vaccine-induced antibody response against HPV16/18 after a two-dose schedule by measuring these antibody responses at approximately 7, 12, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months following the first dose of HPV-16/-18 vaccination in a two-dose schedule and study whether thise levels remains above plateau up to 24 months (397.8 EU/ml for HPV-16 and 297.3 EU/ml for HPV-18).

- To study whether HPV16/18- antibody responses are non-inferior after a two-dose HPV 16/18-vaccination schedulecompared to a three-dose schedule at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years after the first dose.

- To study the level and quality of antibody response at approximately 1 *, 2 *, 3 *, 4 *, 5 *, 6 * and 7 * years following one dose of HPV-16/18 vaccination.

- To study the kinetics of the antibody response against HPV types 16 and 18 at approximately 7, 12, 24, and 36 months after the first dose of HPV vaccination in a two-dose schedule among boys.

- To study whether the antibody response against HPV types 16 and 18 after HPV vaccination in a two-dose schedule among boys vaccinated at 9-10 years of age is non-inferior to a two-dose schedule among girls vaccinated at 12-13 years of age at approximately 7, 12, 24, and 36 months after the first dose.

Study design

Avidity and quality of antibodies will be studied in a prospective cohort, also cellulair immunity will be studied. In addition, a similar study arm is set up among boys. To compare the antibody levels after a two-dose schedule with a three-dose schedule, cross-sectional observational sampling will be performed. Also cross-sectional sampling will be performed to study the cellular immunity, the level and quality of vaccine-induced antibodies in girls who were vaccinated by one dose. The study design and recruitment of participants is described in detail in the study protocol starting on page 36.

A sample of boys will be obtained as a nationwide sample in the Netherlands. Recruitment will be done by a personal letter in which the boy is invited to participate and in which the parents/legal representative are informed about the study and the possibility for the invited boy to participate. Selection of eligible boys will be performed via Praeventis. The *Dienst Vaccinvoorziening en Preventieprogramma's* (DVP) of the RIVM is responsible for managing Praeventis. For the current study, the DVP department is responsible for sending the personal invitation letters.
The involved researchers do not have access to the subject*s data at that time. The subjects will receive the personal invitation letter and an informed consent by regular mail at least four weeks before the time since first vaccination approaches 7 months. The invitation letters will be send out around September. A telephone number of an involded researcher and independent doctor will be provided for questions. Parents and boys are advised to calmy read all the information before deciding to participate in the study. If the subject decides to participate, his parents/legal representatives fill in the informed consent (for participation for 4 years) and send it back to the RIVM. After returning the informed consent, the involved researcher from the RIVM will also sign the informed consent and a copy will be sent to the parents. The researchers will also send the research package to the participants to draw a fingerprick blood at home. In this package a link to the online questionnaire is also provided. The subject will fill in the questionnaire on a secured website (url and code to log in are provided in the personal invitation letter and research package). The finger prick blood should be sent back to the RIVM within two weeks. When the boy reaches 12 years of age, another informed consent will be sent by regular mail. If a subject decides to continue with the participation in the study, the boy needs to fill in the informed consent (for participation for another year) and send it back to the RIVM.

Study burden and risks

For girls 1997-2003 participation involves one blood sample by finger prick and fill out one online questionnaire. For girls born in 2001 participation involves six research moments, including an online questionnaire and vene puncture blood sampling, the sampling moments on 72, 84, 96, 108 and 120 months involves blood sampling by finger prick. A part of the girls born in 1997-2003 who gave a finger-prick blood sample, will participate in an additional one-time blood collection by venepuncture. These birth cohorts are considered because they were applicable for routine HPV vaccination. For boys born in 2012, there are four research occasions over a period of four years, consisting of the completion of a questionnaire via the Internet and a blood collection by means of a finger prick. The sensation of blood collection is uncomfortable to minor extent for some participants. The risk of blood collection is generally accepted.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

In order to be eligible to participate in the cohort study among girls, a subject must meet all of the following criteria:
- Vaccinated with the bivalent HPV vaccine (Cervarix)
- Received one-, two- (with at least five months interval) or three-doses (0,1,6 months) of the
vaccine
- Born between 1997 and 2003
- Female

The inclusion criteria for the cohort study among boys are as follows:
- Vaccinated with the bivalent HPV vaccine (Cervarix)
- Received two-doses (with at least five months interval) of the vaccine

- Born in 2012
- Male

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- unknown or incorrect address
- participated in tolerability study and stated to no longer be approachable for further research

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-08-2014
Enrollment:	1305
Type:	Actual

Ethics review

Approved WMO

Date:	02-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	21-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 29611
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL48754.029.14