



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, mensgebode, RIVM, Periscope@rivm.nl |
| Scientific contact | Clinical Expertise Centre IIV, National Institute for Public Health and the Environment, mensgebode, 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 | Kiinamylynkatu 10, Turku, Finland, 20520 Turke |
| Public contact | Prof Qiushui He, Department of Biomedicine, Medisiina D, |

| | |
|--------------------|--|
| | University of Turku, Turun Yliopisto, Jussi.mertsola@tyks.fi |
| Scientific contact | Prof Qiushui He, Department of Biomedicine, Medisiina D, University of Turku, Turun Yliopisto, Jussi.mertsola@tyks.fi |

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>