Clinical trial results:
Immunological effects of an acellular pertussis booster vaccination in children, young adults and elderly with different immunisation background.
An international study in Finland, the Netherlands and the United Kingdom

Summary

EudraCT number	2016-003678-42
Trial protocol	NL FI GB
Global end of trial date	28 May 2020
Results information	
Result version number	v1 (current)
This version publication date	08 May 2022
First version publication date	08 May 2022

Trial information

Trial identification	
Sponsor protocol code	BERTIIV-316
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03697798
WHO universal trial number (UTN)	-
Other trial identifiers	ABR: NL60807.100.17

Notes:

Sponsors	
Sponsor organisation name	National Institute for Public Health and the Environment
Sponsor organisation address	Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands, 3721 MA
Public contact	Clinical Expertise Centre IIV, National Institute for Public Health and the Environment, mensgebonde, RIVM, Periscope@rivm.nl
Scientific contact	Clinical Expertise Centre IIV, National Institute for Public Health and the Environment, mensgebonde, RIVM, Periscope@rivm.nl
Sponsor organisation name	University of Oxford, Research Governance, Ethics and Assurance
Sponsor organisation address	Boundary Brook House, Churchill Drive, Oxford, United Kingdom, OX3 7LA
Public contact	Dr Dominic F Kelly, Oxford Vaccine Group, University of Oxford Department of Paediatrics, dominic.kelly@paediatrics.ox.ac.uk
Scientific contact	Dr Dominic F Kelly, Oxford Vaccine Group, University of Oxford Department of Paediatrics, dominic.kelly@paediatrics.ox.ac.uk
Sponsor organisation name	University of Turku
Sponsor organisation address	Kiinamyllynkatu 10, Turku, Finland, 20520 Turke
Public contact	Prof Qiushui He, Department of Biomedicine, Medisiina D,

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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2020
Global end of trial reached?	Yes
Global end of trial date	28 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess magnitude and changes in pertussis toxin (PT) specific IgG antibody levels just before (T0) and 28 days (T4) after the booster vaccination in 2 cohorts of children (7-10 and 11-15 years of age), 1 cohort of young adults (20-34 years of age) and 1 cohort of elderly (60-70 years of age) in three different countries.

Protection of trial subjects:

Where appropriate, local anaesthetic was used.
They were observed for 15 minutes post vaccination.
They had access through phone 24 hours to medical staff

Background therapy:

N/A

Evidence for comparator:

N/A
All participants received the same study vaccine.

Actual start date of recruitment	03 July 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 126
Country: Number of subjects enrolled	Netherlands: 149
Country: Number of subjects enrolled	United Kingdom: 131
Worldwide total number of subjects	406
EEA total number of subjects	275

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	143
Adolescents (12-17 years)	109
Adults (18-64 years)	116
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

United Kingdom: The first participant was recruited on 18/04/18 and the last participant was recruited on 14/01/20.

Netherlands:

Finland:The first participant was recruited on 06/08/18 and the last participant was recruited on 21/01/19.

Pre-assignment

Screening details:

United Kingdom:
Assessed for eligibility - (n)342
Excluded - (n) 212, not meeting inclusion criteria = 104, Other reasons = 108

Finland:
Assessed for eligibility - (n)182
Excluded - (n) 54, not meeting inclusion criteria =35, Other reasons = 19

Netherlands:
Assessed for eligibility - (n)324
Excluded - (n) 174, not meeting inclusion 1

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Single dose acellular pertussis arm

Arm description:

All participants given single dose of Boostrix-IPV

Arm type	Experimental
Investigational medicinal product name	Boostrix-IPV
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Single dose given intramuscularly

Number of subjects in period 1	Single dose acellular pertussis arm
Started	406
Completed	374
Not completed	32
Lost to follow-up	2
Discontinued study	30

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	406	406	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	143	143	
Adolescents (12-17 years)	109	109	
Adults (18-64 years)	116	116	
From 65-84 years	38	38	
85 years and over	0	0	
Children (7-10 years)	0	0	
Children (11-15 years)	0	0	
Young adult (20-34 years)	0	0	
Older adults (60-70 years)	0	0	
Gender categorical			
Gender information on all subjects across all trial sites			
Units: Subjects			
Female	212	212	
Male	194	194	

Subject analysis sets	
Subject analysis set title	Child (7-10 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All children 7-10 years across all trial sites contributing to serological analysis

Subject analysis set title	Child (11-15 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All children 11-15 years across all trial sites contributing to serological analysis

Subject analysis set title	Young adults (20-34 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All adults 20-34 years across all trial sites contributing to serological analysis

Subject analysis set title	Older adults (60-70 years)
Subject analysis set type	Full analysis

Subject analysis set description:

All adults 60-70 years across all trial sites contributing to serological analysis

Reporting group values	Child (7-10 years)	Child (11-15 years)	Young adults (20-34 years)
Number of subjects	109	121	74
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Children (7-10 years)	109	0	0
Children (11-15 years)	0	121	0
Young adult (20-34 years)	0	0	74
Older adults (60-70 years)	0	0	0
Gender categorical			
Gender information on all subjects across all trial sites			
Units: Subjects			
Female	52	54	47
Male	57	67	27

Reporting group values	Older adults (60-70 years)		
Number of subjects	75		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Children (7-10 years)	0		
Children (11-15 years)	0		
Young adult (20-34 years)	0		
Older adults (60-70 years)	75		
Gender categorical			
Gender information on all subjects across all trial sites			
Units: Subjects			
Female	48		
Male	27		

End points

End points reporting groups

Reporting group title	Single dose acellular pertussis arm
Reporting group description: All participants given single dose of Boostrix-IPV	
Subject analysis set title	Child (7-10 years)
Subject analysis set type	Full analysis
Subject analysis set description: All children 7-10 years across all trial sites contributing to serological analysis	
Subject analysis set title	Child (11-15 years)
Subject analysis set type	Full analysis
Subject analysis set description: All children 11-15 years across all trial sites contributing to serological analysis	
Subject analysis set title	Young adults (20-34 years)
Subject analysis set type	Full analysis
Subject analysis set description: All adults 20-34 years across all trial sites contributing to serological analysis	
Subject analysis set title	Older adults (60-70 years)
Subject analysis set type	Full analysis
Subject analysis set description: All adults 60-70 years across all trial sites contributing to serological analysis	

Primary: PT antibody

End point title	PT antibody
End point description:	
End point type	Primary
End point timeframe: Day 28 post-vaccine	

End point values	Child (7-10 years)	Child (11-15 years)	Young adults (20-34 years)	Older adults (60-70 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	121	74	75
Units: International units /ml				
geometric mean (confidence interval 95%)				
Geometric mean concentration	147 (120 to 181)	161 (132 to 196)	108 (80 to 133)	121 (94 to 155)

Statistical analyses

Statistical analysis title	PT concentration between age-groups at day 28

Statistical analysis description:

A linear mixed model was fitted to the log-transformed antibody concentrations. Timepoint of blood

sampling and age group were included as a two-way interaction as fixed effects. Participant ID was included as a random intercept in the model and by the random intercept the baseline concentration of each participant was taken into account. Overall significance of the fixed effect terms was assessed by a type III ANOVA.

Comparison groups	Child (7-10 years) v Child (11-15 years) v Young adults (20-34 years) v Older adults (60-70 years)
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	ANOVA

Notes:

[1] - GMCs and their corresponding 95% confidence intervals (95% CI), as well as their mutual GMC ratios, corresponding 95% CI and p-values were obtained by post hoc analysis using Satterthwaite's method.P-values were adjusted by applying the Benjamini-Hochberg procedure for multiple comparisons, controlling the false discovery rate [46]. Non-relevant comparisons were excluded.

Secondary: FHA antibody

End point title	FHA antibody

End point description:

End point type	Secondary

End point timeframe:

Day 28 post-vaccine

End point values	Child (7-10 years)	Child (11-15 years)	Young adults (20-34 years)	Older adults (60-70 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	121	74	75
Units: IU/ml				
geometric mean (confidence interval 95%)	290 (248 to 340)	313 (269 to 364)	299 (247 to 361)	255 (211 to 308)

Statistical analyses

Statistical analysis title	FHA concentration between age-groups at day 28

Statistical analysis description:

A linear mixed model was fitted to the log-transformed antibody concentrations. Timepoint of blood sampling and age group were included as a two-way interaction as fixed effects. Participant ID was included as a random intercept in the model and by the random intercept the baseline concentration of each participant was taken into account. Overall significance of the fixed effect terms was assessed by a type III ANOVA.

Comparison groups	Older adults (60-70 years) v Young adults (20-34 years) v Child (11-15 years) v Child (7-10 years)
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	≤ 0.05
Method	ANOVA

Notes:

[2] - GMCs and their corresponding 95% confidence intervals (95% CI), as well as their mutual GMC ratios, corresponding 95% CI and p-values were obtained by post hoc analysis using Satterthwaite's method.P-values were adjusted by applying the Benjamini-Hochberg procedure for multiple comparisons, controlling the false discovery rate . Non-relevant comparisons were excluded.

Secondary: PRN antibody at day 28

End point title	PRN antibody at day 28

End point description:

End point type	Secondary

End point timeframe:

Day 28 post-vaccine

End point values	Child (7-10 years)	Child (11-15 years)	Young adults (20-34 years)	Older adults (60-70 years)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	121	74	75
Units: IU/ml				
geometric mean (confidence interval 95%)	293 (223 to 386)	318 (245 to 414)	331 (237 to 463)	171 (123 to 239)

Statistical analyses

Statistical analysis title	PRN concentration between age-groups at day 28

Statistical analysis description:

A linear mixed model was fitted to the log-transformed antibody concentrations. Timepoint of blood sampling and age group were included as a two-way interaction as fixed effects. Participant ID was included as a random intercept in the model and by the random intercept the baseline concentration of each participant was taken into account. Overall significance of the fixed effect terms was assessed by a type III ANOVA.

Comparison groups	Child (7-10 years) v Child (11-15 years) v Young adults (20-34 years) v Older adults (60-70 years)
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.05
Method	ANOVA

Notes:

[3] - GMCs and their corresponding 95% confidence intervals (95% CI), as well as their mutual GMC ratios, corresponding 95% CI and p-values were obtained by post hoc analysis using Satterthwaite's method.P-values were adjusted by applying the Benjamini-Hochberg procedure for multiple comparisons, controlling the false discovery rate . Non-relevant comparisons were excluded.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Duration of the study from first participant first visit through to last participant last visit for each country

Adverse event reporting additional description:

Reactogenicity was not an outcome for this study
Only Serious Adverse Events reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Total study population

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This study was not collecting data on non-serious adverse events

Serious adverse events	Total study population		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 379 (1.58%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 379 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Hospitalisation			
subjects affected / exposed	1 / 379 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	1 / 379 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hospitalisation			

subjects affected / exposed	2 / 379 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Hospitalisation			
subjects affected / exposed	2 / 379 (0.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Total study population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 379 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2018	Finland: addition of EMLA cream (lidocaine and prilocaline) for local anaesthesia of skin before venepuncture
25 May 2018	This amendment concerns increasing the number of participants in group B of the BERT study, children in the age of 11 to 15 years, in order to obtain a more equal distribution of children with either an aP vaccine background or a wP vaccine background. The reason for the submission of this amendment is to be able to restore the impaired distribution between the children with an aP vaccine background and a wP vaccine background (12 versus 24) which has consequences for the analysis of the humoral assays but mainly for the interpretation of the outcome of the cellular immunological assays. In order to restore this distorted distribution, we want to include an extra 12 participants with an aP vaccine background within this group B
31 July 2018	United Kingdom: clarification of exclusion criteria and the procedures for further Td-IPV vaccinations in cohort B, as well as the inclusion of reimbursement details on the recruitment materials and GDPR text on the information booklets
27 May 2020	United Kingdom: The substantial amendment involved clarification regarding the use of the stored serum samples from the BERT study in the exceptional circumstances of the SARS-CoV2 public-health emergency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33647770