Clinical trial results:
Immune responses to influenza and pneumococcal conjugate vaccines in older adults compared to middle-aged adults and adults.

Summary

EudraCT number	2019-000836-24
Trial protocol	NL
Global end of trial date	07 October 2024

Results information

Result version number	v1 (current)
This version publication date	29 October 2025
First version publication date	29 October 2025

Trial information

Trial identification

Sponsor protocol code	IIV-406

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ABR number: NL69701.041.19

Notes:

Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	PO box 1, Bilthoven, Netherlands, 3720BA
Public contact	VITAL studyteam, National Institute of Health and the Environment (RIVM), VITAL-studie@rivm.nl
Scientific contact	VITAL studyteam, National Institute of Health and the Environment (RIVM), VITAL-studie@rivm.nl

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	Interim
Date of interim/final analysis	07 October 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2024
Global end of trial reached?	Yes
Global end of trial date	07 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To get a better insight in the influence of age and age-related changes by internal and external factors on vaccine-induced immune responses and gain knowledge on the trajectory of immune decline in older adults, pre-elderly (middle-aged) adults in comparison to adults with the ultimate goal to formulate evidence-based strategies to improve immunity to vaccines in the ageing population.

Protection of trial subjects:

The vaccins used in this trial are registered vaccins which are used according to the indication. The particpants are all eligible for the influenza and (booster) COVID-19 vaccinations. Only the pneumcoccal vaccination will be given as an extra vaccination. However, this vaccin is registered in Europe and in the USA, and is used for several years in children and adults. Furthermore, the risk of sampling of blood via finger pricks and venipuncture, faeces and nasal mucosal fluid is considered low. Blood collection could result in a small bruise at the site of blood withdrawal, which will disappear within a few days. The amount of blood drawn per two months within the study is maximum 269 mL and is well within the standard that is maintained by Sanquin Bloodbank.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 326
Worldwide total number of subjects	326
EEA total number of subjects	326

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)	160
From 65 to 84 years	140
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

The older adults were recruited by the wetenschapsbureau of the Spaarne hospital from a previous Influenza-like illness (ILI) study sponsored by the RIVM. Middle-aged and adults subjects were health care workers or laboratory personnel in the Utrecht area recruited via email, flyers and posters.

Pre-assignment

Screening details:

Screening was performed during visit T0. During this visit, the following tasks were executed: checking of subject information was received and understood; questions were answered; Informed consent (IC) was obtained; An inclusion number was assigned and Inclusion and exclusion criteria were checked.

Period 1

Period 1 title	QIV and PCV13 vaccination
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	25-49 years of age, QIV + PCV13

Arm description:

25-49 years of age, QIV + PCV13

Arm type	Experimental
Investigational medicinal product name	Influvac Tetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of 0,5 mL contains the following strains:
- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180): 15 microgram HA
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016,NIB-104): 15 microgram HA
- B/Colorado/06/2017-like strain (B/Maryland/15/2016,NYMC BX-69A): 15 microgram HA
- B/Phuket.3073.2013-like strain (B/Phuket/3073/2013, wild type) 15 microgram HA

Investigational medicinal product name	Prevanar 13
Investigational medicinal product code	
Other name	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 ml) contains:
- Pneumococcal polysaccharide serotype 1: 2,2 µg
- Pneumococcal polysaccharide serotype 3: 2,2 µg
- Pneumococcal polysaccharide serotype 4: 2,2 µg
- Pneumococcal polysaccharide serotype 5: 2,2 µg
- Pneumococcal polysaccharide serotype 6A: 2,2 µg
- Pneumococcal polysaccharide serotype 6B: 4,4 µg
- Pneumococcal polysaccharide serotype 7F: 2,2 µg
- Pneumococcal polysaccharide serotype 9V: 2,2 µg
- Pneumococcal polysaccharide serotype 14: 2,2 µg
- Pneumococcal polysaccharide serotype 18C: 2,2 µg

- Pneumococcal polysaccharide serotype 19A: 4,4 µg
- Pneumococcal polysaccharide serotype 19F: 2,2 µg
- Pneumococcal polysaccharide serotype 23F: 2,2 µg

All serotypes are conjugated to CRM197 carrier protein, adsorbed on aluminium phosphate
1 dos (0,5ml) contains approcimately 32 µg CRM 197 carrier proterin and 0,125 mg aluminium

Arm title	50-64 years of age, QIV + PCV13

Arm description:

50-64 years of age, QIV + PCV13

Arm type	Experimental
Investigational medicinal product name	Influvac Tetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of 0,5 mL contains the following strains:
- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180): 15 microgram HA
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016,NIB-104): 15 microgram HA
- B/Colorado/06/2017-like strain (B/Maryland/15/2016,NYMC BX-69A): 15 microgram HA
- B/Phuket.3073.2013-like strain (B/Phuket/3073/2013, wild type) 15 microgram HA

Investigational medicinal product name	Prevanar 13
Investigational medicinal product code	
Other name	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 ml) contains:
- Pneumococcal polysaccharide serotype 1: 2,2 µg
- Pneumococcal polysaccharide serotype 3: 2,2 µg
- Pneumococcal polysaccharide serotype 4: 2,2 µg
- Pneumococcal polysaccharide serotype 5: 2,2 µg
- Pneumococcal polysaccharide serotype 6A: 2,2 µg
- Pneumococcal polysaccharide serotype 6B: 4,4 µg
- Pneumococcal polysaccharide serotype 7F: 2,2 µg
- Pneumococcal polysaccharide serotype 9V: 2,2 µg
- Pneumococcal polysaccharide serotype 14: 2,2 µg
- Pneumococcal polysaccharide serotype 18C: 2,2 µg
- Pneumococcal polysaccharide serotype 19A: 4,4 µg
- Pneumococcal polysaccharide serotype 19F: 2,2 µg
- Pneumococcal polysaccharide serotype 23F: 2,2 µg

All serotypes are conjugated to CRM197 carrier protein, adsorbed on aluminium phosphate
1 dos (0,5ml) contains approcimately 32 µg CRM 197 carrier proterin and 0,125 mg aluminium

Arm title	65+ years of age, QIV + PCV13

Arm description:

65+ years of age, QIV + PCV13

Arm type	Experimental
Investigational medicinal product name	Influvac Tetra
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

One dose of 0,5 mL contains the following strains:
- A/Michigan/45/2015 (H1N1)pdm09-like strain (A/Singapore/GP1908/2015, IVR-180): 15 microgram HA
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like strain (A/Singapore/INFIMH-16-0019/2016,NIB-104): 15 microgram HA
- B/Colorado/06/2017-like strain (B/Maryland/15/2016,NYMC BX-69A): 15 microgram HA
- B/Phuket.3073.2013-like strain (B/Phuket/3073/2013, wild type) 15 microgram HA

Investigational medicinal product name	Prevanar 13
Investigational medicinal product code	
Other name	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 ml) contains:
- Pneumococcal polysaccharide serotype 1: 2,2 µg
- Pneumococcal polysaccharide serotype 3: 2,2 µg
- Pneumococcal polysaccharide serotype 4: 2,2 µg
- Pneumococcal polysaccharide serotype 5: 2,2 µg
- Pneumococcal polysaccharide serotype 6A: 2,2 µg
- Pneumococcal polysaccharide serotype 6B: 4,4 µg
- Pneumococcal polysaccharide serotype 7F: 2,2 µg
- Pneumococcal polysaccharide serotype 9V: 2,2 µg
- Pneumococcal polysaccharide serotype 14: 2,2 µg
- Pneumococcal polysaccharide serotype 18C: 2,2 µg
- Pneumococcal polysaccharide serotype 19A: 4,4 µg
- Pneumococcal polysaccharide serotype 19F: 2,2 µg
- Pneumococcal polysaccharide serotype 23F: 2,2 µg

All serotypes are conjugated to CRM197 carrier protein, adsorbed on aluminium phosphate
1 dos (0,5ml) contains approcimately 32 µg CRM 197 carrier proterin and 0,125 mg aluminium

Number of subjects in period 1	25-49 years of age, QIV + PCV13	50-64 years of age, QIV + PCV13	65+ years of age, QIV + PCV13
Started	62	98	166
QIV vaccination (T1)	60	96	163
1 or 2 days post QIV vaccination (T2)	59	94	161
7 days post QIV vaccination (T3)	58	96	162
28 days post QIV vaccination (T4)	59	95	159
6 months post QIV vaccination (TE1)	42 [1]	77 [2]	140 [3]
5-8 months post QIV+ PCV 13 (T5)	55	89	148
1 or 2 days post PCV13 vaccination (T6)	49	85 [4]	146
7 days post PCV13 vaccination (T7)	48	84 [5]	145
28 days post PCV13 vaccination (T8)	51	88	143 [6]
12 months pt QIV + 6months pt PCV13 (T9)	48	87	145
12 months post PCV13 vaccination (T10)	45	84 [7]	143 [8]
Completed	45	87	145
Not completed	17	11	21

Physician decision	3	2	5
Covid-19 pandemic	1	3	4
Pregnancy	1	-	-
Received vaccine via other route	1	-	-
Participant discontinuation	2	5	9
Death (unrelated to study)	-	-	1
Transferred to other period	3	-	-
Logistical issues	3	-	-
Lost to follow-up	2	-	-
Study burden	1	1	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 2

Period 2 title	COVID vaccination, primary series
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	50-64 years of age, Comirnaty (Pfizer/BioNTech)

Arm description:

50-64 years of age, Comirnaty (Pfizer/BioNTech)
Only 2 late inclusions at Tc, no subjects truly started at starting point. Starting point set at 2 instead of 0 due to technical limitations.

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine is in a multidose vial and must be diluted before use.
One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).

2 dosages were given with an interval of 28 days (+7days).

Arm title	65+ years of age, Comirnaty (Pfizer/BioNTech)

Arm description:

65+ years of age, Comirnaty (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine is in a multidose vial and must be diluted before use.
One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).

2 dosages were given with an interval of 28 days (+7days).

Arm title	25-49 years of age, Spikevax (Moderna)

Arm description:

25-49 years of age, Spikevax (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	
Other name	COIVD-19 mRNA vaccine, Moderna
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles)
Preferred site of administration is the deltoid muscle of the upper arm.

2 dosages were given with an interval of 28 days (+7days).

Arm title	50-64 years of age, Spikevax (Moderna)

Arm description:

50-64 years of age, Spikevax (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	
Other name	COIVD-19 mRNA vaccine, Moderna
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles)
Preferred site of administration is the deltoid muscle of the upper arm.

2 dosages were given with an interval of 28 days (+7days).

Arm title	65+ years of age, Spikevax (Moderna)

Arm description:

65+ years of age, Spikevax (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	
Other name	COIVD-19 mRNA vaccine, Moderna
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles)
Preferred site of administration is the deltoid muscle of the upper arm.

2 dosages were given with an interval of 28 days (+7days).

Arm title	50-64 years of age, Vaxzevria (AstraZeneca)

Arm description:

50-64 years of age, Vaxzevria (AstraZeneca)
Only 1 late inclusions at Tc, no subjects truly started at starting point. Starting point set at 1 instead of 0 due to technical limitations.

Arm type	Experimental
Investigational medicinal product name	Vaxzevria
Investigational medicinal product code	J07BN02
Other name	AstraZeneca
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,5 ml) contains Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S), not less than 2,5x10^8 infectious units (Inf.U).
The product contains genetically modified organisms.

Preferable place of administration is the deltoid muscle of the upper arm.

2 dosages were given with an interval of 4 to 12 weeks

Number of subjects in period 2[9]	50-64 years of age, Comirnaty (Pfizer/BioNTech)	65+ years of age, Comirnaty (Pfizer/BioNTech)	25-49 years of age, Spikevax (Moderna)
Started	2	2	44
28d pt vaccination1 = vaccination2 (Tb)	0 [10]	36	44
1 month after vaccination 2 (Tc)	2	43	44
6 months after vaccination 2 (Td)	2	41	42
12 months after vaccination 2 (Te)	0 [11]	0	2 [12]
Completed	2	39	33
Not completed	0	4	11
Physician decision	-	-	-
Death	-	2	-
Received additional booster before timepoint	-	-	9
Participant discontinuation	-	2	-
Death (unrelated to study)	-	-	-
Logistical issues	-	-	1
Lost to follow-up	-	-	1
Joined	0	41	0
Late recruitment	-	41	-
Late recruitment reason		Logistical issues	

Number of subjects in period 2[9]	50-64 years of age, Spikevax (Moderna)	65+ years of age, Spikevax (Moderna)	50-64 years of age, Vaxzevria (AstraZeneca)
Started	76	91	1
28d pt vaccination1 = vaccination2 (Tb)	76	91	0
1 month after vaccination 2 (Tc)	76	90	1
6 months after vaccination 2 (Td)	75	89	1
12 months after vaccination 2 (Te)	0 [13]	3 [14]	0
Completed	72	89	0
Not completed	4	2	1
Physician decision	-	1	-
Death	-	-	-
Received additional booster before timepoint	3	-	-
Participant discontinuation	-	-	-
Death (unrelated to study)	1	1	-
Logistical issues	-	-	-
Lost to follow-up	-	-	1
Joined	0	0	0
Late recruitment	-	-	-
Late recruitment reason			

Notes:

[9] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial started with the QIV +PCV series. COVID + booster vaccinations were later available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the following period. Group allocation in the other periods was based on the corresponding vaccination, irrespective of former vaccinations. The number of participants starting another period is thus not equal to the number completing a previous period.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 3

Period 3 title	COVID vaccination, first booster
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	25-49 years of age, first booster, Comirnaty (Pfizer/BioNTech)

Arm description:

25-49 years of age, first booster, Comirnaty (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine is in a multidose vial and must be diluted before use.
One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).

Arm title	50-64 years of age, first booster, Comirnaty (Pfizer/BioNTech)

Arm description:	
50-64 years of age, first booster, Comirnaty (Pfizer/BioNTech)	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
The vaccine is in a multidose vial and must be diluted before use. One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).	
Arm title	65+ years of age, first booster, Comirnaty (Pfizer/BioNTech)
Arm description:	
65+ years of age, first booster, Comirnaty (Pfizer/BioNTech)	
Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
The vaccine is in a multidose vial and must be diluted before use. One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).	

Number of subjects in period 3[15]	25-49 years of age, first booster, Comirnaty (Pfizer/BioNTech)	50-64 years of age, first booster, Comirnaty (Pfizer/BioNTech)	65+ years of age, first booster, Comirnaty (Pfizer/BioNTech)
Started	28	73	123
28 days post booster 1 vaccination (B1)	30	73	125
3-5months post booster1 vaccination (B2)	25	56	6 [16]
6 months post booster 1 vaccination (B3)	23	45	26 [17]
12months post booster 1 vaccination (B4)	4	5 [18]	9 [19]
Completed	4	43	124
Not completed	27	31	2
Received additional booster before timepoint	-	2	-
Participant discontinuation	-	3	1
Death (unrelated to study)	-	-	1
Logistical issues	20	25	-
Lost to follow-up	7	1	-
Joined	3	1	3
Late recruitment	3	1	3
Late recruitment reason	Logistical issues	Logistical issues	Logistical issues

Notes:

[15] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial started with the QIV +PCV series. COVID + booster vaccinations were later available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the following period. Group allocation in the other periods was based on the corresponding vaccination, irrespective of former vaccinations. The number of participants starting another period is thus not equal to the number completing a previous period.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 4

Period 4 title	COVID vaccination, second booster
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	50-64 years of age, booster 2, Comirnaty (Pfizer/BioNTech)

Arm description:

50-64 years of age, booster 2, Comirnaty (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine is in a multidose vial and must be diluted before use.
One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).

Arm title	65+ years of age, booster 2, Comirnaty (Pfizer/BioNTech)

Arm description:

65+ years of age, booster 2, Comirnaty (Pfizer/BioNTech)

Arm type	Experimental

Investigational medicinal product name	Comirnaty
Investigational medicinal product code	
Other name	COVID-19 mRNA Vaccine, Pfizer–BioNTech COVID-19 vaccine
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine is in a multidose vial and must be diluted before use.
One dose (0,3mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embeded in lipid nanoparticles).

Arm title	50-64 years of age, booster 2, Spikevax (Moderna)

Arm description:

50-64 years of age, booster 2, Spikevax (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	
Other name	COIVD-19 mRNA vaccine, Moderna
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,25 mL) contains 50 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles)
Preferred site of administration is the deltoid muscle of the upper arm.

Arm title	65+ years of age, booster 2, Spikevax (Moderna)

Arm description:

65+ years of age, booster 2, Spikevax (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax
Investigational medicinal product code	
Other name	COIVD-19 mRNA vaccine, Moderna
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,25 mL) contains 50 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles)
Preferred site of administration is the deltoid muscle of the upper arm.

Number of subjects in period 4[20]	50-64 years of age, booster 2, Comirnaty (Pfizer/BioNTech)	65+ years of age, booster 2, Comirnaty (Pfizer/BioNTech)	50-64 years of age, booster 2, Spikevax (Moderna)
Started	7	91	12
28 days post booster 12 vaccination (C1)	9	91	14
6 months post booster 2 vaccination (C2)	0 [21]	11 [22]	3 [23]
12 months post booster2 vaccination (C3)	0 [24]	9 [25]	0 [26]
Completed	7	86	26
Not completed	2	7	4

Physician decision	-	1	-
Received additional booster before timepoint	2	2	1
Participant discontinuation	-	2	1
Missed essential timepoint	-	-	1
Logistical issues	-	1	-
Lost to follow-up	-	1	1
Joined	2	2	18
Late recruitment	2	2	3
Late recruitment reason	Logistical issues	Logistical issues	Logistical issues
Directly started in next period	-	-	15

Number of subjects in period 4[20]	65+ years of age, booster 2, Spikevax (Moderna)
Started	7
28 days post booster 12 vaccination (C1)	7
6 months post booster 2 vaccination (C2)	1 [27]
12 months post booster2 vaccination (C3)	1 [28]
Completed	8
Not completed	0
Physician decision	-
Received additional booster before timepoint	-
Participant discontinuation	-
Missed essential timepoint	-
Logistical issues	-
Lost to follow-up	-
Joined	1
Late recruitment	1
Late recruitment reason	Logistical issues
Directly started in next period	-

Notes:

[20] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The trial started with the QIV +PCV series. COVID + booster vaccinations were later available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the following period. Group allocation in the other periods was based on the corresponding vaccination, irrespective of former vaccinations. The number of participants starting another period is thus not equal to the number completing a previous period.

[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[25] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[26] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[27] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.
[28] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 5

Period 5 title	COVID vaccination, third booster
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	50-64 years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)

Arm description:

50-64 years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	COMIRNATY Original/Omicron BA.1 (15/15 microgram)
Investigational medicinal product code	
Other name	COVID-19-mRNA-vaccin
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Eén dosis bevat 15 microgram tozinameran en 15 microgram riltozinameran

Arm title	65+ years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)

Arm description:

65+ years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	COMIRNATY Original/Omicron BA.1 (15/15 microgram)
Investigational medicinal product code	
Other name	COVID-19-mRNA-vaccin
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Eén dosis bevat 15 microgram tozinameran en 15 microgram riltozinameran

Arm title	50-64 years of age, Spikevax Orig/BA.1 (Moderna)

Arm description:

50-64 years of age, Spikevax Orig/BA.1 (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax bivalent Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles).

Arm title	65+ years of age, Spikevax Orig/BA.1 (Moderna)

Arm description:

65+ years of age, Spikevax Orig/BA.1 (Moderna)

Arm type	Experimental
Investigational medicinal product name	Spikevax bivalent Original/Omicron BA.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0.5 mL) contains 25 micrograms of elasomeran and 25 micrograms of imelasomeran, a COVID-19 mRNA Vaccine (nucleoside modified) (embedded in lipid nanoparticles).

Arm title	50-64 years of age, unknown mRNA vaccine

Arm description:

50-64 years of age, unknown mRNA vaccine

Arm type	Experimental
Investigational medicinal product name	Unknown vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

These participants didn't communicate the vaccination they received. Therefore the COVID-19 vaccination is unknown.

Arm title	65+ years of age, unknown mRNA vaccine

Arm description:

65+ years of age, unknown mRNA vaccine

Arm type	Experimental

Investigational medicinal product name	Unknown vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

These participants didn't communicate the vaccination they received. Therefore the COVID-19 vaccination is unknown.

Number of subjects in period 5[29]	50-64 years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)	65+ years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)	50-64 years of age, Spikevax Orig/BA.1 (Moderna)
Started	3	2	12
28 days post booster 3 vaccination (D1)	5	2	15
6 months post booster 3 vaccination (D2)	5	2	14
12 months post booster3 vaccination (D3)	4	2	11
Completed	4	2	14
Not completed	1	0	1
Participant discontinuation	-	-	-
Death (unrelated to study)	-	-	-
Missed essential timepoint	-	-	-
Logistical issues	-	-	1
Lost to follow-up	1	-	-
Joined	2	0	3
Late recruitment	2	-	3
Late recruitment reason	Logistical issues		Logistical issues

Number of subjects in period 5[29]	65+ years of age, Spikevax Orig/BA.1 (Moderna)	50-64 years of age, unknown mRNA vaccine	65+ years of age, unknown mRNA vaccine
Started	94	13	1
28 days post booster 3 vaccination (D1)	93	7	1
6 months post booster 3 vaccination (D2)	92	7	1
12 months post booster3 vaccination (D3)	8 [30]	6	1
Completed	91	6	1
Not completed	3	7	0
Participant discontinuation	1	-	-
Death (unrelated to study)	2	-	-
Missed essential timepoint	-	6	-
Logistical issues	-	-	-
Lost to follow-up	-	1	-
Joined	0	0	0
Late recruitment	-	-	-
Late recruitment reason			

Notes:

[29] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial started with the QIV +PCV series. COVID + booster vaccinations were later available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the following period. Group allocation in the other periods was based on the corresponding vaccination, irrespective of former vaccinations. The number of participants starting another period is thus not equal to the number completing a previous period.
[30] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: It is correct that it seems that the number of subjects in the milestones are inconsistent with the total number of subjects in the arm. Because not all participants were included in all of the timepoints (milestones), due to missing data/blood samples for some timepoints.

Period 6

Period 6 title	COVID vaccination, fourth booster
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	50-64 years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)

Arm description:

50-64 years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	Comirnaty Omicron XBB.1.5
Investigational medicinal product code	
Other name	COVID-19-mRNA-vaccin
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,3 mL) contains 30 microgram tozinameran. There must been at least 3 months between the vaccination with this vaccin and the last COVID-19 vaccination

Arm title	65+ years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)

Arm description:

65+ years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)

Arm type	Experimental
Investigational medicinal product name	Comirnaty Omicron XBB.1.5
Investigational medicinal product code	
Other name	COVID-19-mRNA-vaccin
Pharmaceutical forms	Dispersion for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One dose (0,3 mL) contains 30 microgram tozinameran. There must been at least 3 months between the vaccination with this vaccin and the last COVID-19 vaccination

Number of subjects in period 6[31]	50-64 years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)	65+ years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)
Started	3	83
28 days post booster 4 vaccination (E1)	3	83
12 months post booster4 vaccination (E3)	3	79
Completed	3	79
Not completed	0	4
Received vaccine via other route	-	2
Death (unrelated to study)	-	2

Notes:

[31] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The trial started with the QIV +PCV series. COVID + booster vaccinations were later available that not all participants took. Each period is a separate part of the trial. Participants could then choose to enroll in the following period. Group allocation in the other periods was based on the corresponding vaccination, irrespective of former vaccinations. The number of participants starting another period is thus not equal to the number completing a previous period.

Baseline characteristics

Reporting groups	
Reporting group title	QIV and PCV13 vaccination

Reporting group description: -

Reporting group values	QIV and PCV13 vaccination	Total	
Number of subjects	326	326	
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)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	160	160	
From 65-84 years	140	140	
85 years and over	26	26	
Age continuous Units: years			
arithmetic mean	62.7		
full range (min-max)	25 to 98	-	
Gender categorical Units: Subjects			
Female	146	146	
Male	180	180	

End points reporting groups

Reporting group title	25-49 years of age, QIV + PCV13
Reporting group description: 25-49 years of age, QIV + PCV13	
Reporting group title	50-64 years of age, QIV + PCV13
Reporting group description: 50-64 years of age, QIV + PCV13	
Reporting group title	65+ years of age, QIV + PCV13
Reporting group description: 65+ years of age, QIV + PCV13	
Reporting group title	50-64 years of age, Comirnaty (Pfizer/BioNTech)
Reporting group description: 50-64 years of age, Comirnaty (Pfizer/BioNTech) Only 2 late inclusions at Tc, no subjects truly started at starting point. Starting point set at 2 instead of 0 due to technical limitations.	
Reporting group title	65+ years of age, Comirnaty (Pfizer/BioNTech)
Reporting group description: 65+ years of age, Comirnaty (Pfizer/BioNTech)	
Reporting group title	25-49 years of age, Spikevax (Moderna)
Reporting group description: 25-49 years of age, Spikevax (Moderna)	
Reporting group title	50-64 years of age, Spikevax (Moderna)
Reporting group description: 50-64 years of age, Spikevax (Moderna)	
Reporting group title	65+ years of age, Spikevax (Moderna)
Reporting group description: 65+ years of age, Spikevax (Moderna)	
Reporting group title	50-64 years of age, Vaxzevria (AstraZeneca)
Reporting group description: 50-64 years of age, Vaxzevria (AstraZeneca) Only 1 late inclusions at Tc, no subjects truly started at starting point. Starting point set at 1 instead of 0 due to technical limitations.	
Reporting group title	25-49 years of age, first booster, Comirnaty (Pfizer/BioNTech)
Reporting group description: 25-49 years of age, first booster, Comirnaty (Pfizer/BioNTech)	
Reporting group title	50-64 years of age, first booster, Comirnaty (Pfizer/BioNTech)
Reporting group description: 50-64 years of age, first booster, Comirnaty (Pfizer/BioNTech)	
Reporting group title	65+ years of age, first booster, Comirnaty (Pfizer/BioNTech)
Reporting group description: 65+ years of age, first booster, Comirnaty (Pfizer/BioNTech)	
Reporting group title	50-64 years of age, booster 2, Comirnaty (Pfizer/BioNTech)
Reporting group description: 50-64 years of age, booster 2, Comirnaty (Pfizer/BioNTech)	
Reporting group title	65+ years of age, booster 2, Comirnaty (Pfizer/BioNTech)
Reporting group description: 65+ years of age, booster 2, Comirnaty (Pfizer/BioNTech)	
Reporting group title	50-64 years of age, booster 2, Spikevax (Moderna)
Reporting group description: 50-64 years of age, booster 2, Spikevax (Moderna)	

Reporting group title	65+ years of age, booster 2, Spikevax (Moderna)
Reporting group description:	
65+ years of age, booster 2, Spikevax (Moderna)	
Reporting group title	50-64 years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)
Reporting group description:	
50-64 years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)	
Reporting group title	65+ years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)
Reporting group description:	
65+ years of age, Comirnaty Orig/BA.1 (Pfizer/BioNTech)	
Reporting group title	50-64 years of age, Spikevax Orig/BA.1 (Moderna)
Reporting group description:	
50-64 years of age, Spikevax Orig/BA.1 (Moderna)	
Reporting group title	65+ years of age, Spikevax Orig/BA.1 (Moderna)
Reporting group description:	
65+ years of age, Spikevax Orig/BA.1 (Moderna)	
Reporting group title	50-64 years of age, unknown mRNA vaccine
Reporting group description:	
50-64 years of age, unknown mRNA vaccine	
Reporting group title	65+ years of age, unknown mRNA vaccine
Reporting group description:	
65+ years of age, unknown mRNA vaccine	
Reporting group title	50-64 years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)
Reporting group description:	
50-64 years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)	
Reporting group title	65+ years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)
Reporting group description:	
65+ years of age, Comirnaty XBB.1.5 (Pfizer/BioNTech)	
Subject analysis set title	QIV serology - Pre QIV timepoint - 25-49 y/o
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.	
Subject analysis set title	QIV serology - Pre QIV timepoint - 50-64 y/o
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.	
Subject analysis set title	QIV serology - Pre QIV timepoint - 65+ y/o
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.	
Subject analysis set title	QIV serology - 28-days post QIV timepoint - 25-49 y/o
Subject analysis set type	Per protocol
Subject analysis set description:	
Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 28-days post QIV vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.	

Subject analysis set title	QIV serology - 28-days post QIV timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 28-days post QIV vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.

Subject analysis set title	QIV serology - 28-days post QIV timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 28-days post QIV vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post QIV vaccination timepoints.

Subject analysis set title	QIV serology - 6-months post QIV timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 6-months post QIV vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	QIV serology - 6-months post QIV timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 6-months post QIV vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	QIV serology - 6-months post QIV timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this serology analysis selection for the 6-months post QIV vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - Pre PCV-13 timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - Pre PCV-13 timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - Pre PCV-13 timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the pre-vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - 7-days post PCV-13 timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 7-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 7-days post PCV-13 timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 7-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 7-days post PCV-13 timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 7-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 28-days post PCV-13 timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 28-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - 28-days post PCV-13 timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 28-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - 28-days post PCV-13 timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 28-days post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at pre-vaccination and 28-days post PCV-13 vaccination timepoints.

Subject analysis set title	PCV-13 serology - 6-months post PCV-13 timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 6-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 6-months post PCV-13 timepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 6-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 6-months post PCV-13 timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 6-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 12-months post PCV-13 timepoint - 25-49 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 12-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 12-months post PCV-13 tmepoint - 50-64 y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 12-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	PCV-13 serology - 12-months post PCV-13 timepoint - 65+ y/o
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this serology analysis selection for the 12-months post PCV-13 vaccination timepoint are based on availability of per-protocol measurements at this timepoint.

Subject analysis set title	QIV ELISpot - Pre QIV timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the pre-QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - Pre QIV timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the pre-QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - Pre QIV timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the pre-QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 7-days post QIV timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 7-days post QIV timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 7-days post QIV timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 28-days post QIV timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 28-days post QIV timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 28-days post QIV timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 6-months post QIV timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 6-months post QIV timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	QIV ELISpot - 6-months post QIV timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a QIV vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post QIV vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - Pre PCV-13 timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the pre-PCV-13 vaccination timepoint only if all

measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - Pre PCV-13 timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the pre-PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - Pre PCV-13 timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the pre-PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 7-days post PCV-13 timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 7-days post PCV-13 timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 7-days post PCV-13 timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 7-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 28-days post PCV-13 timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 28-days post PCV-13 timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 28-days post PCV-13 timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 28-days post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 25-49y

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a PCV-13 vaccination in this study. Participants included in this ELISpot analysis selection for the 6-months post PCV-13 vaccination timepoint only if all measurements are available for this timepoint.

Subject analysis set title	FACS analysis - younger adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participant 25-45 years of age included in analysis requiring FACS measurement at the timepoint 28-days post primary mRNA vaccination series. Due to participant selection and comparison with other cohorts, the age groups for this analysis differs from the general VITAL age groups.

Subject analysis set title	FACS analysis - older adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participant 60+ years of age included in analysis requiring FACS measurement at the timepoint 28-days post primary mRNA vaccination series. Due to participant selection and comparison with other cohorts, the age groups for this analysis differs from the general VITAL age groups.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the pre-vaccination timepoint for T-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the pre-vaccination timepoint for T-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the pre-vaccination timepoint for T-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for T-cell ELISpot

analysis.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for T-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for T-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a SARS-CoV-2 mRNA primary vaccination series, included at the timepoint 28-days post 2nd vaccination of primary series for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - Pre booster - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - Pre booster - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - Pre booster - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a first SARS-CoV-2 mRNA booster, included at the28-days post booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a first SARS-CoV-2 mRNA booster, included at the28-days post booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a first SARS-CoV-2 mRNA booster, included at the28-days post booster vaccination timepoint for B-cell ELISpot analysis.

Subject analysis set title	mucosal antibody analysis - Pre 1st booster - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for mucosal antibody analysis.

Subject analysis set title	mucosal antibody analysis - Pre 1st booster - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for mucosal antibody analysis.

Subject analysis set title	mucosal antibody analysis - Pre 1st booster -65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a first SARS-CoV-2 mRNA booster, included at the pre-booster vaccination timepoint for mucosal antibody analysis.

Subject analysis set title	mucosal antibody analysis - 28-days post 1st booster - 25-49y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (25-49 years of age) who received a first SARS-CoV-2 mRNA booster, included at the timepoint 28-days post first booster for mucosal antibody analysis.

Subject analysis set title	mucosal antibody analysis - 28-days post 1st booster -50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a first SARS-CoV-2 mRNA booster, included at the timepoint 28-days post first booster for mucosal antibody analysis.

Subject analysis set title	mucosal antibody analysis - 28-days post 1st booster - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a first SARS-CoV-2 mRNA booster, included at the timepoint 28-days post first booster for mucosal antibody analysis.

Subject analysis set title	Spikevax serology - Pre primary series - 25-49y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the pre-vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 1st primary vaccine - 25-49y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a Spikevax (Moderna) mRNA primary series

(consisting of 2 vaccinations), included at the 28-days post 1st vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 2nd primary vaccine - 25-49y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 2nd vaccination timepoint.

Subject analysis set title	Spikevax serology - 6-months post primary series - 25-49y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (25-49 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 6-months post primary vaccination series timepoint.

Subject analysis set title	Spikevax serology - Pre primary series - 50-64y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the pre-vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 1st primary vaccine - 50-64y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 1st vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 2nd primary vaccine - 50-64y
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (50-64 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 2nd vaccination timepoint.

Subject analysis set title	Spikevax serology - 6-months post primary series - 50-64y
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (50-64 years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 6-months post primary vaccination series timepoint.

Subject analysis set title	Spikevax serology - Pre primary series - 65+
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the pre-vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 1st primary vaccine - 65+
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 1st vaccination timepoint.

Subject analysis set title	Spikevax serology - 28-days post 2nd primary vaccine - 65+
Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 2nd vaccination timepoint.

Subject analysis set title	Spikevax serology - 6-months post primary series - 65+

Subject analysis set type	Per protocol

Subject analysis set description:

Subset of participants (65+ years of age) who received a Spikevax (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 6-months post primary vaccination series timepoint.

Subject analysis set title	Comirnaty serology - Pre primary series - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a Comirnaty (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the pre-vaccination timepoint.

Subject analysis set title	Comirnaty serology - 28-days post 1st primary vaccine - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a Comirnaty (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 1st vaccination timepoint.

Subject analysis set title	Comirnaty serology - 28-days post 2nd primary vaccine - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a Comirnaty (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 28-days post 2nd vaccination timepoint.

Subject analysis set title	Comirnaty serology - 6-months post primary series - 65+
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subset of participants (65+ years of age) who received a Comirnaty (Moderna) mRNA primary series (consisting of 2 vaccinations), included at the 6-months post primary vaccination series timepoint.

Primary: Pneumococcal serotype-specific serum IgG antibody concentrations (GMCs) pre and one-month post PCV13 vaccination.

End point title	Pneumococcal serotype-specific serum IgG antibody concentrations (GMCs) pre and one-month post PCV13 vaccination.

End point description:

Pneumococcal serotype- specific serum IgG antibody concentrations pre-vaccination and one-month post PCV13 vaccination measured by bead-based multiplex immune assay.
Full analysis is published in Van der Heiden et al., Nat Commun 2024, https://doi.org/10.1038/s41467-024-50760-9

End point type	Primary

End point timeframe:

Period 1

End point values	PCV-13 serology - Pre PCV-13 timepoint - 25-49 y/o	PCV-13 serology - Pre PCV-13 timepoint - 50-64 y/o	PCV-13 serology - Pre PCV-13 timepoint - 65+ y/o	PCV-13 serology - 28-days post PCV-13 timepoint - 25-49 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51	84	140	51
Units: ug/mL				
geometric mean (confidence interval 95%)				

Ps1-specific IgG antibody GMC	0.29 (0.18 to 0.48)	0.22 (0.14 to 0.32)	0.12 (0.09 to 0.16)	9.80 (5.85 to 16.4)
Ps3-specific IgG antibody GMC	0.38 (0.27 to 0.55)	0.44 (0.32 to 0.59)	0.17 (0.13 to 0.22)	2.25 (1.65 to 3.06)
Ps4-specific IgG antibody GMC	0.05 (0.03 to 0.08)	0.06 (0.04 to 0.07)	0.05 (0.04 to 0.07)	4.64 (3.34 to 6.43)
Ps5-specific IgG antibody GMC	0.45 (0.31 to 0.66)	0.58 (0.45 to 0.76)	0.54 (0.41 to 0.70)	17.67 (11.35 to 27.51)
Ps6A-specific IgG antibody GMC	0.18 (0.10 to 0.31)	0.41 (0.27 to 0.6)	0.24 (0.17 to 0.34)	13.35 (8.13 to 21.93)
Ps6B-specific IgG antibody GMC	0.15 (0.09 to 0.24)	0.24 (0.16 to 0.35)	0.14 (0.10 to 0.19)	9.99 (6.37 to 15.65)
Ps7F-specific IgG antibody GMC	0.36 (0.22 to 0.59)	0.48 (0.34 to 0.68)	0.44 (0.34 to 0.57)	16.16 (11.20 to 23.33)
Ps9V-specific IgG antibody GMC	0.19 (0.13 to 0.27)	0.23 (0.17 to 0.32)	0.20 (0.15 to 0.27)	4.75 (3.44 to 6.57)
Ps14-specific IgG antibody GMC	0.21 (0.11 to 0.40)	0.62 (0.44 to 0.89)	0.36 (0.25 to 0.50)	4.84 (2.83 to 8.28)
Ps18C-specific IgG antibody GMC	0.26 (0.17 to 0.41)	0.33 (0.23 to 0.49)	0.39 (0.29 to 0.52)	8.14 (5.09 to 13.03)
Ps19A-specific IgG antibody GMC	0.67 (0.45 to 1.00)	0.69 (0.49 to 0.99)	0.71 (0.53 to 0.94)	12.73 (8.79 to 18.44)
Ps19F-specific IgG antibody GMC	0.41 (0.25 to 0.68)	0.56 (0.39 to 0.81)	0.41 (0.32 to 0.52)	8.47 (5.79 to 12.39)
Ps23F-specific IgG antibody GMC	0.16 (0.10 to 0.25)	0.26 (0.18 to 0.39)	0.21 (0.15 to 0.28)	13.24 (8.61 to 20.38)

End point values	PCV-13 serology - 28-days post PCV-13 timepoint - 50-64 y/o	PCV-13 serology - 28-days post PCV-13 timepoint - 65+ y/o		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	140		
Units: ug/mL				
geometric mean (confidence interval 95%)				
Ps1-specific IgG antibody GMC	5.56 (3.62 to 8.53)	4.11 (2.85 to 5.92)		
Ps3-specific IgG antibody GMC	1.82 (1.39 to 2.37)	1.48 (1.14 to 1.93)		
Ps4-specific IgG antibody GMC	2.07 (1.47 to 2.94)	1.37 (1.00 to 1.88)		
Ps5-specific IgG antibody GMC	14.53 (10.00 to 21.13)	9.18 (6.59 to 12.79)		
Ps6A-specific IgG antibody GMC	7.49 (4.82 to 11.64)	5.19 (3.67 to 7.33)		
Ps6B-specific IgG antibody GMC	4.46 (2.82 to 7.07)	2.77 (1.93 to 3.98)		
Ps7F-specific IgG antibody GMC	13.59 (10.23 to 18.07)	11.62 (8.68 to 15.55)		
Ps9V-specific IgG antibody GMC	3.92 (2.82 to 5.45)	3.30 (2.36 to 4.60)		
Ps14-specific IgG antibody GMC	4.73 (3.13 to 7.14)	3.54 (2.42 to 5.19)		
Ps18C-specific IgG antibody GMC	8.05 (5.54 to 11.69)	10.09 (7.34 to 13.86)		

Ps19A-specific IgG antibody GMC	8.96 (6.46 to 12.43)	10.07 (7.57 to 13.40)		
Ps19F-specific IgG antibody GMC	6.25 (4.56 to 8.57)	6.00 (4.48 to 8.05)		
Ps23F-specific IgG antibody GMC	4.87 (2.98 to 7.94)	3.07 (2.13 to 4.42)		

Statistical analyses

Statistical analysis title	primary PCV-13 serology
Comparison groups	PCV-13 serology - Pre PCV-13 timepoint - 25-49 y/o v PCV-13 serology - Pre PCV-13 timepoint - 50-64 y/o v PCV-13 serology - Pre PCV-13 timepoint - 65+ y/o v PCV-13 serology - 28-days post PCV-13 timepoint - 25-49 y/o v PCV-13 serology - 28-days post PCV-13 timepoint - 50-64 y/o v PCV-13 serology - 28-days post PCV-13 timepoint - 65+ y/o
Number of subjects included in analysis	550
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Kruskal-wallis

Primary: Influenza vaccine strain-specific serum antibody titers (GMTs) pre- and one-month post-influenza vaccination.

End point title	Influenza vaccine strain-specific serum antibody titers (GMTs) pre- and one-month post-influenza vaccination.

End point description:

Influenza vaccine strain-specific serum antibody titers measured pre-vaccination and one-month post-influenza vaccination by Hemagglutinin Inhibition (HI) assay.
Full analysis is published in Van der Heiden et al., Nat Commun 2024, https://doi.org/10.1038/s41467-024-50760-9

End point type	Primary

End point timeframe:

Period 1

End point values	QIV serology - Pre QIV timepoint - 25-49 y/o	QIV serology - Pre QIV timepoint - 50-64 y/o	QIV serology - Pre QIV timepoint - 65+ y/o	QIV serology - 28-days post QIV timepoint - 25-49 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	94	157	56
Units: titre				
geometric mean (confidence interval 95%)				
HI titer A/Kansas/14/2017 (H3N2)	82.51 (58.90 to 115.59)	40.74 (32.32 to 51.36)	35.23 (29.66 to 41.86)	105.36 (74.7 to 148.63)
HI titer A/Brisbane/02/2018 (H1N1)	19.90 (14.15 to 27.99)	16.98 (13.18 to 21.87)	15.93 (13.18 to 19.26)	126.61 (93.49 to 171.47)

End point values	QIV serology - 28-days post QIV timepoint - 50-64 y/o	QIV serology - 28-days post QIV timepoint - 65+ y/o		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	94	157		
Units: titre				
geometric mean (confidence interval 95%)				
HI titer A/Kansas/14/2017 (H3N2)	63.18 (50.04 to 79.78)	59.06 (50.43 to 69.16)		
HI titer A/Brisbane/02/2018 (H1N1)	108.13 (84.02 to 139.16)	98.67 (79.25 to 122.84)		

Statistical analyses

Statistical analysis title	primary QIV serology
Comparison groups	QIV serology - Pre QIV timepoint - 50-64 y/o v QIV serology - Pre QIV timepoint - 65+ y/o v QIV serology - 28-days post QIV timepoint - 25-49 y/o v QIV serology - 28-days post QIV timepoint - 50-64 y/o v QIV serology - 28-days post QIV timepoint - 65+ y/o v QIV serology - Pre QIV timepoint - 25-49 y/o
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Kruskal-wallis

Secondary: Influenza vaccin strain-specific serum antibody titers (GMTs) for additional post-vaccination timepoints.

End point title	Influenza vaccin strain-specific serum antibody titers (GMTs) for additional post-vaccination timepoints.

End point description:

Influenza vaccine strain-specific serum antibody titers measured Hemagglutinin Inhibition (HI) assay. Due to technical limitations during measurements, only H3N2-specific antibody titers at 6-9 months post vaccination are available.
Full analysis is published in Van der Heiden et al., Nat Commun 2024, https://doi.org/10.1038/s41467-024-50760-9

End point type	Secondary

End point timeframe:

Period 1

End point values	QIV serology - 6-months post QIV timepoint - 25-49 y/o	QIV serology - 6-months post QIV timepoint - 50-64 y/o	QIV serology - 6-months post QIV timepoint - 65+ y/o	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	52	87	142	
Units: titre				
geometric mean (confidence interval 95%)				
HI titer A/Kansas/14/2017 (H3N2)	77.93 (55.71 to 109.01)	42.97 (33.27 to 55.51)	47.00 (37.39 to 59.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pneumococcal serotype-specific serum IgG antibody concentrations (GMCs) for additional post-vaccination timepoints.

End point title	Pneumococcal serotype-specific serum IgG antibody concentrations (GMCs) for additional post-vaccination timepoints.

End point description:

Pneumococcal serotype- specific serum IgG antibody concentrations (GMCs) at 7 days, 6 months, and 12 months post PCV13 vaccination measured by beadbased multiplex immune assay.
Further analysis included in Van der Heiden et al., Nat Commun 2024, https://doi.org/10.1038/s41467-024-50760-9 & Visser et al., npj Vaccines 2025, https://doi.org/10.1038/s41541-025-01152-7

End point type	Secondary

End point timeframe:

Period 1

End point values	PCV-13 serology - 7-days post PCV-13 timepoint - 25-49 y/o	PCV-13 serology - 7-days post PCV-13 timepoint - 50-64 y/o	PCV-13 serology - 7-days post PCV-13 timepoint - 65+ y/o	PCV-13 serology - 6-months post PCV-13 timepoint - 25-49 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45	78	134	45
Units: ug/mL				
geometric mean (confidence interval 95%)				
Ps1-specific IgG antibody GMC	2.08 (1.25 to 3.46)	0.80 (0.51 to 1.25)	0.32 (0.23 to 0.44)	6.34 (4.00 to 10.05)
Ps3-specific IgG antibody GMC	1.02 (0.69 to 1.50)	0.71 (0.54 to 0.95)	0.28 (0.21 to 0.37)	1.26 (0.90 to 1.75)
Ps4-specific IgG antibody GMC	0.91 (0.59 to 1.42)	0.26 (0.17 to 0.38)	0.14 (0.11 to 0.19)	1.96 (1.42 to 2.72)
Ps5-specific IgG antibody GMC	2.26 (1.39 to 3.67)	1.97 (1.33 to 2.92)	0.98 (0.73 to 1.31)	8.36 (5.39 to 12.98)
Ps6A-specific IgG antibody GMC	1.31 (0.74 to 2.31)	1.05 (0.68 to 1.63)	0.43 (0.31 to 0.6)	5.63 (3.15 to 10.06)

Ps6B-specific IgG antibody GMC	1.21 (0.73 to 2.00)	0.68 (0.44 to 1.06)	0.27 (0.19 to 0.37)	4.92 (3.04 to 7.97)
Ps7F-specific IgG antibody GMC	2.91 (1.88 to 4.52)	1.74 (1.25 to 2.41)	0.95 (0.72 to 1.25)	7.50 (5.25 to 10.72)
Ps9V-specific IgG antibody GMC	1.16 (0.79 to 1.7)	0.77 (0.57 to 1.05)	0.45 (0.32 to 0.63)	2.81 (1.92 to 4.11)
Ps14-specific IgG antibody GMC	0.72 (0.36 to 1.44)	1.07 (0.71 to 1.62)	0.60 (0.41 to 0.86)	4.67 (2.61 to 8.37)
Ps18C-specific IgG antibody GMC	1.68 (0.94 to 3.00)	1.10 (0.74 to 1.64)	0.79 (0.58 to 1.08)	3.76 (2.40 to 5.90)
Ps19A-specific IgG antibody GMC	3.27 (2.19 to 4.89)	1.98 (1.39 to 2.82)	1.44 (1.10 to 1.89)	5.74 (3.89 to 8.47)
Ps19F-specific IgG antibody GMC	2.01 (1.23 to 3.27)	1.65 (1.18 to 2.30)	0.87 (0.67 to 1.12)	3.72 (2.45 to 5.65)
Ps23F-specific IgG antibody GMC	1.46 (0.86 to 2.50)	0.67 (0.43 to 1.04)	0.34 (0.24 to 0.49)	6.80 (4.24 to 10.89)

End point values	PCV-13 serology - 6-months post PCV-13 timepoint - 50-64 y/o	PCV-13 serology - 6-months post PCV-13 timepoint - 65+ y/o	PCV-13 serology - 12-months post PCV-13 timepoint - 25-49 y/o	PCV-13 serology - 12-months post PCV-13 tmepoint - 50-64 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	134	40	73
Units: ug/mL				
geometric mean (confidence interval 95%)				
Ps1-specific IgG antibody GMC	4.06 (2.58 to 6.39)	2.54 (1.75 to 3.69)	5.82 (3.69 to 9.19)	3.12 (2.03 to 4.82)
Ps3-specific IgG antibody GMC	1.14 (0.84 to 1.53)	0.73 (0.57 to 0.94)	0.95 (0.69 to 1.31)	1.05 (0.77 to 1.44)
Ps4-specific IgG antibody GMC	1.21 (0.86 to 1.72)	0.89 (0.64 to 1.22)	1.42 (1.02 to 1.99)	0.93 (0.65 to 1.32)
Ps5-specific IgG antibody GMC	8.72 (5.89 to 12.91)	5.83 (4.22 to 8.04)	6.96 (4.31 to 11.23)	6.41 (4.27 to 9.61)
Ps6A-specific IgG antibody GMC	4.89 (3.06 to 7.84)	2.93 (2.03 to 4.23)	4.33 (2.30 to 8.17)	4.02 (2.46 to 6.58)
Ps6B-specific IgG antibody GMC	2.55 (1.56 to 4.17)	1.60 (1.11 to 2.31)	3.53 (2.08 to 5.98)	1.92 (1.17 to 3.16)
Ps7F-specific IgG antibody GMC	8.47 (6.29 to 11.4)	6.75 (5.18 to 8.80)	5.49 (3.63 to 8.31)	6.14 (4.57 to 8.25)
Ps9V-specific IgG antibody GMC	2.26 (1.63 to 3.15)	2.33 (1.69 to 3.20)	2.15 (1.43 to 3.22)	1.62 (1.16 to 2.25)
Ps14-specific IgG antibody GMC	3.72 (2.6 to 5.33)	3.35 (2.36 to 4.74)	3.85 (2.13 to 6.95)	3.28 (2.28 to 4.74)
Ps18C-specific IgG antibody GMC	4.78 (3.32 to 6.88)	6.50 (4.83 to 8.73)	3.19 (2.01 to 5.04)	3.70 (2.59 to 5.28)
Ps19A-specific IgG antibody GMC	5.60 (3.90 to 8.04)	6.03 (4.54 to 8.02)	4.29 (2.77 to 6.63)	4.44 (3.10 to 6.35)
Ps19F-specific IgG antibody GMC	3.61 (2.59 to 5.02)	3.28 (2.49 to 4.33)	2.93 (1.85 to 4.64)	2.82 (2.02 to 3.95)
Ps23F-specific IgG antibody GMC	2.82 (1.74 to 4.56)	1.89 (1.34 to 2.65)	5.25 (3.19 to 8.66)	2.40 (1.52 to 3.77)

End point values	PCV-13 serology - 12-months post PCV-13 timepoint - 65+ y/o			
Subject group type	Subject analysis set			
Number of subjects analysed	128			
Units: ug/mL				
geometric mean (confidence interval 95%)				
Ps1-specific IgG antibody GMC	1.88 (1.32 to 2.67)			
Ps3-specific IgG antibody GMC	0.64 (0.49 to 0.83)			
Ps4-specific IgG antibody GMC	0.64 (0.46 to 0.88)			
Ps5-specific IgG antibody GMC	4.16 (3.05 to 5.69)			
Ps6A-specific IgG antibody GMC	2.22 (1.55 to 3.18)			
Ps6B-specific IgG antibody GMC	1.08 (0.75 to 1.56)			
Ps7F-specific IgG antibody GMC	4.52 (3.46 to 5.89)			
Ps9V-specific IgG antibody GMC	1.69 (1.22 to 2.33)			
Ps14-specific IgG antibody GMC	2.75 (1.96 to 3.87)			
Ps18C-specific IgG antibody GMC	4.42 (3.28 to 5.95)			
Ps19A-specific IgG antibody GMC	4.27 (3.24 to 5.63)			
Ps19F-specific IgG antibody GMC	2.27 (1.71 to 3.02)			
Ps23F-specific IgG antibody GMC	1.41 (1.01 to 1.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: CRM197-specific serum antibody titers before, at 7 days, at 1 month, and at 6 months post pneumococcal vaccination.

End point title	CRM197-specific serum antibody titers before, at 7 days, at 1 month, and at 6 months post pneumococcal vaccination.

End point description:

CRM197-specific serum antibody titers before, at 7 days, at 1 month, and at 6 months post pneumococcal vaccination.

End point type	Secondary

End point timeframe:

Period 1

End point values	PCV-13 serology - Pre PCV-13 timepoint - 25-49 y/o	PCV-13 serology - Pre PCV-13 timepoint - 50-64 y/o	PCV-13 serology - Pre PCV-13 timepoint - 65+ y/o	PCV-13 serology - 7-days post PCV-13 timepoint - 25-49 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51	84	139[1]	45
Units: titre				
geometric mean (confidence interval 95%)				
CRM197-specific IgG antibody titer	0.25 (0.20 to 0.32)	0.26 (0.22 to 0.32)	0.17 (0.14 to 0.21)	0.96 (0.65 to 1.44)

Notes:

[1] - 1 excluded: missing measurement

End point values	PCV-13 serology - 7-days post PCV-13 timepoint - 50-64 y/o	PCV-13 serology - 7-days post PCV-13 timepoint - 65+ y/o	PCV-13 serology - 28-days post PCV-13 timepoint - 25-49 y/o	PCV-13 serology - 28-days post PCV-13 timepoint - 50-64 y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	78	134	51	83[2]
Units: titre				
geometric mean (confidence interval 95%)				
CRM197-specific IgG antibody titer	0.79 (0.59 to 1.07)	0.44 (0.34 to 0.56)	2.10 (1.41 to 3.13)	1.54 (1.15 to 2.07)

Notes:

[2] - 1 excluded: missing measurement

End point values	PCV-13 serology - 28-days post PCV-13 timepoint - 65+ y/o	PCV-13 serology - 6-months post PCV-13 timepoint - 25-49 y/o	PCV-13 serology - 6-months post PCV-13 timepoint - 50-64 y/o	PCV-13 serology - 6-months post PCV-13 timepoint - 65+ y/o
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	140	45	78	134
Units: titre				
geometric mean (confidence interval 95%)				
CRM197-specific IgG antibody titer	1.10 (0.82 to 1.48)	0.87 (0.57 to 1.32)	0.86 (0.66 to 1.12)	0.53 (0.40 to 0.69)

Statistical analyses

No statistical analyses for this end point

Secondary: Influenza-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-

vaccination samples.

End point title	Influenza-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.

End point description:

Influenza-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.
Full analysis will be published, manuscript in preparation.

End point type	Secondary

End point timeframe:

Period 1

End point values	QIV ELISpot - Pre QIV timepoint - 25-49y	QIV ELISpot - Pre QIV timepoint - 50-64y	QIV ELISpot - Pre QIV timepoint - 65+	QIV ELISpot - 7-days post QIV timepoint - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	68	115	43
Units: countable unit(s)				
median (confidence interval 95%)				
Influenza A H1N1-specific counts	24.00 (11.83 to 29.00)	14.33 (12.33 to 18.42)	7.00 (4.33 to 11.5)	29.00 (22.5 to 42.33)
Influenza A H3N2-specific counts	5.67 (3 to 8.67)	4.58 (2.33 to 6.50)	2.00 (0.83 to 3.17)	12.67 (8 to 20.33)
Influenza B Victoria-specific counts	28.83 (21 to 42.33)	21.67 (14.33 to 23.08)	12.33 (8 to 17.33)	31.33 (25.33 to 44.33)
Influenza B Yamagata-specific counts	25.83 (19.08 to 39)	22.17 (15.33 to 27.17)	15.67 (7.5 to 23)	34.00 (30.67 to 60)

End point values	QIV ELISpot - 7-days post QIV timepoint - 50-64y	QIV ELISpot - 7-days post QIV timepoint - 65+	QIV ELISpot - 28-days post QIV timepoint - 25-49y	QIV ELISpot - 28-days post QIV timepoint - 50-64y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	111	43	48
Units: countable unit(s)				
median (confidence interval 95%)				
Influenza A H1N1-specific counts	24.00 (21.5 to 27.83)	18.33 (11.67 to 24.33)	25.00 (22.33 to 29)	18.92 (15.25 to 23.83)
Influenza A H3N2-specific counts	14.5 (12.25 to 19.67)	8.33 (4 to 11.83)	11.67 (7.33 to 14.67)	9.83 (7 to 12.5)
Influenza B Victoria-specific counts	35.17 (28.92 to 43.67)	25.00 (16 to 30)	25.50 (20 to 33.67)	22.67 (14.33 to 30.5)
Influenza B Yamagata-specific counts	37.83 (32.67 to 43)	29.33 (23 to 36)	33.00 (24 to 40.67)	23.33 (19 to 32.33)

End point values	QIV ELISpot - 28-days post QIV timepoint -	QIV ELISpot - 6-months post QIV timepoint -	QIV ELISpot - 6-months post QIV timepoint -	QIV ELISpot - 6-months post QIV timepoint -

	65+	25-49y	50-64y	65+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	107	42	67	111
Units: countable unit(s)				
median (confidence interval 95%)				
Influenza A H1N1-specific counts	14.00 (11.33 to 22)	18.25 (14.08 to 27.25)	18.00 (13.67 to 23)	14.33 (10 to 21.33)
Influenza A H3N2-specific counts	6.50 (3.83 to 10.5)	5.50 (4.08 to 9.75)	7.83 (4 to 11)	7.67 (5.33 to 11.33)
Influenza B Victoria-specific counts	20.00 (14.33 to 23.67)	28.75 (21.83 to 35.42)	29.00 (16.5 to 36.33)	18.67 (14.67 to 26.5)
Influenza B Yamagata-specific counts	19.50 (15 to 30.33)	34.83 (25.5 to 40.42)	27.00 (20.67 to 39)	20.67 (18.67 to 28.67)

Statistical analyses

No statistical analyses for this end point

Secondary: CRM197-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.

End point title	CRM197-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.

End point description:

CRM197-specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.
Full analysis will be published, manuscript in preparation.

End point type	Secondary

End point timeframe:

Period 1

End point values	PCV-13 ELISpot - Pre PCV-13 timepoint - 25-49y	PCV-13 ELISpot - Pre PCV-13 timepoint - 50-64y	PCV-13 ELISpot - Pre PCV-13 timepoint - 65+	PCV-13 ELISpot - 7-days post PCV-13 timepoint - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	67	123	29
Units: countable unit(s)				
median (confidence interval 95%)				
CRM197-specific counts	0 (0 to 0)	0.33 (0 to 0.67)	0 (0 to 0)	15.33 (4 to 32)

End point values	PCV-13 ELISpot - 7-days post PCV-13 timepoint -	PCV-13 ELISpot - 7-days post PCV-13 timepoint -	PCV-13 ELISpot - 28-days post PCV-13 timepoint -	PCV-13 ELISpot - 28-days post PCV-13 timepoint -

	50-64y	65+	25-49y	50-64y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	101	33	65
Units: countable unit(s)				
median (confidence interval 95%)				
CRM197-specific counts	9.58 (4.83 to 17.75)	4.67 (2.33 to 14.67)	4.67 (2 to 9)	1 (0.33 to 2.67)

End point values	PCV-13 ELISpot - 28-days post PCV-13 timepoint - 65+	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 25-49y	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 50-64y	PCV-13 ELISpot - 6-months post PCV-13 timepoint - 65+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104	39	68	123
Units: countable unit(s)				
median (confidence interval 95%)				
CRM197-specific counts	1 (0.67 to 2.67)	1.67 (1 to 2.33)	2.5 (1.42 to 3)	1 (0.5 to 1.67)

Statistical analyses

No statistical analyses for this end point

Secondary: A deficit accumulation index will be calculated for each subject and the subjects will be ranked based on this index.

End point title	A deficit accumulation index will be calculated for each subject and the subjects will be ranked based on this index.

End point description:

A deficit accumulation index will be calculated for each subject and the subjects will be ranked based on this index.
Further details on composition of deficit score and statistics can be found in Van Sleen et al., Immunity & Ageing 2023, https://doi.org/10.1186/s12979-023-00391-3

End point type	Secondary

End point timeframe:

Period 1

End point values	25-49 years of age, QIV + PCV13	50-64 years of age, QIV + PCV13	65+ years of age, QIV + PCV13	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60[3]	96[4]	163[5]	
Units: score				
arithmetic mean (confidence interval 95%)				
deficit score	0.08 (0.06 to 0.09)	0.11 (0.10 to 0.13)	0.19 (0.18 to 0.21)	

Notes:

[3] - 2 excluded: missing data

[4] - 2 excluded: missing data

[5] - 3 excluded: missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute numbers of immune cell types, a.o. lymphocytes, granulocytes and monocytes, measured in whole blood by Trucount.

End point title	Absolute numbers of immune cell types, a.o. lymphocytes, granulocytes and monocytes, measured in whole blood by Trucount.

End point description:

Absolute numbers of a selection of immune cell subtypes as measured by Trucount.
Full analysis and additional subsets are published in Cevirgel et al., Aging Cell 2022, https://doi.org/10.1111/acel.13703

End point type	Secondary

End point timeframe:

Period 1

End point values	25-49 years of age, QIV + PCV13	50-64 years of age, QIV + PCV13	65+ years of age, QIV + PCV13	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60[6]	89[7]	154[8]	
Units: absolute numbers				
median (confidence interval 95%)				
absolute numbers of CD19+ subset	178.48 (161.64 to 199.96)	161.63 (146.84 to 191.42)	137.72 (130.53 to 147.49)	
absolute numbers of CD3+ subset	1076.31 (1036.01 to 1170.49)	1038.55 (967.27 to 1118.67)	975.56 (929.79 to 1039.76)	
absolute numbers of CD4+ subset	688.69 (647.7 to 717.88)	668.87 (641.67 to 732.92)	629.96 (597.55 to 671.93)	
absolute numbers of CD56+ subset	9.34 (8.81 to 10.20)	8.95 (7.85 to 9.7)	8.32 (7.95 to 8.76)	
absolute numbers of CD8+ subset	314.54 (281.36 to 335.37)	259.71 (228.66 to 284.09)	217.02 (196.67 to 229.89)	
absolute numbers of granulocytes	2532.61 (2322.22 to 2841.13)	2680.28 (2445.7 to 2825.42)	2933.68 (2792.31 to 3046.82)	
absolute numbers of lymphocytes	1469.19 (1410.08 to 1617.53)	1435.74 (1374.82 to 1530.35)	1427.90 (1316.12 to 1495.76)	
absolute numbers of monocytes+ subset	308.19 (302.59 to 332.46)	351.22 (324.83 to 377.09)	409.10 (388.84 to 425.34)	

Notes:

[6] - 2 excluded: missing Trucount data

[7] - 6 excluded: missing Trucount data
3 excluded: technical outliers

[8] - 9 excluded: missing Trucount data
3 excluded: technical outliers

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of immune and inflammatory profiles in serum, and measurement of biomarkers in plasma.

End point title	Measurement of immune and inflammatory profiles in serum, and measurement of biomarkers in plasma.

End point description:

Measurement of immune and inflammatory profiles in serum, and measurement of biomarkers in plasma.
Full analysis is published in Van Sleen et al., Immun Ageing 2023, https://doi.org/10.1186/s12979-023-00391-3

End point type	Secondary

End point timeframe:

Period 1

End point values	25-49 years of age, QIV + PCV13	50-64 years of age, QIV + PCV13	65+ years of age, QIV + PCV13	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60[9]	96[10]	158[11]	
Units: concentrations				
geometric mean (confidence interval 95%)				
A1AT-Elastase_ng/mL	50.61 (38.13 to 67.19)	63.11 (50.35 to 79.10)	54.53 (49.37 to 60.22)	
Angiopoeietin-2_pg/mL	1827.09 (1620.22 to 2060.36)	1947.27 (1801.56 to 2104.77)	2396.65 (2235.37 to 2569.58)	
C5a_ng/mL	19.87 (17.96 to 21.99)	20.80 (18.96 to 22.82)	22.07 (20.39 to 23.87)	
Calprotectin_ng/mL	1504.28 (1231.36 to 1837.7)	1674.46 (1473.87 to 1902.35)	1631.19 (1493.54 to 1781.51)	
CathepsinG_ng/mL	6.17 (5.56 to 6.85)	6.27 (5.74 to 6.84)	6.37 (5.85 to 6.93)	
CCL2_pg/mL	341.97 (318.13 to 367.6)	409.57 (386.89 to 433.57)	432.40 (406.87 to 459.53)	
CRP_ng/mL	0.74 (0.54 to 1.01)	1.02 (0.81 to 1.27)	1.54 (1.30 to 1.83)	
CXCL10_pg/mL	19.17 (17.44 to 21.08)	23.01 (21.02 to 25.2)	29.12 (27.43 to 30.93)	
Elastase_ng/mL	183.88 (159.23 to 212.33)	217.24 (191.55 to 246.36)	265.01 (238.59 to 294.37)	
GM-CSF_pg/mL	0.18 (0.16 to 0.20)	0.15 (0.12 to 0.19)	0.15 (0.12 to 0.18)	

iFABP2_pg/mL	927.92 (807.15 to 1066.77)	1145.60 (1054.05 to 1245.09)	1289.26 (1189.78 to 1397.06)	
IFNa_pg/mL	0.01 (0 to 0.01)	0.01 (0.01 to 0.01)	0.01 (0.01 to 0.01)	
IFNy_pg/mL	0.03 (0.03 to 0.04)	0.04 (0.03 to 0.05)	0.05 (0.05 to 0.06)	
IL-10_pg/mL	0.56 (0.49 to 0.64)	0.66 (0.58 to 0.74)	0.56 (0.47 to 0.67)	
IL-1b_pg/mL	0.02 (0.01 to 0.03)	0.03 (0.02 to 0.04)	0.01 (0.01 to 0.02)	
IL-1RA_pg/mL	738.04 (661.56 to 823.36)	805.89 (749.49 to 866.54)	990.09 (931.54 to 1052.31)	
IL-6_g/mL	0.39 (0.32 to 0.49)	0.83 (0.69 to 1)	1.16 (1.02 to 1.32)	
IL8_pg/mL	17.49 (14.35 to 21.33)	25.75 (22.13 to 29.96)	25.26 (22.99 to 27.76)	
Neopterin_nmol/L	5.87 (5.22 to 6.60)	7.58 (6.94 to 8.27)	9.87 (9.13 to 10.68)	
PR3_ng/mL	30.42 (26.04 to 35.53)	30.54 (26.69 to 34.94)	43.15 (38.14 to 48.82)	
PTX3_pg/mL	5197.44 (4557.69 to 5926.99)	4853.04 (4271.71 to 5513.48)	5576.36 (5172.39 to 6011.88)	
SAA_ng/mL	0.05 (0.03 to 0.09)	0.06 (0.04 to 0.09)	0.16 (0.12 to 0.22)	
sCD14_ng/mL	1331.4 (1268.34 to 1397.59)	1385.62 (1324.78 to 1449.26)	1525.07 (1460.53 to 1592.47)	
sCD163_pg/mL	567.43 (504.95 to 637.64)	749.76 (675.78 to 831.84)	859.67 (791.9 to 933.24)	
sCD25_pg/mL	467.07 (438.66 to 497.32)	483.09 (454.08 to 513.96)	603.96 (569.95 to 640.01)	
sGP130_ng/mL	129.09 (122.44 to 136.12)	138.47 (133.41 to 143.73)	143.88 (140.19 to 147.67)	
sIL-6R_ng/mL	43.42 (41.49 to 45.44)	46.39 (44.52 to 48.33)	47.77 (46.48 to 49.1)	
TNFa_pg/mL	2.09 (1.92 to 2.28)	2.50 (2.26 to 2.76)	2.22 (2.10 to 2.34)	
YKL-40_ng/mL	24.32 (21.93 to 26.97)	31.42 (28.14 to 35.07)	61.51 (55.44 to 68.24)	
bl.ALAT_U/L	16.02 (14.08 to 18.23)	15.05 (14 to 16.19)	13.68 (12.92 to 14.49)	
bl.Albumine_g/L	48.37 (47.72 to 49.02)	47.57 (47.07 to 48.08)	43.1 (42.68 to 43.52)	
bl.ASAT_U/L	23.8 (22.09 to 25.64)	25.25 (24.18 to 26.36)	24.67 (23.66 to 25.72)	
bl.Creatinin_umol/L	73.88 (71.13 to 76.73)	76.75 (73.77 to 79.86)	79.55 (76.92 to 82.26)	
bl.HDL.Chol_mmol/L	1.52 (1.44 to 1.60)	1.55 (1.48 to 1.64)	1.42 (1.36 to 1.48)	
bl.LDL.Chol_mmol/L	3.02 (2.85 to 3.21)	3.19 (2.96 to 3.43)	2.69 (2.54 to 2.84)	
bl.Triglyceride_mmol/L	1.25 (1.1 to 1.41)	1.46 (1.35 to 1.59)	1.49 (1.40 to 1.59)	
bl.Ureum_mmol/L	4.89 (4.55 to 5.25)	5.82 (5.56 to 6.1)	6.37 (6.11 to 6.65)	

Notes:

[9] - 2 excluded: missing multiple measurements

[10] - 2 excluded: missing multiple measurements

[11] - 8 excluded: missing multiple measurements

Statistical analyses

No statistical analyses for this end point

Secondary: Cell frequency, phenotype and functional capacity of SARS-CoV-2 specific immune cells measured by Fluorescence-Activated Cell Sorting (FACS).

End point title	Cell frequency, phenotype and functional capacity of SARS-CoV-2 specific immune cells measured by Fluorescence-Activated Cell Sorting (FACS).

End point description:

Measurement of cell frequency, phenotype and functional capacity of SARS-CoV-2 specific immune cells by Fluorescence-Activated Cell Sorting (FACS), determined in a subset of participants in their 28-days post 2nd primary SARS-CoV-2 vaccination timepoint.
Full analysis will be published, manuscript in preparation.

End point type	Secondary

End point timeframe:

Period 2

End point values	FACS analysis - younger adults	FACS analysis - older adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	28		
Units: frequencies				
median (confidence interval 95%)				
% Spike-specific CD4+ T cells	0.85 (0.58 to 1.48)	0.58 (0.28 to 1.18)		
% CD69+CD134+ subset of CD4+ T cells	0.63 (0.37 to 1.26)	0.22 (0.10 to 0.32)		
% CD137+CD154+ subset of CD4+ T cells	0.36 (0.23 to 0.56)	0.175 (0.097 to 0.26)		
% cytokine+ producing subset of CD4+ T cells	0.58 (0.36 to 0.75)	0.225 (0.19 to 0.33)		
% IFNy+ producing subset of CD4+ T cells	0.18 (0.13 to 0.24)	0.081 (0.063 to 0.099)		
% TNFa+ producing subset of CD4+ T cells	0.32 (0.18 to 0.47)	0.13 (0.11 to 0.22)		
% IL-2+ producing subset of CD4+ T cells	0.27 (0.17 to 0.34)	0.11 (0.081 to 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific IgG GMC in serum at pre- and post- SARS-CoV-2

mRNA vaccination.

End point title	SARS-CoV-2 specific IgG GMC in serum at pre- and post-SARS-CoV-2 mRNA vaccination.

End point description:

SARS-CoV-2 specific IgG GMC in serum at pre- and post- SARS-CoV-2 (booster) vaccination.
Full analysis on primary vaccination series is published in Van der Heiden et al., Nat Commun 2024, https://doi.org/10.1038/s41467-024-50760-9. Later timepoints will be included in future publications.

End point type	Secondary

End point timeframe:

Period 2

End point values	Spikevax serology - Pre primary series - 25-49y	Spikevax serology - 28-days post 1st primary vaccine - 25-49y	Spikevax serology - 28-days post 2nd primary vaccine - 25-49y	Spikevax serology - 6-months post primary series - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	43	43	41
Units: BAU/ml				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	0.7 (0.44 to 1.09)	308.51 (178.13 to 534.31)	2587.76 (2214.12 to 3024.46)	2.85 (2.13 to 3.82)
N-specific IgG antibody GMC	1.45 (1.04 to 2.01)	2.41 (1.67 to 3.48)	414.28 (338.75 to 506.66)	1.88 (1.46 to 2.43)

End point values	Spikevax serology - Pre primary series - 50-64y	Spikevax serology - 28-days post 1st primary vaccine - 50-64y	Spikevax serology - 28-days post 2nd primary vaccine - 50-64y	Spikevax serology - 6-months post primary series - 50-64y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	75	75	75	73
Units: BAU/ml				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	1.01 (0.71 to 1.44)	245.06 (151.97 to 395.18)	2217.94 (1879.65 to 2617.12)	323.89 (264.83 to 396.12)
N-specific IgG antibody GMC	1.58 (1.21 to 2.06)	1.81 (1.34 to 2.45)	2.68 (2.14 to 3.35)	2.02 (1.62 to 2.52)

End point values	Spikevax serology - Pre primary series - 65+	Spikevax serology - 28-days post 1st primary vaccine - 65+	Spikevax serology - 28-days post 2nd primary vaccine - 65+	Spikevax serology - 6-months post primary series - 65+

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	84	84	84	82
Units: BAU/ml				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	0.92 (0.7 to 1.21)	312.62 (241.82 to 404.15)	1832.32 (1517.73 to 2212.13)	257.59 (205.56 to 322.79)
N-specific IgG antibody GMC	1.26 (1.03 to 1.54)	3.13 (2.57 to 3.81)	2.1 (1.77 to 2.49)	1.77 (1.44 to 2.17)

End point values	Comirnaty serology - Pre primary series - 65+	Comirnaty serology - 28-days post 1st primary vaccine - 65+	Comirnaty serology - 28-days post 2nd primary vaccine - 65+	Comirnaty serology - 6-months post primary series - 65+
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	42	33	41	38
Units: BAU/ml				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	0.22 (0.16 to 0.3)	105.98 (56.42 to 199.06)	717.87 (483.92 to 1064.94)	90.64 (53.87 to 152.5)
N-specific IgG antibody GMC	0.96 (0.69 to 1.35)	2.69 (1.86 to 3.89)	1.59 (1.1 to 2.29)	1.57 (1.02 to 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) pre- and post-vaccination.

End point title	SARS-CoV-2 specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) pre- and post-vaccination.

End point description:

SARS-CoV-2 specific T-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.
Analysis is included in Brummelman et al., Front. Immunol. 2024, https://doi.org/10.1186/s12979-023-00391-3

End point type	Secondary

End point timeframe:

Period 2

End point values	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 25-49y	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 50-64y	SARS-CoV-2 T-cell ELISpot - Pre vaccination timepoint - 65+	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	18	28	16
Units: countable unit(s)				
median (confidence interval 95%)				
NCAP-specific counts	0.33 (0 to 0.83)	0 (0 to 0.17)	0 (0 to 0.17)	0.17 (0 to 0.5)
S1+S2-specific counts	0.83 (0.33 to 2.58)	0 (0 to 0.5)	0 (0 to 0.5)	22.67 (15.83 to 46)

End point values	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 50-64y	SARS-CoV-2 T-cell ELISpot - 28-days post vaccination - 65+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	34		
Units: countable unit(s)				
median (confidence interval 95%)				
NCAP-specific counts	0 (0 to 0.17)	0 (0 to 0)		
S1+S2-specific counts	24.67 (16.92 to 35.33)	6.17 (4 to 9.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific B-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) pre- and post-vaccination.

End point title	SARS-CoV-2 specific B-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) pre- and post-vaccination.

End point description:

SARS-CoV-2 specific B-cells measured by Enzyme-Linked Immunosorbent Spot (ELISPOT) in peripheral blood mononuclear cells (PBMCs) of pre- and post-vaccination samples.
Analysis is included in Verheul et al., Vaccines 2023, https://doi.org/10.3390/vaccines11071196

End point type	Secondary

End point timeframe:

Period 2 - Period 3

End point values	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 25-49y	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 50-64y	SARS-CoV-2 B-cell ELISpot - 28-days post vaccination - 65+	SARS-CoV-2 B-cell ELISpot - Pre booster - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	11	13	3
Units: countable unit(s)				
median (confidence interval 95%)				
NCAP-specific counts	0 (0 to 0.25)	0 (0 to 0.5)	0 (0 to 0)	0 (0 to 0)
S1-specific counts	10 (7.25 to 12)	7 (1.3 to 14.3)	4.3 (1.8 to 9)	1.8 (1.8 to 7.8)

End point values	SARS-CoV-2 B-cell ELISpot - Pre booster - 50-64y	SARS-CoV-2 B-cell ELISpot - Pre booster - 65+	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 25-49y	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 50-64y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	13	3	7
Units: countable unit(s)				
median (confidence interval 95%)				
NCAP-specific counts	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
S1-specific counts	12 (8 to 27)	8 (2.8 to 13.8)	3.8 (2.3 to 107.6)	23.8 (23 to 42)

End point values	SARS-CoV-2 B-cell ELISpot - 28-days post booster - 65+			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: countable unit(s)				
median (confidence interval 95%)				
NCAP-specific counts	0 (0 to 0)			
S1-specific counts	69.4 (25.05 to 100.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 specific antibody concentrations (GMCs) in nasal lining fluid of pre- and post-vaccination samples.

End point title	SARS-CoV-2 specific antibody concentrations (GMCs) in nasal lining fluid of pre- and post-vaccination samples.

End point description:

SARS-CoV-2 specific antibody concentrations (GMCs) in nasal lining fluid of pre- and post-vaccination samples measured by bead-based multiplex immune assay.
Full analysis will be publised, manuscript in preparation.

End point type	Secondary
End point timeframe:	
Period 2 - Period 3	

End point values	mucosal antibody analysis - Pre 1st booster - 25-49y	mucosal antibody analysis - Pre 1st booster - 50-64y	mucosal antibody analysis - Pre 1st booster - 65+	mucosal antibody analysis - 28-days post 1st booster - 25-49y
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	31	40	9
Units: BAU/mL				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	1.38 (0.69 to 2.73)	0.85 (0.42 to 1.72)	0.28 (0.15 to 0.53)	19.03 (9.42 to 38.45)
N-specific IgG antibody GMC	0.03 (0.01 to 0.06)	0.03 (0.02 to 0.06)	0.03 (0.02 to 0.04)	0.04 (0.02 to 0.12)

End point values	mucosal antibody analysis - 28-days post 1st booster -50-64y	mucosal antibody analysis - 28-days post 1st booster - 65+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	40		
Units: BAU/mL				
geometric mean (confidence interval 95%)				
S1-specific IgG antibody GMC	35.21 (25.65 to 48.32)	19.75 (12.92 to 30.2)		
N-specific IgG antibody GMC	0.09 (0.05 to 0.17)	0.06 (0.03 to 0.09)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Any adverse event spontaneously reported by the subject occurring within 28 days after vaccination, or within one week after swab collection or blood sampling.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	QIV, PCV-13 and SARS-CoV-2 immunization

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: It is correct that no non-serious adverse events are recorded. As described in the protocol, only adverse events that were reported spontaneously by the subject or observed by the investigator or study staff were recorded. Adverse events were not actively recorded or requested. As a result, no adverse event occurred in more than 5% of participants. Therefore, reporting these data would not provide an accurate or representative overview of the adverse events in this study.

Serious adverse events	QIV, PCV-13 and SARS-CoV-2 immunization		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 326 (2.76%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Periprothetic fracture			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Miscarriage			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 326 (0.31%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	QIV, PCV-13 and SARS-CoV-2 immunization		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 326 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2020	This amendment concerns: a) Additional small blood sample collection by finger stick for all participants to asses Influenza- specific antibodies. Due to the COVID-19 pandemic, the T5 visits were postponed. Because it was unclear if the T5 visits could be resumed within the 5-8 month follow-up window, it was proposed to collect a small additional blood sample by self-sampling. Hereby, long term follow-up evaluation of influenza specific antibodies 5-9 months after influenza vaccination was still allowed. b) Determine the impact of potential COVID-19 infections on baseline and vaccine induced immune responses in the participants: All participants in the study have been asked to report any influenza like illness symptoms during the influenza season, they will be asked to continue reporting these symptoms during the whole study period to also record COVID related symptoms. In addition, SARS-CoV-2 serology will be included in the analyses. c) Extend the period of Influenza Like Infection (ILI) monitoring due to the COVID-19 pandemic. d) Changes in ILI monitoring form. With the adaptations also COVID-19 specific symptoms were monitored. e) Additional questionnaire "Zorgnetwerk en COVID-19". This questionnaire will assess changes in healthcare networks due to the COVID19 pandemic and shed light on the impact of the pandemic on healthcare networks and the implications thereof for the participant f) Change in pneumococcal vaccination letter for elderly and their general practitioner. Because of the COVID19 pandemic the State Secretary of Health, Welfare and Sports decided to change the age groups eligible for PPV23 vaccination based on a recent report of the "gezondheidsraad". g) QIV 2020-2021 vaccination at T8 visit
14 January 2021	The amendment concerns a change of no longer analyzing the long term effect of PCV13 vaccination on pneumococcal specific cellular immunity and carriage at 12 months post vaccination. Pneumococcal antibody responses will still be evaluated at 12 months post vaccination. This post vaccination analysis can be done in a small blood volume so the T10 (home) visit will be replaced by a fingerstick blood collection performed by the participants themselves. This also has the advantage that there will be one contact moment less between the study participants and members of the study teams in case of the COVID-19 pandemic.
22 February 2021	An addition of a evaluation of the immune response to COVID-19 vaccination. Humoral and cellular responses in older adults will be compared with the responses elicited in the other adult age groups. Moreover, the immune response to the COVID-19 vaccine will be compared to responses to influenza and pneumococcal vaccinations, that have been analyzed as part of the study protocol, within the different age groups. The COVID-19 vaccination schedule for the the vaccines used in this study, consists of two vaccine doses to be given with a 4 week interval. A total of 5 additional evaluation timepoints, four visits and one self sampling timepoints, will be added to the protocol. At visit Ta and Tb the COVID-19 vaccination will be given. For evaluation of the COVID-19 vaccine induced immune response samples will be collected at 1st and 2nd vaccination visit, during a visit 1 month later as well as 6 and 12 months post second COVID-19 vaccination. At timepoint 6 months after vaccination blood samples will be collected by fingerprick self sampling.

03 November 2021	Evaluate the immune response induced by a COVID-19 booster vaccination as a measurement for its effectiveness of the Dutch national vaccination program. Determine the SARS-CoV-2 booster vaccination induced humoral and cellular immune response and compare the responses between elderly and younger age groups of a well characterized cohort. This will result in extra timepoints; Pre booster (B0), at 28 days (-7/+14 days; B1), 6 months (+/- 4 weeks; B2) and 12 months (+/- 4 weeks; B3) post booster vaccination. Depending on the timing of the SARS-CoV-2 booster vaccination timepoints after the second vaccination can be skipped. A subgroup of participants will be asked to participate in the analysis of the cellular immune response.
09 March 2022	Determine the immune response induced by additional COVID-19 booster vaccinations as part of the evaluation of the effectiveness of the Dutch national COVID vaccination program, similar to the scheme as originally planned and compare the 3 month post 1st booster immune response between the different age groups of the Vital cohort. This booster vaccination is followed in persons above 70+ years of age. this will result in extra timepoints for blood sampling; pre booster, at 28 days (-7 till +14 days) post, 6 months (+/- 4 weeks) and 12 months (+/- 4 weeks) post booster vaccination.
24 August 2023	Determine the immune response induced by additional COVID-19 booster vaccination as part of the evaluation of the effectiveness of the Dutch national COVID vaccination program. Of the healthy population only persons of 60 years and older will be eligible for the autumn 2023 COVID-19 vaccination round. Therefore only participants from the Spaarne Hospital in this age group will be invited for participation in the autumn 2023 COVID-19 vaccine immune response follow-up extension of the study. This will result in extra timepoints; Pre booster (E0), at 28 days (-7/+14 days; E1) and 12 months (+/- 4 weeks; E3) post booster vaccination. The study for the middle-aged and adult subjects will be ended. These groups will not be followed after a booster SARS-CoV-2 vaccination obtained in autumn 2023. To complete the protocol, information about the booster in autumn 2022 was included. The follow up of this booster was covered by amendment 4 and notification from November 2022
06 October 2023	Correct the age of participants who were eligible for follow-up after the second booster in February 2022, mentioned in amendment 5. Originally individuals of 70 years and older were eligible for the additional booster dose to be given in the spring of 2022. Based on this information protocol amendment 5 added follow-up of the additional booster dose in Vital-corona participants of 70 years and older to the study. However, after submission of amendment 5, the minister decided that persons -70 years of age were also eligible for a second booster dose. Therefore these participants older than 60 years of age were invited for participation in the additional follow-up of this study after the second booster vaccination.
21 August 2024	Including the collection of nasal lining fluid at timepoint 12 months after booster 2023. Adding the collection of an MLF sample at 12 months post 2023 booster vaccination will give an indication of the duration of the mucosal antibody response.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

12 March 2020	Due to the COVID-19 pandemic the visits were temporarily stopped. The most important reason was the fragility of the participants 70 years and older. Furthermore, the participants who where working at the UMCU/RIVM and who had visits planned at the locations, were asked to work from home. That's why these visits also couldn't continue. Another reason was, the tasks planned at the visits couldn't be executed at 1.5m distance, which was the regulation at that time.	13 July 2020

Notes:

Limitations and caveats

None reported