



## Clinical trial results:

### The effects of BCG-vaccination on the immune response induced by influenza-vaccination in healthy volunteers A pilot proof-of-principle study

#### Summary

EudraCT number	2014-000966-23
Trial protocol	NL
Global end of trial date	31 July 2014

#### Results information

Result version number	v1 (current)
This version publication date	26 May 2021
First version publication date	26 May 2021
Summary attachment (see zip file)	BCG Vaccination Enhances the Immunogenicity of Subsequent Influenza Vaccination in Healthy Volunteers: A Randomized, Placebo-Controlled Pilot Study (Publication 2014-000966-23.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	BCG_influenza
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	clinical trials.gov: volgt

Notes:

##### Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	Geert Grooteplein Zuid 10, Nijmegen, Netherlands, 6525 HB
Public contact	Jenneke Leentjens, Radboud University Nijmegen Medical Centre, 0031 243668420, jenneke.leentjens@radboudumc.nl
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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	31 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2014
Global end of trial reached?	Yes
Global end of trial date	31 July 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the effects of BCG-vaccination on the immune response induced by subsequent influenza vaccination in healthy volunteers. This will be determined by measuring the Th1/Th2 response, and antibody titers induced by influenza vaccination in seronegative healthy volunteers who are, prior to influenza vaccination, vaccinated with either BCG or placebo in a double-blind randomized manner.

Protection of trial subjects:

Physical examination prior to start of experiment. Informed consent required.

Background therapy:

intramuscular injection of 0.5 mL of trivalent 2013–2014 seasonal influenza vaccine containing A/California/7/2009 (A[H1N1]pdm09)–derived strain, Victoria/361/2011-related strain derived from A/Texas/50/2012 (A[H3N2]2012), and B/Massachusetts/2/2012 (B/2012)–derived strain surface antigens and no adjuvants (Batrevac; Abbot Biologicals, Weesp, the Netherlands)

Evidence for comparator: -

Actual start date of recruitment	01 May 2014
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	Netherlands: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:  
healthy, nonsmoking

### Pre-assignment

Screening details:

Subjects who received BCG vaccine before, received influenza vaccination in the previous year, or had febrile illness during the 2 weeks before the experiment were excluded. Subjects were not allowed to use prescription drugs.

### Period 1

Period 1 title	BCG vaccine/placebo (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	BCG vaccine and influenza

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Bacille Calmette Guérin vaccination
Investigational medicinal product code	RVG 17661
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

0.1 mL of live attenuated BCG vaccine (BCG vaccine SSI/Danish strain 1331; Bilthoven Biologicals, Bilthoven, the Netherlands)

Investigational medicinal product name	influenza vaccin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

intramuscular  
injection of 0.5 mL of trivalent 2013–2014 seasonal influenza vaccine containing A/California/7/2009 (A[H1N1] pdm09)–derived strain, Victoria/361/2011-related strain derived from A/Texas/50/2012 (A[H3N2]2012), and B/Massachusetts/2/2012 (B/2012)–derived strain surface antigens and no adjuvants (Batrevac; Abbot Biologicals, Weesp, the Netherlands)

<b>Arm title</b>	Placebo and influenza
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

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**Dosage and administration details:**

0.1 mL NaCl 0.9%

Investigational medicinal product name	influenza vaccin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

**Dosage and administration details:**

intramuscular

injection of 0.5 mL of trivalent 2013–2014 seasonal

influenza vaccine containing A/California/7/2009 (A[H1N1]  
pdm09)–derived strain, Victoria/361/2011-related strain derived  
from A/Texas/50/2012 (A[H3N2]2012), and B/Massachusetts/  
2/2012 (B/2012)–derived strain surface antigens and no  
adjuvants (Batrevac; Abbot Biologicals, Weesp, the Netherlands)

<b>Number of subjects in period 1</b>	BCG vaccine and influenza	Placebo and influenza
Started	20	20
Completed	20	20

## Baseline characteristics

### Reporting groups

Reporting group title	BCG vaccine and influenza
Reporting group description: -	
Reporting group title	Placebo and influenza
Reporting group description: -	

Reporting group values	BCG vaccine and influenza	Placebo and influenza	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	40
Age continuous Units: years			
median	21	20.5	
inter-quartile range (Q1-Q3)	20 to 24	20.3 to 25	-
Gender categorical Units: Subjects			
Male	20	20	40

### Subject analysis sets

Subject analysis set title	BCG
Subject analysis set type	Full analysis
Subject analysis set description: BCG group	
Subject analysis set title	PLacebo
Subject analysis set type	Full analysis
Subject analysis set description: Placebo group	

Reporting group values	BCG	PLacebo	
Number of subjects	20	20	
Age categorical Units: Subjects			
Adults (18-64 years)	20	20	
Age continuous Units: years			
median	21	20.5	
inter-quartile range (Q1-Q3)	20 to 24	20.3 to 25	
Gender categorical Units: Subjects			
Male	20	20	

## End points

### End points reporting groups

Reporting group title	BCG vaccine and influenza
Reporting group description: -	
Reporting group title	Placebo and influenza
Reporting group description: -	
Subject analysis set title	BCG
Subject analysis set type	Full analysis
Subject analysis set description:	
BCG group	
Subject analysis set title	PLacebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo group	

### Primary: Difference in HI antibody titers

End point title	Difference in HI antibody titers
End point description:	
End point type	Primary
End point timeframe:	
between day 0 and 28	

End point values	BCG vaccine and influenza	Placebo and influenza		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: fold change				
median (full range (min-max))				
for A(H1N1)pdm09 strain between day 0 and 7	5.14 (2.11 to 28.62)	2.31 (1.04 to 8.93)		
for A(H1N1)pdm09 strain between day 0 and 14	14.93 (4.08 to 40.00)	4.31 (1.64 to 9.24)		
for A(H1N1)pdm09 strain between day 0 and 28	11.43 (3.0 to 37.39)	3.73 (1.64 to 9.24)		
for A(H3N2)2012 strain between day 0 and 7	6.63 (1.25 to 10.93)	3.047 (1.80 to 12.12)		
for A(H3N2)2012 strain between day 0 and 14	9.46 (2.00 to 18.94)	6.73 (4.00 to 32.00)		
for A(H3N2)2012 strain between day 0 and 28	8.00 (2.00 to 16.00)	7.27 (2.94 to 30.93)		
for B/2012 strain between day 0 and 7	6.09 (1.0 to 10.45)	2.23 (1.24 to 8.00)		
for B/2012 strain between day 0 and 14	4.44 (1.32 to 29.33)	2.73 (1.00 to 8.00)		
for B/2012 strain between day 0 and 28	4.67 (2.00 to 28.9)	3.15 (1.41 to 8.00)		

<b>Attachments (see zip file)</b>	raw data HAI assays/HAI 201400811Resultaat Radboudsera. HAI + GMT uitgewerkt/HAI + GMT.xlsx
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### Statistical analyses

<b>Statistical analysis title</b>	A(H1N1) titer increase
Comparison groups	BCG vaccine and influenza v Placebo and influenza
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	2-fold change
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.025
Variability estimate	Standard deviation



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

day 0 till 28

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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### Reporting groups

Reporting group title	BCG vaccine and influenza
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Reporting group description: -

Reporting group title	Placebo and influenza
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Reporting group description: -

Serious adverse events	BCG vaccine and influenza	Placebo and influenza	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	BCG vaccine and influenza	Placebo and influenza	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	6 / 20 (30.00%)	
General disorders and administration site conditions			
mild complaints	Additional description: including fatigue, headache, malaise, and muscle pain at the injection site, which resolved within 2 days after vaccination in all cases.		
subjects affected / exposed	6 / 20 (30.00%)	6 / 20 (30.00%)	
occurrences (all)	6	6	
Skin and subcutaneous tissue disorders			
inflammatory reaction	Additional description: local inflammatory reaction at the injection site, which resolved in all cases within 4 weeks after injection.		
subjects affected / exposed	10 / 20 (50.00%)	0 / 20 (0.00%)	
occurrences (all)	10	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

relatively small sample size, humoral immunity is not the only mechanism involved in the protection against influenza virus infection. It is not clear what the optimal timing of the BCG vaccinations in context of influenza is.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26071565>