Pfizer	**STUDY STATUS UPDATE FORM: CLINICAL**	

IIR Grant Specialist IIR Grant Specialist EMAIL	[redacted]	IIR Grant Specialist PHONE IIR Grant Specialist FAX	[redacted]

PLEASE COMPLETE AND RETURN BY November 27, 2018

Per contractual requirements, we are requesting a status update on your IIR study supported by Pfizer via funding and/or drug. Please answer the following questions regarding the above referenced study by the due date. Answers from your last submitted update have been incorporated below; please update as needed and answer the remaining questions.

GENERAL INFORMATION

Pfizer Tracking #	**WI203144**	**Institutional Protocol #**	**2014 192, CE 13.212, BSP**
Principal Investigator	**Dr. Brigitte Lefebvre**		
Study Title	**Serotype monitoring of S. pneumoniae invasive strains in adult population in the province of Quebec_ a 3 years study evaluation.**		

STUDY UPDATE INFORMATION

Has this study been initiated?	☐ NO ☒ YES	**Date of initiation**	mm/dd/yyyy **01/01/2016**
Has the protocol been amended since last update?	☒ NO ☐ YES *(If YES, please provide the revised protocol)*		
Current IRB/IEC approval/renewal expires on **November 5, 2018**	This is not current, please forward the most recent letter		
Have there been any personnel changes? *(If YES, please provide name and full contact info on Page 3)*	☒ NO ☐ YES		
Target protocol enrollment	**550 strains**	Date of first subject enrolled	mm/dd/yyyy **01/01/2016**
Last reported enrollment	**N/A**	Actual enrollment to date *(this should not include screen failures)*	420 strains
Targeted last subject last visit	550 strains	Actual last subject last visit	N/A
Do you have current drug supply sufficient to complete the study? *(If NO, please complete the Drug Section on Page 3)*	☐ NO ☐ YES **Not applicable**		
Is this protocol closed to enrollment? *(patients may still be receiving therapy)*	☒ NO ☐ YES		
Targeted study completion date *(primary objectives met; patient therapy and final study analysis complete)*	mm/dd/yyyy 12/31/2018		
Actual study completion date *(if applicable)*	12/31/2018		
Targeted date to provide results to Pfizer	12/31/2019		

PUBLICATION INFORMATION

Do you plan to publish? *(If YES, please complete the information below.)* ☐ NO ☒ YES

Please be aware that, according to the IIR agreement, the investigator is required to provide Pfizer with an opportunity to prospectively review any proposed publication, abstract or other type of disclosure that reports the results of the study.

FORMAT	PUBLICATION	PLANNED	ACTUAL	SUBMISSION

Pfizer	**STUDY STATUS UPDATE FORM: CLINICAL**	

IIR Grant Specialist	Pina Mustillo	IIR Grant Specialist PHONE	514-426-7021
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	(please include anticipated journal or audience)		DATE
Abstract	ISPPD	☒	☐
Manuscript	Vaccine/PloseOne	☒	☐
Poster	CACMID	☒	☐
Other		☐	☐

SIGNATURE

NAME Doualla-Bell for Lefébvre

DATE mm/dd/yyyy

SIGNATURE (ONLY if fax [redacted]

11/22/2018

Pfizer	**STUDY STATUS UPDATE FORM: CLINICAL**	

IIR Grant Specialist IIR Grant Specialist EMAIL	[redacted]	IIR Grant Specialist PHONE IIR Grant Specialist FAX	[redacted]

DRUG SUPPLY INFORMATION

SUPPLY CURRENTLY ON SITE	**ACTIVE**	**PLACEBO**
ESTIMATED REMAINDER REQUIRED TO COMPLETE STUDY	**ACTIVE**	**PLACEBO**
CAN PHARMACY ACCOMODATE TOTAL REMAINDER?	☐ **YES**	☐ **NO**

PERSONNEL INFORMATION

	PRINCIPAL INVESTIGATOR	**COORDINATOR**
NAME		
INSTITUTION		
MAILING ADDRESS		
TELEPHONE		
FAX		
EMAIL		

	PHARMACIST	**OTHER** *(specify in additional comments)*
NAME		
INSTITUTION		
MAILING ADDRESS		
TELEPHONE		
FAX		
EMAIL		

ADDITIONAL COMMENTS	

LOGOUT

Confirmation of Patient Enrollment Receipt:

Your Patient Enrollment form was successfully submitted to the Pfizer. Thank you for providing this information, no further action on your part is required at this time. To print a copy of this completed form go to 'File', then 'Print' on your browser toolbar. Click here to return to the homepage when you are finished.

Original Study Information

Request ID	
Project Title	WI203144 Serotype monitoring of S. pneumoniae invasive strains in adult population in the province of Quebec_ a 3 years study evaluation.
Principal Investigator First Name	Brigitte
PI Middle Name	
Principal Investigator Last Name	Lefebvre
PI Primary Degree	
Project Start Date	11/20/2015
Project End Date	11/04/2020
Total Subject Enrollment	3000
Number of Arms	

Patient Enrollment

* indicates required field

* Current Total Enrollment	1401
* Estimated Date for Completion of Enrollment	12/31/2018

Technical Questions

Serotype monitoring of *S. pneumoniae* invasive strains in adult population in the province of Quebec, a 5 years study evaluation (2014-2018)

Pfizer IIR grant number: **WI203144**

Authors

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Date: November 18th, 2019

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Abbreviation List

CLSI	Clinical Laboratory Standards Institute
IPD	Invasive pneumococcal disease
IR	Incidence rate
LSPQ	Laboratoire de santé publique du Québec
NT	Non-typeable strain
NVT	Non-vaccine serotype
MIC	Minimum inhibitory concentration
PCR	Polymerase chain reaction
PCV7	7-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PEN	Penicillin G
PPV23	23-valent pneumococcal polysaccharide vaccine

Summary

The Laboratoire de santé publique du Québec (LSPQ) conducts the provincial laboratory surveillance program for invasive pneumococcal diseases (IPD). Provincial surveillance is based on all Quebec hospitals sending all strains from children < 5 years old as well as strains from ≥ 5 years old patients originating from northern regions and those having a penicillin minimum inhibitory concentration (MIC) ≥ 0.12 mg/L. Also, sentinel surveillance is based on 20 sentinel hospitals transmitting all strains detected. The Pfizer research project went from January 2014 to December 2018 and allowed the collection of strains from ≥ 5 years old patients with penicillin MIC < 0.12 mg/L from non-sentinel hospitals in the province in addition to standard provincial surveillance. Ethical approval for the Pfizer research project was obtained from the Comité d'éthique de la recherche du CHUM. The combination of the provincial surveillance program and the Pfizer research project is defined as the universal surveillance in this report.

Invasive pneumococcal disease in Quebec

- Between 2014 and 2018, a total of 4192 IPD cases occurred in Quebec, in all age groups.
- The patterns observed between the years is similar for the frequency and the IR of IPD strains. During the period 2014-2017, IPD was stable and a slight increase can be observed in 2018.
- The universal surveillance allowed to increase the number of IPDs treated by the LSPQ during the study period.
- The region that has the highest IR during this period is Nunavik with 52 cases/100 000 person-year.

Serotypes

- For all age groups and when considering only ≥ 5 years old, the most frequently isolated serotypes between January 2014 and December 2018 are serotypes 22F, 3, 19A, 15A, 9N and 7F. Serotype 7F is included in PCV10 and PCV13. Serotypes 3 and 19A are PCV13-specific serotypes. Serotypes 9N and 22F are PPV23-specific serotypes and 15A is a non-vaccine serotype (NVT).
- Between January 2014 and December 2018, there seems to be increases in PCV7-specific, PCV13-specific and PPV23-specific serotypes. There is also a decrease in PCV10-specific serotypes over the study period. The non-vaccine serotypes' number of strains show an increase, while the percentage of annual strains remained stable between 2014 and 2018.
- The proportions of vaccine-specific serotypes are significantly different between sentinel and non-sentinel surveillance with Pfizer data (p=0.0003). Hence, the serotype profiles obtained by sentinel surveillance are different from the profiles detected by universal surveillance.
- There is more PCV7-specific serotypes and less of additional PCV13-specific serotypes detected by the sentinel surveillance compared with universal surveillance.
- The total proportion of PCV13-specific serotypes is not different between sentinel (34.0%) and universal surveillance (33.1%).

Antimicrobial susceptibility

- The only antibiotics that present relevant levels of resistance are erythromycin, clindamycin, doxycycline, penicillin G (meningitis criteria) as well as trimethoprim-sulfamethoxazole.
- Among the penicillin G susceptible strains, 8.2% were multiresistants, while among the strains resistant to penicillin G, 87.5% were multiresistants.
- Serotypes 3, 7F and 9N have mainly strains that are susceptible to all classes of antibiotics.
- Serotype 15A has mainly strains that are resistant to three classes and four classes of antibiotics.
- Serotype 19A has an almost equal amount of strains that are susceptible to all classes of antibiotics and that are resistant to two classes of antibiotics. It is also important to note that 19A is the only serotype with strains that are resistant to six classes of antibiotics (n=2).
- Serotype 22F has mainly strains that are susceptible to all classes of antibiotics, but also several strains that are resistant to one antibiotics class.
- Between 22.6% and 32.5% of multiresistance profiles (resistant to 2 classes or more) were detected by the sentinel network in the ≥ 5 years old group.

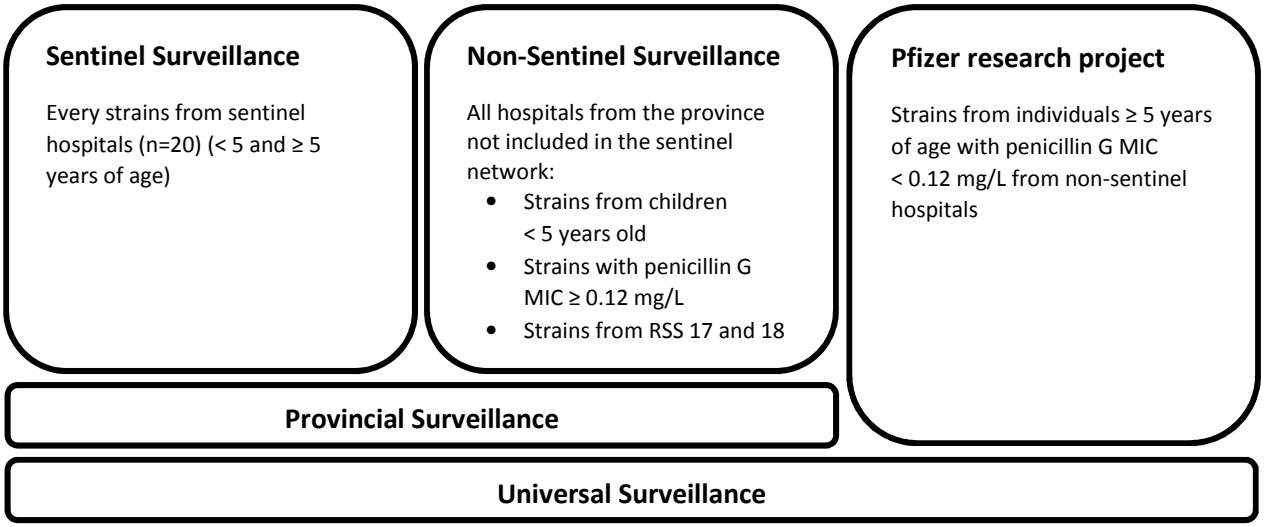
Background

Infections with *Streptococcus pneumoniae* can result in invasive pneumococcal disease (IPD). Infections are considered invasive when they are located in normally sterile clinical sites (for example, blood, central nervous system tissue/fluid, peritoneal fluid, pericardial fluid, synovial fluid, or other deep abscesses and tissues). IPD can cause meningitis as well as bacteremia (1).

IPD is mainly a burden in children < 5 years old and elderly adults (≥ 60 years old) (2). Since the burden reaches two very different age groups, the vaccination policy in Quebec targets these two specific groups. Government funded vaccination of children at high-risk as well as children living in two northern regions of the province with the 7-valent pneumococcal conjugate vaccine (PCV7 : 4, 6B, 9V, 14, 18C, 19F and 23F) was offered in October 2002 (3). The publicly funded program was expanded to offer immunization to low-risk children with the same vaccine in December 2004 with a catch-up program for children < 5 years of age (3). The 10-valent pneumococcal conjugate vaccine (PCV10 : PCV7 + 1, 5 and 7F) was introduced without a catch-up program in the summer of 2009 in the same age group (4). The 13-valent pneumococcal conjugate vaccine (PCV13 : PCV10 + 3, 6A and 19A) was introduced in January 2011, again without a catch-up program (5). A change in 2018 in the vaccination policy promoted the replacement of PCV13 by PCV10 for the immunization of children < 5 years of age in the province (6). Since 2000, the Quebec provincial government offers the 23-valent pneumococcal polysaccharide vaccine (PPV23 : PCV13 without 6A + 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) to all adults ≥ 65 years of age (7,8).

In Quebec, IPD is a notifiable disease since 1996 (9). Currently, there is an active provincial laboratory surveillance program for IPD coordinated by LSPQ that allows the collection of all strains from children < 5 years old, all strains from northern regions of the province, all strains collected from individuals ≥ 5 years old from 20 sentinel hospital sites and all strains with a penicillin minimum inhibitory concentration (MIC) ≥ 0.12 mg/L. Between January 2014 and December 2018, the provincial surveillance was expanded by the Pfizer research project to allow the collection of all strains collected from individuals that are ≥ 5 years old from non-sentinel hospital sites with an penicillin MIC < 0.12 mg/L. The combination of the provincial surveillance program and the Pfizer research project is defined as the universal surveillance in this report (Figure 1).

Figure 1. Definition of the different laboratory surveillance conducted at LSPQ for IPD in place in Quebec between 2014 and 2018



Objectives

- To characterize serotypes and antibiotic resistance profile of all invasive *S. pneumoniae* strains from the population aged ≥ 5 years in Quebec.

- To assess whether the serotype profile from the entire population (universal surveillance) is comparable to the profile obtained from sentinel sites.

- To follow the incidence of IPD in Quebec over several years and evaluate the impact of current vaccine, PCV13 on IPD incidence.

Methods

A total of 4192 strains of *S. pneumoniae* invasive strains from normally sterile clinical sites isolated between January 2014 and December 2018 were analyzed. Multiple strains collected within 14 days from the same patient with identical serotypes were counted once (1 strain/patient/14 days).

Serotyping was done with the Quellung reaction using antisera from Statens Serum Institut (SSI). Serotyping was successfully done on 4184 strains.

Antimicrobial susceptibility testing was performed by broth microdilution according to the Clinical Laboratory Standards Institute (CLSI) guidelines (10). The interpretation criteria for the MIC used are those of the CLSI. The following antibiotics were tested: ceftriaxone, clindamycin, doxycycline, erythromycin, levofloxacin, penicillin G, trimethoprim-sulfamethoxazole and vancomycin. In 2008, the CLSI defined new interpretation criteria for penicillin. These criteria for strains isolated from cerebrospinal fluid are different from those isolated from other sterile sites. The meningitis breakpoints used for the strains isolated from cerebrospinal fluid are ≤ 0.06 mg/L (susceptible) and ≥ 0.12 mg/L (resistant) while non-meningitis breakpoints for strains isolated from other invasive sites are ≤ 2 mg/L (susceptible), 4 mg/L (intermediate) and ≥ 8 mg/L (resistant).

The incidence rate (IR) calculation is based on the population estimates from the Institut de la statistique du Québec (11).

The sentinel network includes 20 laboratories encompassing pediatric hospitals and accounts for about 35% of the invasive strains in patient ≥ 5 years of age. For this report, the sentinel surveillance includes data all strains collected in hospital from patients of RSS 17 and RSS 18. The population covered by the sentinel network remains undefined and can vary from one year to the other (12).

The analyses do not include the duplicates, cases from patients who do not live in Quebec (for example, travelers or foreign students) as well as cases detected by polymerase chain reaction (PCR).

Chi-square analyses were performed with a significance threshold of 0.05 (13).

The year 2013 (n=239) was excluded from the following analyses since the data available for that year is only partial (i.e. the universal surveillance only started in August 2013), hence that year cannot be compared with the following years.

The study protocol for the Pfizer research project was submitted to a research ethics committee. Ethical approval was obtained from the Comité d'éthique de la recherche du CHUM.

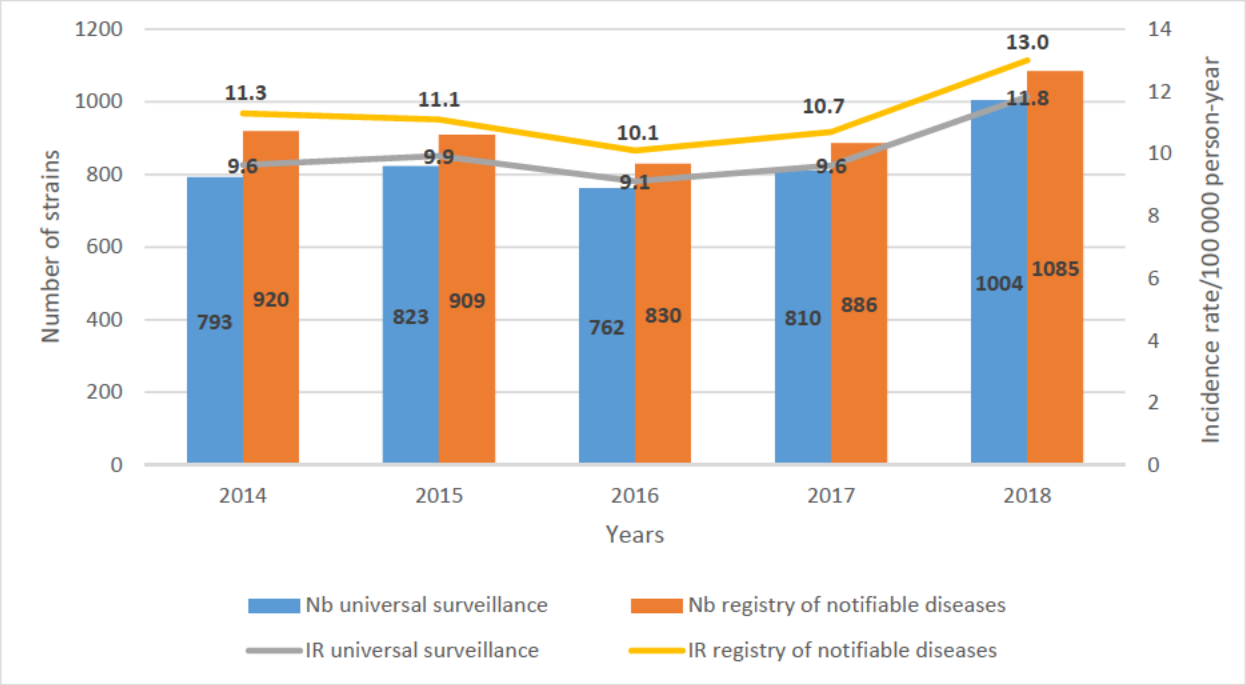
Results

Invasive pneumococcal disease in Quebec

Between 2014 and 2018, a total of 4192 *S. pneumoniae* strains have been isolated in Quebec, in all age groups, according to LSPQ data. The number of strains submitted was stable from 2014 to 2017 (Figure 2). A slight increase in the number of strains can be observed for the year 2018. Universal surveillance allows the detection of about 90% of IPD cases in Quebec (source: MADO, extraction date June 28th 2019). The difference between the number of cases detected by universal surveillance (LSPQ) and the Registry of notifiable diseases of Quebec could be explained by strains not send to LSPQ (non-viable strains or forgotten by hospital), cases detected by PCR or the difference in data collection between the two systems for new cases (i.e. 90 days for notifiable diseases and 1 strain/patient/14 days for LSPQ) (14).

In Quebec, between 2014 and 2018, based on 4192 *S. pneumoniae* strains isolated from all age groups, the incidence rate (IR/100 000 person-year) of IPD varied between 9.1 and 11.8 per 100 000 persons per year (Figure 2).

Figure 2. Temporal trends in frequency of IPD cases and in IPD incidence rates (IR/100 000 person) per year in all age groups of Quebec from 2014 to 2018 detected by universal surveillance and the Registry of notifiable diseases of Quebec



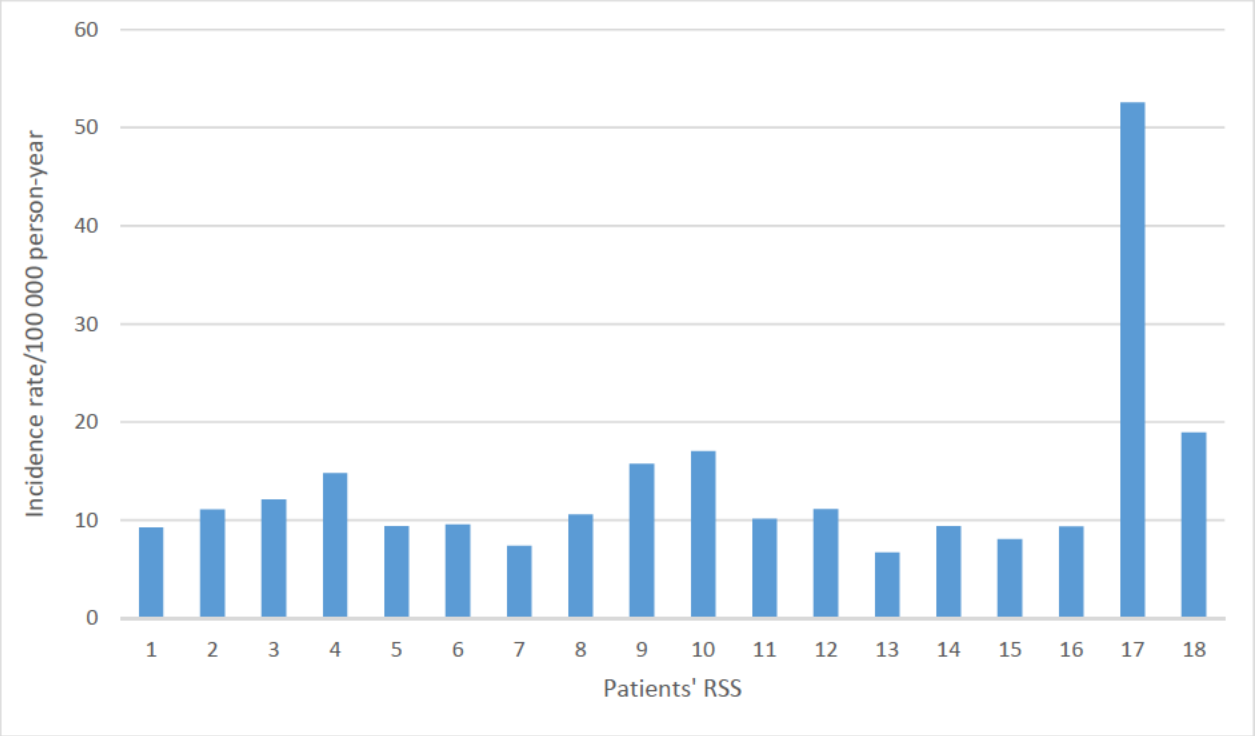
For the period 2014-2018, the additional surveillance with the Pfizer project allowed to collect and analyse 53.8% of the 2014-2018 IPD strains, hence a doubling in the number of IPDs (Table 1).

Table 1. Repartition of strains from individuals from all age groups obtained through surveillance in Quebec, 2014-2018

Type of surveillance	IPD strains	
	n	%
Provincial surveillance	1937	46.2
Pfizer research project	2255	53.8
Total	4192	100.0

Figure 3 presents the incidence rate of IPD (IR/100 000 person-year) per patients' RSS between 2014 and 2018 according to LSPQ data. The region that has the highest IR during this period is Nunavik (52.5 cases/100 000 person-year). Regional IR should be interpreted with caution because of declaration method and population demographics. Also, there is a risk of overestimating or underestimating number of cases in different regions because of the customers served by the different hospitals and the ease of access of the different types of services for the ambulatory clientele (12).

Figure 3. IPD incidence rate (IR/100 000 person-year) per patients' RSS between 2014 and 2018 in Quebec in all age groups, according to LSPQ data



Legend: **RSS 01**: Bas-Saint-Laurent; **RSS 02**: Saguenay–Lac-St-Jean; **RSS 03**: Capitale-Nationale; **RSS 04**: Mauricie et Centre-du-Québec; **RSS 05**: Estrie; **RSS 06**: Montréal; **RSS 07**: Outaouais; **RSS 08**: Abitibi-Témiscamingue; **RSS 09**: Côte-Nord; **RSS 10**: Nord-du-Québec; **RSS 11**: Gaspésie–Îles-de-la-Madeleine; **RSS 12**: Chaudière-Appalaches; **RSS 13**: Laval; **RSS 14**: Lanaudière; **RSS 15**: Laurentides; **RSS 16**: Montérégie; **RSS 17**: Nunavik; **RSS 18**: Terres-Cries-de-la-Baie-James.

Distribution of *Streptococcus pneumoniae* serotypes in ≥ 5 years old

Among a total of 4192 *S. pneumoniae* strains isolated in the province for 2014-2018 period, 3894 strains were from the ≥ 5 years old patients. Table 2 shows the serotype profile of all these strains per year from January 2014 to December 2018. The serotypes for which more than 80 strains were collected in 2018 are the following: 3 (n=132, 14%), 22F (n=108, 11%), 19A (n=94, 10%) and 9N (n=85, 9%). Serotypes that have between 30 and 79 strains in 2018 are: 15A (n=48, 5%), 11A (n=44, 5%), 4 (n=38, 4%), 23A (n=36, 4%), 8 (n=33, 3%) and 16F (n=31, 3%). The serotypes with more than 200 strains in total between 2014 and 2018 are: 22F (n=487/3894, 13%), 3 (n=447/3894, 12%), 19A (n=383/3894, 10%), 9N (n=274/3894, 7%), 15A (n=214/3894, 6%) and 7F (n=209/3894, 5%). Serotype 7F is included in PCV10 and PCV13. Serotypes 3 and 19A are PCV13-specific serotypes. On the other hand, serotypes 9N and 22F are PPV23-specific serotypes and 15A is a non-vaccine serotype (NVT).

Table 2. Distribution of invasive *S. pneumoniae* serotypes per year in ≥ 5 years old patients in Quebec from 2014 to 2018

Serotype		Year					Total
		2014	2015	2016	2017	2018	
PCV7-included	4*	7	23	22	15	38	105
	6B*	6	4	6	3	3	22
	9V*	2	4	1	3	1	11
	14*	4	3	4	4	2	17
	18C*	2	1	1	3	2	9
	19F*	4	9	7	19	15	54
	23F*	4	2	2	1	1	10
Additional PCV10 serotypes	1**	2	1	1	0	0	4
	5**	0	0	0	0	0	0
	7F**	74	56	35	24	20	209
Additional PCV13 serotypes	3***	76	103	76	60	132	447
	6A***	8	2	2	3	3	18
	19A***	64	71	65	89	94	383
Additional PPV23 serotypes	2^	0	0	0	1	1	2
	8^	12	8	16	23	33	92
	9N^	44	39	46	60	85	274
	10A^	15	4	13	19	13	64
	11A^	25	26	33	28	44	156
	12F^	27	20	12	13	21	93
	15B^	14	14	16	20	16	80
	17F^	2	6	6	9	5	28
	20^	8	12	9	7	12	48
	22F^	89	104	92	94	108	487
	33F^	11	43	28	32	22	136

Serotype		Year					Total
		2014	2015	2016	2017	2018	
NVT	6C	26	20	13	18	22	99
	6D	0	1	1	0	1	3
	7A	1	1	0	0	0	2
	7B	1	2	0	0	0	3
	7C	9	5	12	13	10	49
	10F	0	0	0	0	0	0
	11B	1	3	0	0	0	4
	12A	0	1	0	0	0	1
	12B	0	0	0	1	0	1
	13	1	1	1	0	2	5
	15A	41	34	39	52	48	214
	15C	2	2	4	2	3	13
	16F	32	29	34	24	31	150
	18A	0	0	0	0	0	0
	18F	0	0	1	0	1	2
	21	0	3	1	4	4	12
	22A	2	0	0	1	0	3
	23A	32	28	30	23	36	149
	23B	15	21	15	21	26	98
	24B	1	0	0	0	0	1
	24F	5	6	6	6	10	33
	27	0	0	0	0	0	0
	28A	0	1	1	0	0	2
	29	4	4	0	2	2	12
	31	5	6	9	14	10	44
	33A	0	0	0	1	2	3
	34	6	5	9	2	7	29
	35A	0	0	1	2	0	3
	35B	10	10	21	20	28	89
	35F	10	10	16	11	22	69
	37	0	0	0	1	1	2
	38	5	5	6	11	16	43
	42	0	0	1	0	0	1
	NT	2	1	1	1	1	5
Total		711	754	715	760	954	3894

* Component of PCV7; ** Component of PCV10; *** Component of PCV13; ^ Component of PPV23; NT: non-typeable strains

Figure 4 and Figure 5 show the strains associated with PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) and the additional serotypes entering in the composition of PCV10 (1, 5, 7F), PCV13 (3, 6A, 19A) and PPV23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F) according to year. When comparing the temporal evolution of vaccine-specific serotypes from January 2014 to December 2018, it is possible to observe a few trends. The annual number of strains was higher in 2018 in all serotype categories except for PCV10-specific serotypes. There was a trend to increase in number of PCV7-specific, PCV13-specific, PPV23-specific serotypes of isolated strains as well as non-vaccine serotypes but a decrease in PCV10-specific serotypes over the study period (Figure 4). The percentages of PCV7-specific, PPV23-specific serotypes and non-vaccine serotypes exhibit a slight increase with stabilisation since 2016 (6%, 38% and 30% respectively), while PCV10-specific serotypes show a decrease (Figure 5). PCV13 specific serotypes tended to decrease from 2014 to 2017, but in 2018, with 24% of cases, they showed a trend to increase compared to the 20%-23% observed in 2014-2017 (p=0.03).

Figure 4. Temporal evolution of the number of strains from vaccine-specific serotypes between 2014 and 2018 in ≥ 5 years old patients in Quebec

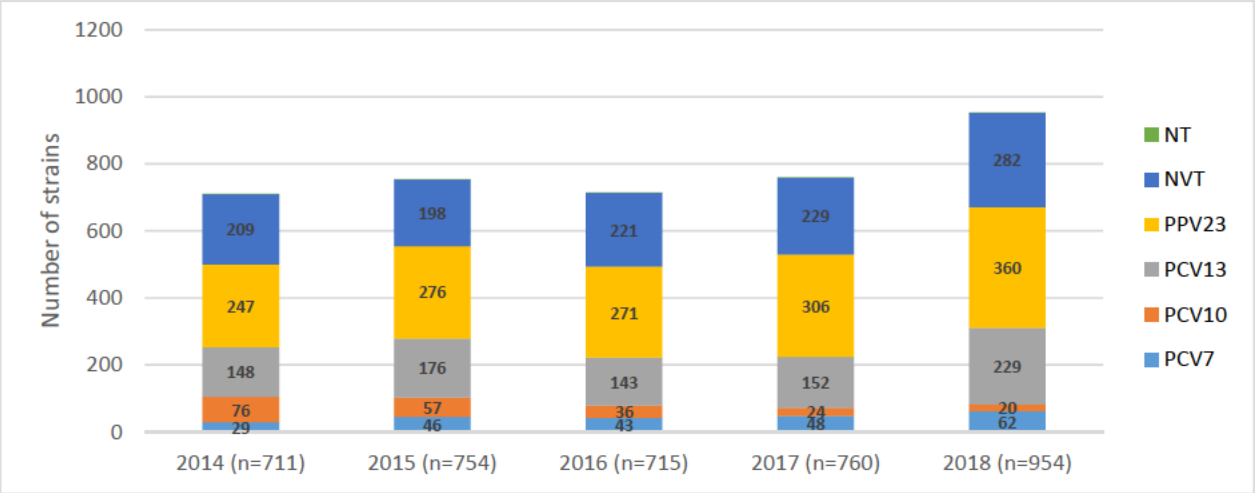
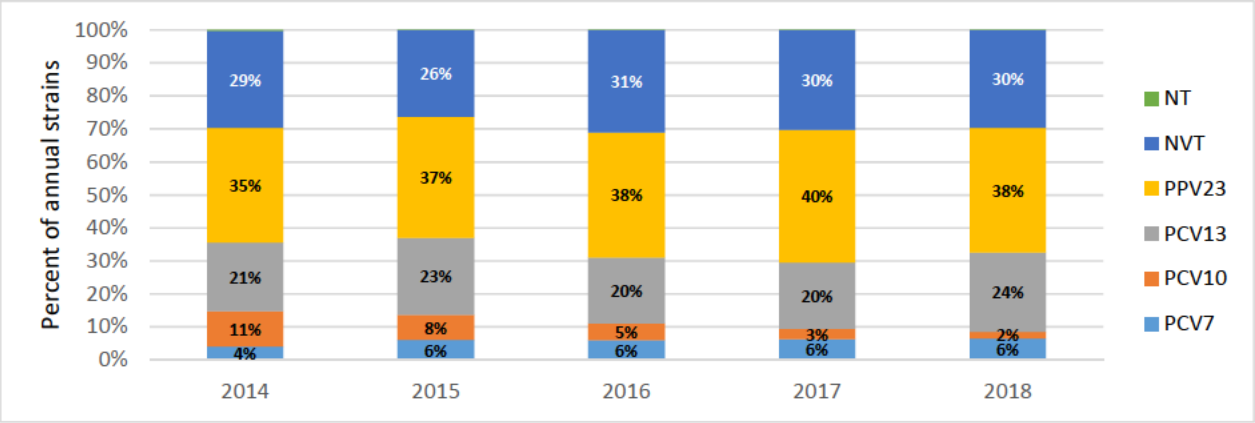


Figure 5. Temporal evolution of the proportion of strains from vaccine-specific serotypes between 2014 and 2018 in ≥ 5 years old patients in Quebec



*NT: non-typeable strains; NVT: non-vaccine serotypes; PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; PCV10 includes serotypes 1, 5 and 7F; PCV13 includes serotypes 3, 6A and 19A; PPV23 includes serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F

Comparison of *Streptococcus pneumoniae* serotypes in ≥ 5 years old patients obtained from sentinel and universal surveillance programs

A method to compare data obtained from two different surveillance programs is to observe the numbers and proportions of strains per age group and per serotype. Table 3 presents the distribution of *S. pneumoniae* serotypes detected by the surveillance levels for the 2014-2018 period associated with PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F) and the additional serotypes entering in the composition of PCV10 (1, 5, 7F), PCV13 (3, 6A, 19A) and PPV23 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F) as well as non-vaccine serotypes. A chi-square analysis determined that the proportions of vaccine-specific serotypes are significantly different between sentinel and non-sentinel surveillance with Pfizer data (p=0.0003). Hence, the serotype profiles obtained by sentinel surveillance are different from the profiles detected by universal surveillance. The difference is mainly due to 2.1% more PCV7-specific serotypes and 2.0% less of the additional PCV13-specific serotypes detected by the sentinel surveillance compared with universal surveillance. The total proportion of PCV13-specific serotypes is not different between sentinel (34.0%, n=456/1342) and universal surveillance (33.1%, n=1289/3894). The complete table is shown in Annex 1.

Table 3. Distribution of *S. pneumoniae* serotypes in sentinel (n=1342), non-sentinel with Pfizer data (n=2552) and universal surveillance (n=3894) for the 2014-2018 period in ≥ 5 years old patients

Age group	Sentinel surveillance						Non-sentinel with Pfizer data						Universal surveillance					
	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%
PCV7-specific serotypes																		
Total	3	28	31	45	107	8.0%	5	31	39	46	121	4.7%	8	59	70	91	228	5.9%
%	5.2%	12.3%	8.1%	6.7%			9.1%	8.1%	5.5%	3.3%			7.1%	9.7%	6.4%	4.4%		
Additionnal PCV10-specific serotypes																		
Total	6	30	31	16	83	6.2%	7	38	46	39	130	5.1%	13	68	77	55	213	5.5%
%	10.3%	13.2%	8.1%	2.4%			12.7%	9.9%	6.4%	2.8%			11.5%	11.1%	7.0%	2.7%		
Additionnal PCV13-specific serotypes																		
Total	11	45	77	133	266	19.8%	18	85	182	297	582	22.8%	29	130	259	430	848	21.8%
%	19.0%	19.8%	20.1%	19.8%			32.7%	22.1%	25.5%	21.2%			25.7%	21.3%	23.6%	20.8%		
Additionnal PPV23-specific serotypes																		
Total	13	82	147	254	496	37.0%	12	152	286	514	964	37.8%	25	234	433	768	1460	37.5%
%	22.4%	36.1%	38.3%	37.7%			21.8%	39.6%	40.0%	36.8%			22.1%	38.3%	39.4%	37.1%		
Non-vaccine serotypes																		
Total	25	42	98	225	390	29.1%	13	78	162	502	755	29.6%	38	120	260	727	1145	29.4%
%	43.1%	18.5%	25.5%	33.4%			23.6%	20.3%	22.7%	35.9%			33.6%	19.6%	23.7%	35.1%		
TOTAL	**58**	**227**	**384**	**673**	**1342**	**34.5%**	**55**	**384**	**715**	**1398**	**2552**	**65.5%**	**113**	**611**	**1099**	**2071**	**3894**	**100.0%**
%	**4.3%**	**16.9%**	**28.6%**	**50.1%**			**2.2%**	**15.0%**	**28.0%**	**54.8%**			**2.9%**	**15.7%**	**28.2%**	**53.2%**		

Antimicrobial resistance in *S. pneumoniae* strains from ≥ 5 year old patients

The results of antibiotic susceptibility testing for the 3891 IPD strains from patients that are ≥ 5 years of age from all provincial laboratories are shown in table 4. Three strains are not included in the table because they were not tested or showed no growth on microbroth dilution plates. Based on these results, the only antibiotics that show relevant levels of resistance are erythromycin (22.9%), clindamycin (14.0%), doxycycline (11.2%), penicillin G (meningitis criteria) (11.1%) as well as trimethoprim-sulfamethoxazole (4.1%) (Table 4).

Table 4. Susceptibility to antibiotics of *S. pneumoniae* strains isolated in ≥ 5 years old patients in all provincial laboratories from 2014 to 2018 (n=3891)

Antibiotics	Number of strains (%)					
	Susceptible		Intermediate		Resistant	
	N	%	N	%	N	%
Penicillin G – oral breakpoints	3459	88.9%	360	9.3%	72	1.9%
Penicillin G – meningitis breakpoints	3459	88.9%	0	0.0%	432	11.1%
Penicillin G – non-meningitis breakpoints	3873	99.5%	18	0.5%	0	0.0%
Ceftriaxone - meningitis breakpoints	3823	98.3%	59	1.5%	9	0.2%
Ceftriaxone – non-meningitis breakpoints	3882	99.8%	8	0.2%	1	0.0%
Clindamycin	3339	85.8%	9	0.2%	543	14.0%
Doxycycline*	2027	88.1%	16	0.7%	257	11.2%
Erythromycin	2994	76.9%	6	0.2%	891	22.9%
Levofloxacin	3868	99.4%	7	0.2%	16	0.4%
Trimethoprim-sulfamethoxazole	3498	89.9%	231	5.9%	161	4.1%
Vancomycin	3891	100.0%	0	0.0%	0	0.0%

*Doxycycline is not calculated on the same denominator as the other antibiotics because testing was introduced at the LSPQ in 2016. Hence there are only 2300 IPD strains from patients that are ≥ 5 years old that were tested for doxycycline susceptibility.

Multiresistance in *S. pneumoniae* strains from ≥ 5 year old patients

Susceptibility profiles have been also established for 3891 IPD strains from patients that are ≥ 5 years of age from all provincial laboratories (Table 5). Strains from ≥ 5 years old patients came from the sentinel surveillance system (34.4%, n=1340), from the non-sentinel surveillance (7.6%, n=297) and from the Pfizer research project (57.9%, n=2254) that took place between January 2014 and December 2018. This sample includes 3459 (89%) strains susceptible to penicillin G (meningitis breakpoints) and 432 (11%) strains non-susceptible to penicillin G (i.e. intermediate or resistant). Among the susceptible strains, 282 (8.2%) were multiresistants (i.e. resistance to 2 or more antibiotic classes), while among the 432 strains resistant to penicillin G, 378 (87.5%) were multiresistants.

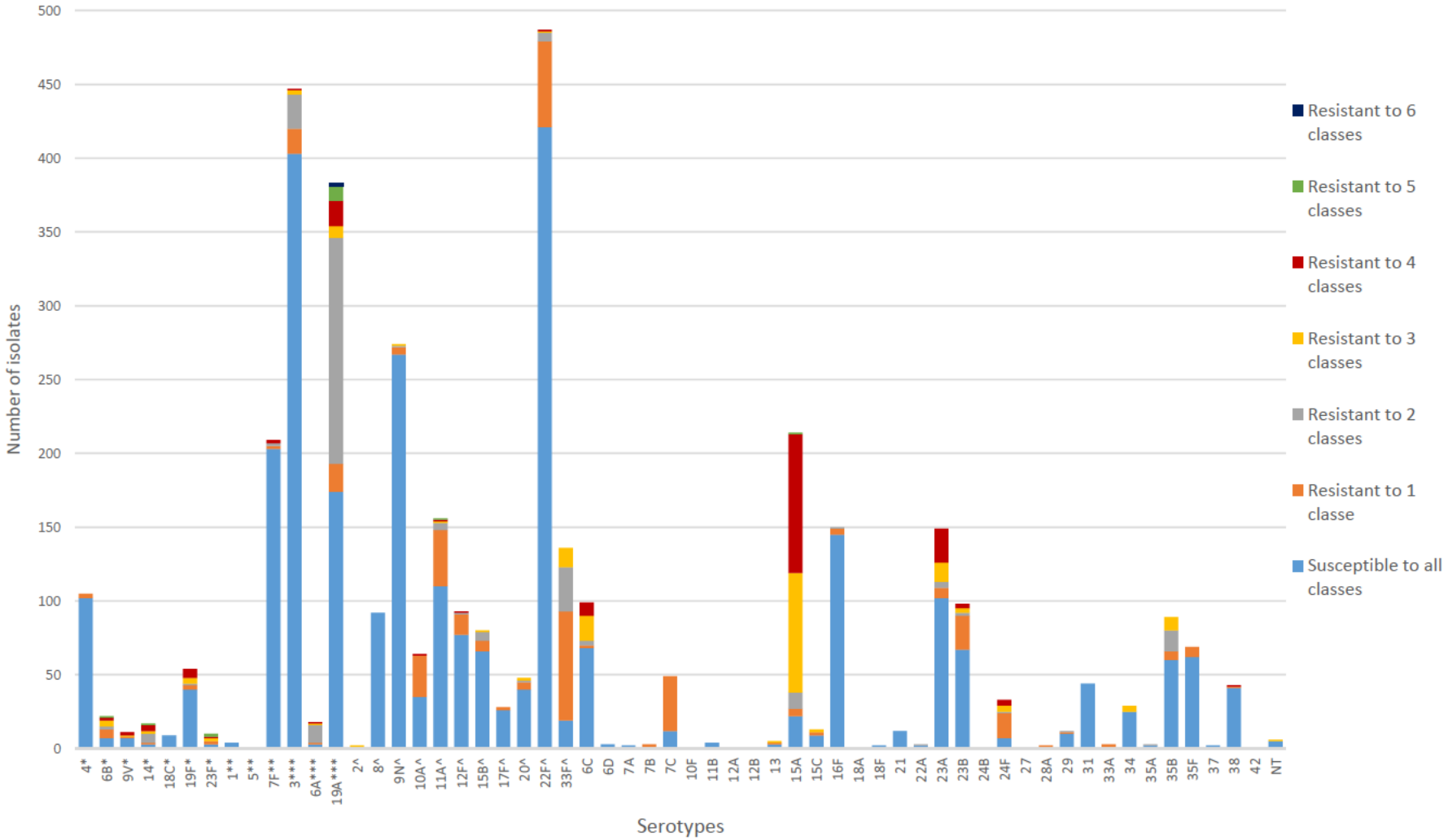
Table 5. Antibiotic susceptibility of *S. pneumoniae* strains susceptible (n=3459) and non-susceptible (n=432) to penicillin G (meningitis breakpoints) in ≥ 5 years old patients between 2014 and 2018

Antibiotics	Strains susceptible to PEN (n=3459)			Strains non-susceptible* to PEN (n=432)		
	S	I	R	S	I	R
Ceftriaxone – meningitis breakpoints	3459 100%	0 0%	0 0.0%	363 84.2%	59 13.7%	9 2.1%
Ceftriaxone – non-meningitis breakpoints	3459 100%	0 0%	0 0.0%	422 97.9%	8 1.9%	1 0.2%
Clindamycin	3196 92.4%	4 0.1%	259 7.5%	143 33.2%	5 1.2%	283 65.7%
Doxycycline†	1944 95.9%	14 0.7%	69 3.4%	83 30.4%	2 0.7%	188 68.9%
Erythromycin	2910 84.1%	5 0.1%	544 15.7%	84 19.5%	1 0.2%	346 80.3%
Levofloxacin	3439 99.4%	7 0.2%	13 0.4%	428 99.3%	0 0%	3 0.7%
TMP-SMX	3203 92.6%	171 4.9%	84 2.4%	295 68.4%	59 13.7%	77 17.9%
Vancomycin	3459 100%	0 0%	0 0%	432 100%	0 0%	0 0%

*Non-susceptible: intermediate and resistant to PEN; S: susceptible; I: intermediate; R: resistant; †Doxycycline is not calculated on the same denominator as the other antibiotics because testing was introduced at the LSPQ in 2016. Hence there are 2027 strains susceptible to PEN and 273 strains resistant to PEN that were tested for doxycycline susceptibility.

The multidrug resistance profiles of the different serotypes is shown in Figure 6. The six most frequently isolated serotypes are described in more details. Serotype 3, 7F and 9N have mainly strains that are susceptible to all classes of antibiotics (403/447, 203/209 and 267/274 strains respectively). Serotype 15A has mainly strains that are resistant to three classes (81/214) or four classes of antibiotics (94/214). Serotype 19A has an almost equal amount of strains that are susceptible to all classes of antibiotics (174/383) and that are resistant to two classes of antibiotics (153/383). It is also important to note that 19A is the only serotype with strains that are resistant to six classes of antibiotics (n=2). Serotype 22F has mainly strains that are susceptible to all classes of antibiotics (421/487), but also several strains that are resistant to one antibiotic class (58/487).

Figure 6. Multiresistance profile of *S. pneumoniae* serotypes between 2014 and 2018 in ≥ 5 years old patients in Quebec



*The antibiotics' classes tested are: β-lactams (penicillin G), cephalosporin (ceftriaxone), glycopeptides (vancomycin), macrolides (erythromycin), fluoroquinolones (levofloxacin), tetracyclines (doxycycline), folate pathway inhibitors (trimethoprim-sulfamethoxazole), lincosamides (clindamycin). The "intermediate" interpretation classification has been considered as "susceptible" in this analysis.

It is important to know the efficiency of the sentinel surveillance to detect certain multiresistance strains to ensure that the profile depicted reflects the reality of the entire province. Efficiency can be estimated by comparing the number of strains detected by the sentinel surveillance to the number of strains detected by the non-sentinel surveillance with the Pfizer research project (Table 6). Between January 2014 and December 2018, the sentinel surveillance program detected between 22.6% and 32.5% of strains depending on their resistance profiles (resistance to 2 classes or more). The complete table is presented in Annex 2.

Table 6. Resistance of *S. pneumoniae* strains in ≥ 5 years old patients detected by the sentinel surveillance (n=1342) and non-sentinel surveillance with the Pfizer research project (N=2850) between 2014 and 2018

Serotypes	Susceptible to all classes			Resistant to 1 class			Resistant to 2 classes			Resistant to 3 classes			Resistant to 4 classes			Resistant to 5 classes			Resistant to 6 classes			Total		
	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%
PCV7-specific serotypes	82	82	50.0%	16	7	30.4%	3	3	50.0%	9	5	35.7%	9	2	18.2%	4	7	63.6%	2	1	33.3%	125	107	46.1%
Additionnal PCV10 serotypes	125	80	39.0%	3	2	40.0%	2	0	0.0%	0	0	0.0%	1	1	50.0%	0	0	0.0%	0	0	0.0%	131	83	38.8%
Additionnal PCV13 serotypes	419	190	31.2%	26	9	25.7%	142	59	29.4%	12	1	7.7%	4	3	42.9%	13	0	0.0%	10	4	28.6%	626	266	29.8%
Additionnal PPV23 serotypes	800	376	32.0%	180	83	31.6%	101	30	22.9%	28	6	17.6%	7	1	12.5%	3	0	0.0%	0	0	0.0%	1120	495	30.7%
NVT	508	249	32.9%	80	39	32.8%	45	18	28.6%	100	33	24.8%	86	45	34.4%	21	5	19.2%	2	0	0.0%	842	389	31.6%
NT	4	1	20.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	1	0	0.0%	7	1	12.5%
Total	1938	978	33.5%	305	140	31.5%	294	110	27.2%	149	45	23.2%	108	52	32.5%	41	12	22.6%	15	5	25.0%	2850	1342	32.0%

* Component of PCV7; ** Component of PCV10; *** Component of PCV13; ^ Component of PPV23; NT: non-typeable strains; †Strains collected by the non-sentinel surveillance system with the Pfizer research project; ‡Samples collected by the sentinel surveillance system

Conclusions

- For the study period, the Pfizer research project allowed to increase the number of *S. pneumoniae* invasives strains detected (provincial: 46% (n=1937); Pfizer: 54% (n=2255)).
- The sentinel network detects 34.5% of all serotypes affecting ≥ 5 years old patients in the province.
- The proportions of vaccine-specific serotypes are significantly different between sentinel and non-sentinel surveillance with Pfizer data (p=0.0003). Hence, the serotype profiles obtained by sentinel surveillance are different from the profiles detected by universal surveillance.
- There is more PCV7-specific serotypes and less of additional PCV13-specific serotypes detected by the sentinel surveillance compared with universal surveillance.
- The total proportion of PCV13-specific serotypes is not different between sentinel (34.0%) and universal surveillance (33.1%).
- The sentinel surveillance did not allow the efficient detection of multiresistant strains depending on their resistance profiles (between 22.6% and 32.5% for resistance to 2 classes or more) in ≥ 5 years old patients.

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Annexes

Annex 1

Age group	Sentinel surveillance						Non-sentinel with Pfizer data						Universal surveillance					
	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%
PCV7-specific serotypes																		
4	0	21	18	25	64	4.8%	0	19	13	9	41	1.6%	0	40	31	34	105	2.7%
6B	0	0	3	4	7	0.5%	0	2	5	8	15	0.6%	0	2	8	12	22	0.6%
9V	0	0	0	1	1	0.1%	0	1	4	5	10	0.4%	0	1	4	6	11	0.3%
14	0	1	1	1	3	0.2%	0	2	2	10	14	0.5%	0	3	3	11	17	0.4%
18C	0	0	3	2	5	0.4%	0	1	3	0	4	0.2%	0	1	6	2	9	0.2%
19F	2	5	4	7	18	1.3%	5	6	11	14	36	1.4%	7	11	15	21	54	1.4%
23F	1	1	2	5	9	0.7%	0	0	1	0	1	0.0%	1	1	3	5	10	0.3%
Total	3	28	31	45	107	8.0%	5	31	39	46	121	4.7%	8	59	70	91	228	5.9%
%	1.3%	12.3%	13.6%	19.7%	46.9%		2.2%	13.6%	17.1%	20.2%	53.1%		3.5%	25.9%	30.7%	39.9%	100.0%	
PCV10-specific serotypes																		
1	0	0	0	0	0	0.0%	0	1	2	1	4	0.2%	0	1	2	1	4	0.1%
5	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%
7F	6	30	31	16	83	6.2%	7	37	44	38	126	4.9%	13	67	75	54	209	5.4%
Total	6	30	31	16	83	6.2%	7	38	46	39	130	5.1%	13	68	77	55	213	5.5%
%	2.8%	14.1%	14.6%	7.5%	39.0%		3.3%	17.8%	21.6%	18.3%	61.0%		6.1%	31.9%	36.2%	25.8%	100.0%	
PCV13-specific serotypes																		
3	5	25	45	77	152	11.3%	7	41	101	146	295	11.6%	12	66	146	223	447	11.5%
6A	0	0	3	3	6	0.4%	0	2	3	7	12	0.5%	0	2	6	10	18	0.5%
19A	6	20	29	53	108	8.0%	11	42	78	144	275	10.8%	17	62	107	197	383	9.8%
Total	11	45	77	133	266	19.8%	18	85	182	297	582	22.8%	29	130	259	430	848	21.8%
%	1.3%	5.3%	9.1%	15.7%	31.4%		2.1%	10.0%	21.5%	35.0%	68.6%		3.4%	15.3%	30.5%	50.7%	100.0%	

Age group	Sentinel surveillance						Non-sentinel with Pfizer data						Universal surveillance					
	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%
PPV23-specific serotypes																		
2	1	0	0	0	1	0.1%	0	0	0	1	1	0.0%	1	0	0	1	2	0.1%
8	2	11	9	6	28	2.1%	0	17	22	25	64	2.5%	2	28	31	31	92	2.4%
9N	2	18	35	36	91	6.8%	1	37	54	91	183	7.2%	3	55	89	127	274	7.0%
10A	2	2	13	10	27	2.0%	0	4	12	21	37	1.4%	2	6	25	31	64	1.6%
11A	0	7	10	31	48	3.6%	1	10	27	70	108	4.2%	1	17	37	101	156	4.0%
12F	0	8	12	16	36	2.7%	0	18	18	21	57	2.2%	0	26	30	37	93	2.4%
15B	2	5	3	21	31	2.3%	3	10	14	22	49	1.9%	5	15	17	43	80	2.1%
17F	0	1	0	4	5	0.4%	2	2	9	10	23	0.9%	2	3	9	14	28	0.7%
20	1	1	7	13	22	1.6%	0	3	15	8	26	1.0%	1	4	22	21	48	1.2%
22F	2	22	49	100	173	12.9%	4	32	89	189	314	12.3%	6	54	138	289	487	12.5%
33F	1	7	9	17	34	2.5%	1	19	26	56	102	4.0%	2	26	35	73	136	3.5%
Total	13	82	147	254	496	37.0%	12	152	286	514	964	37.8%	25	234	433	768	1460	37.5%
%	0.9%	5.6%	10.1%	17.4%	34.0%		0.8%	10.4%	19.6%	35.2%	66.0%		1.7%	16.0%	29.7%	52.6%	100.0%	
Non-vaccine serotypes																		
6C	0	3	7	24	34	2.5%	0	6	14	45	65	2.5%	0	9	21	69	99	2.5%
6D	0	0	1	0	1	0.1%	0	0	0	2	2	0.1%	0	0	1	2	3	0.1%
7A	0	1	0	0	1	0.1%	0	0	0	1	1	0.0%	0	1	0	1	2	0.1%
7B	0	0	1	1	2	0.1%	1	0	0	0	1	0.0%	1	0	1	1	3	0.1%
7C	1	1	4	10	16	1.2%	0	3	5	25	33	1.3%	1	4	9	35	49	1.3%
10F	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%
11B	0	0	1	0	1	0.1%	0	0	1	2	3	0.1%	0	0	2	2	4	0.1%
12A	0	0	0	0	0	0.0%	0	0	1	0	1	0.0%	0	0	1	0	1	0.0%
12B	0	0	1	0	1	0.1%	0	0	0	0	0	0.0%	0	0	1	0	1	0.0%
13	1	1	0	0	2	0.1%	0	0	1	2	3	0.1%	1	1	1	2	5	0.1%
15A	4	5	16	44	69	5.1%	1	12	21	111	145	5.7%	5	17	37	155	214	5.5%
15C	1	0	0	5	6	0.4%	0	0	1	6	7	0.3%	1	0	1	11	13	0.3%

Age group	Sentinel surveillance						Non-sentinel with Pfizer data						Universal surveillance					
	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%	5-19	20-49	50-64	≥ 65	Total	%
Non-vaccine serotypes																		
16F	2	7	11	25	45	3.4%	1	9	20	75	105	4.1%	3	16	31	100	150	3.9%
18A	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%	0	0	0	0	0	0.0%
18F	0	0	0	1	1	0.1%	0	1	0	0	1	0.0%	0	1	0	1	2	0.1%
21	0	1	2	2	5	0.4%	0	4	2	1	7	0.3%	0	5	4	3	12	0.3%
22A	0	1	0	0	1	0.1%	1	0	0	1	2	0.1%	1	1	0	1	3	0.1%
23A	4	4	11	28	47	3.5%	1	8	29	64	102	4.0%	5	12	40	92	149	3.8%
23B	4	5	12	21	42	3.1%	1	7	17	31	56	2.2%	5	12	29	52	98	2.5%
24B	0	0	0	0	0	0.0%	0	0	1	0	1	0.0%	0	0	1	0	1	0.0%
24F	1	3	6	5	15	1.1%	0	3	1	14	18	0.7%	1	6	7	19	33	0.8%
28A	0	1	0	0	1	0.1%	0	0	0	1	1	0.0%	0	1	0	1	2	0.1%
29	0	1	0	3	4	0.3%	0	3	3	2	8	0.3%	0	4	3	5	12	0.3%
31	0	2	3	12	17	1.3%	0	1	5	21	27	1.1%	0	3	8	33	44	1.1%
33A	0	0	0	0	0	0.0%	0	0	1	2	3	0.1%	0	0	1	2	3	0.1%
34	0	1	3	5	9	0.7%	0	6	1	13	20	0.8%	0	7	4	18	29	0.7%
35A	0	1	2	0	3	0.2%	0	0	0	0	0	0.0%	0	1	2	0	3	0.1%
35B	3	1	9	18	31	2.3%	2	6	17	33	58	2.3%	5	7	26	51	89	2.3%
35F	2	3	5	12	22	1.6%	2	6	15	24	47	1.8%	4	9	20	36	69	1.8%
37	0	0	0	1	1	0.1%	0	0	0	1	1	0.0%	0	0	0	2	2	0.1%
38	2	0	3	7	12	0.9%	2	2	6	21	31	1.2%	4	2	9	28	43	1.1%
42	0	0	0	0	0	0.0%	0	0	0	1	1	0.0%	0	0	0	1	1	0.0%
NT	0	0	0	1	1	0.1%	1	1	0	3	5	0.2%	1	1	0	4	6	0.2%
Total	25	42	98	225	390	29.1%	13	78	162	502	755	29.6%	38	120	260	727	1145	29.4%
%	2.2%	3.7%	8.6%	19.7%	34.1%		1.1%	6.8%	14.1%	43.8%	65.9%		3.3%	10.5%	22.7%	63.5%	100.0%	
TOTAL	**58**	**227**	**384**	**673**	**1342**	**34.5%**	**55**	**384**	**715**	**1398**	**2552**	**65.5%**	**113**	**611**	**1099**	**2071**	**3894**	**100.0%**
	4.3%	**16.9%**	**28.6%**	**50.1%**			**2.2%**	**15.0%**	**28.0%**	**54.8%**			**2.9%**	**15.7%**	**28.2%**	**53.2%**		

Annex 2

Serotypes	Susceptible to all classes			Resistant to 1 class			Resistant to 2 classes			Resistant to 3 classes			Resistant to 4 classes			Resistant to 5 classes			Resistant to 6 classes			Total		
	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%
4*	39	62	61.4%	2	2	50.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	41	64	61.0%
6B*	3	2	40.0%	6	1	14.3%	1	1	50.0%	2	2	50.0%	3	0	0.0%	0	1	100.0%	1	0	0.0%	16	7	30.4%
9V*	4	0	0.0%	4	0	0.0%	0	0	0.0%	0	0	0.0%	2	1	33.3%	0	0	0.0%	0	0	0.0%	10	1	9.1%
14*	1	0	0.0%	3	0	0.0%	0	1	100.0%	5	1	16.7%	3	0	0.0%	1	1	50.0%	1	0	0.0%	14	3	17.6%
18C*	4	5	55.6%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	5	55.6%
19F*	29	11	27.5%	1	2	66.7%	2	1	33.3%	2	0	0.0%	1	1	50.0%	3	3	50.0%	0	0	0.0%	38	18	32.1%
23F*	2	2	50.0%	0	2	100.0%	0	0	0.0%	0	2	100.0%	0	0	0.0%	0	2	100.0%	0	1	100.0%	2	9	81.8%
1**	4	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	0	0.0%
7F**	121	80	39.8%	3	2	40.0%	2	0	0.0%	0	0	0.0%	1	1	50.0%	0	0	0.0%	0	0	0.0%	127	83	39.5%
3***	278	137	33.0%	12	2	14.3%	17	12	41.4%	3	0	0.0%	0	1	100.0%	0	0	0.0%	0	0	0.0%	310	152	32.9%
6A***	1	0	0.0%	2	1	33.3%	8	5	38.5%	1	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	13	6	31.6%
19A***	140	53	27.5%	12	6	33.3%	117	42	26.4%	8	1	11.1%	3	2	40.0%	13	0	0.0%	10	4	28.6%	303	108	26.3%
2^	0	1	100.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	0	0.0%
8^	66	27	29.0%	1	1	50.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	67	28	29.5%
9N^	174	83	32.3%	10	8	44.4%	2	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	187	91	32.7%
10A^	38	15	28.3%	25	12	32.4%	0	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	64	27	29.7%
11A^	77	32	29.4%	29	14	32.6%	4	2	33.3%	1	0	0.0%	0	0	0.0%	2	0	0.0%	0	0	0.0%	113	48	29.8%
12F^	46	31	40.3%	9	5	35.7%	1	0	0.0%	0	0	0.0%	2	0	0.0%	0	0	0.0%	0	0	0.0%	58	36	38.3%
15B^	29	13	31.0%	52	15	22.4%	1	0	0.0%	6	3	33.3%	2	0	0.0%	0	0	0.0%	0	0	0.0%	90	31	25.6%
17F^	21	5	19.2%	2	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	23	5	17.9%
20^	24	19	44.2%	4	2	33.3%	0	0	0.0%	1	0	0.0%	1	1	50.0%	0	0	0.0%	0	0	0.0%	30	22	42.3%
22F^	307	148	32.5%	43	23	34.8%	6	2	25.0%	2	0	0.0%	1	0	0.0%	1	0	0.0%	0	0	0.0%	360	173	32.5%
33F^	18	2	10.0%	5	3	37.5%	87	26	23.0%	16	3	15.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	126	34	21.3%
6C	43	25	36.8%	1	0	0.0%	3	2	40.0%	12	5	29.4%	7	2	22.2%	0	0	0.0%	0	0	0.0%	66	34	34.0%
6D	1	1	50.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	1	33.3%
7A	1	1	50.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	50.0%

Serotypes	Susceptible to all classes			Resistant to 1 class			Resistant to 2 classes			Resistant to 3 classes			Resistant to 4 classes			Resistant to 5 classes			Resistant to 6 classes			Total		
	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%
7B	0	1	100.0%	2	1	33.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	50.0%
7C	11	3	21.4%	26	13	33.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	37	16	30.2%
10F	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%
11B	3	1	25.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	1	25.0%
12A	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%
12B	0	1	100.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	1	100.0%
13	4	0	0.0%	0	2	100.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	5	2	28.6%
15A	14	10	41.7%	4	0	0.0%	9	4	30.8%	60	23	27.7%	55	28	33.7%	16	4	20.0%	1	0	0.0%	159	69	30.3%
15C	2	3	60.0%	5	3	37.5%	0	0	0.0%	0	0	0.0%	2	0	0.0%	0	0	0.0%	0	0	0.0%	9	6	40.0%
16F	103	45	30.4%	4	0	0.0%	2	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	109	45	29.2%
18F	1	1	50.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	50.0%
21	15	5	25.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	15	5	25.0%
22A	3	1	25.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	1	20.0%
23A	74	32	30.2%	6	1	14.3%	2	0	0.0%	9	3	25.0%	15	11	42.3%	1	0	0.0%	0	0	0.0%	107	47	30.5%
23B	41	29	41.4%	5	6	54.5%	14	6	30.0%	4	0	0.0%	2	1	33.3%	0	0	0.0%	0	0	0.0%	66	42	38.9%
24B	3	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	0	0.0%
24F	2	6	75.0%	15	6	28.6%	1	1	50.0%	0	0	0.0%	4	1	20.0%	4	1	20.0%	1	0	0.0%	27	15	35.7%
27	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%
28A	2	0	0.0%	0	1	100.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	1	33.3%
29	11	4	26.7%	1	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	13	4	23.5%
31	26	17	39.5%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	27	17	38.6%
33A	0	0	0.0%	0	0	0.0%	3	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	0	0.0%
34	18	8	30.8%	0	0	0.0%	0	0	0.0%	3	1	25.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	21	9	30.0%
35A	0	2	100.0%	0	0	0.0%	0	1	100.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	3	100.0%
35B	44	19	30.2%	1	5	83.3%	9	4	30.8%	11	1	8.3%	0	2	100.0%	0	0	0.0%	0	0	0.0%	65	31	32.3%
35F	44	21	32.3%	6	1	14.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	50	22	30.6%
37	1	1	50.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	50.0%

Serotypes	Susceptible to all classes			Resistant to 1 class			Resistant to 2 classes			Resistant to 3 classes			Resistant to 4 classes			Resistant to 5 classes			Resistant to 6 classes			Total		
	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%	N†	n‡	%
38	37	12	24.5%	1	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	39	12	23.5%
42	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%
NT	4	1	20.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	1	0	0.0%	7	1	12.5%
Total	1938	978	33.5%	305	140	31.5%	294	110	27.2%	149	45	23.2%	108	52	32.5%	41	12	22.6%	15	5	25.0%	2850	1342	32.0%

* Component of PCV7; ** Component of PCV10; *** Component of PCV13; ^ Component of PPV23; NT: non-typeable strains; †Strains collected by the non-sentinel surveillance system with the Pfizer research project; ‡Samples collected by the sentinel surveillance system

References

1. Petit G, Wals PD, Law B, Tam T, Erickson LJ, Guay M, et al. Epidemiological and economic burden of pneumococcal diseases in Canadian children. 2003;14(4):6.

2. Streptococcus and STI Unit, National Microbiology Laboratory, Public Health Agency of Canada, Demczuk WHB, Griffith A, Singh R, et al. National Laboratory Surveillance of Invasive Streptococcal Disease in Canada - Annual Summary 2016. 2017.

3. Comité sur l'immunisation du Québec, De Wals P. Évaluation de la pertinence d'un programme d'immunisation contre les infections pneumococciques chez l'enfant comportant un nombre réduit de doses de vaccin conjugué: avis [Internet]. Montréal: Institut national de santé publique; 2005 [cité 16 août 2019]. Disponible sur: https://www.inspq.qc.ca/pdf/publications/344-PneumococciquesEnfantVaccin_EditionRevisee.pdf

4. Comité sur l'immunisation du Québec, De Wals P, Boulianne N, Deceuninck G, Déry P, Guay M, et al. Évaluation de la pertinence d'un nouveau vaccin antipneumococcique conjugué au Québec: rapport [Internet]. Québec: Direction des risques biologiques, environnementaux et occupationnels, Institut national de santé publique Québec; 2009 [cité 16 août 2019]. Disponible sur: https://www.inspq.qc.ca/pdf/publications/933_EvalVaccAntipneumo.pdf

5. Comité sur l'immunisation du Québec, De Wals P. Évaluation de deux nouveaux vaccins pneumococciques conjugués pour l'immunisation des enfants au Québec [Internet]. Montréal, Qué.: Institut national de santé publique du Québec; 2010 [cité 16 août 2019]. Disponible sur: https://www.inspq.qc.ca/pdf/publications/1172_Eval2VaccinsPneumocoConjuguesImmuEnfants.pdf

6. Comité sur l'immunisation du Québec, De Wals P. Utilisation des vaccins pneumococciques conjugués 10- et 13-valent dans les différents groupes d'âge [Internet]. Institut national de santé publique; 2018. Disponible sur: https://www.inspq.qc.ca/sites/default/files/publications/2389_utlisation_vaccins_pneumococciques_10_13_valent.pdf

7. De Wals P, Lefebvre B, Deceuninck G, Longtin J. Incidence of invasive pneumococcal disease before and during an era of use of three different pneumococcal conjugate vaccines in Quebec. Vaccine. 2018;36(3):421‑6.

8. Zhou Z, Deceuninck G, Lefebvre B, De Wals P. Forecasting Trends in Invasive Pneumococcal Disease among Elderly Adults in Quebec. Can J Infect Dis Med Microbiol. 2017;1‑7.

9. Douville-Fradet M, Amini R, Ouakki M, Deceuninck G, Boulianne N, Lefebvre B, et al. Impact du programme d'immunisation contre les maladies invasives à pneumocoque au Québec, 2010-2014: rapport [Internet]. 2017 [cité 26 juill 2019]. Disponible sur: https://www.inspq.qc.ca/sites/default/files/publications/2348_impact_immunisation_maladies_invasives_pneumocoque.pdf

10. CLSI. M100 Performance standards for antimicrobial susceptibility testing. 29th Ed. Informational supplement. Pennsylvania: Wayne; 2019.

11. Ministère de la Santé et des Services sociaux. Estimations et projections de population comparables [Internet]. 2016 [cité 19 août 2019]. Disponible sur: http://publications.msss.gouv.qc.ca/msss/document-001617/

12. Lefebvre B. Programme de surveillance du pneumocoque [Internet]. Rapport 2017. 2019 [cité 26 juill 2019]. Disponible sur: https://www.inspq.qc.ca/sites/default/files/publications/2538_programme_surveillance_pneumocoque_2017.pdf

13. Ancelle T. Utilisation pratique des tests statistiques. In: Statistique Épidémiologique. 4th edition. Paris, France: Maloine Editions; 2017. p. 132‑3. (Sciences fondamentales).

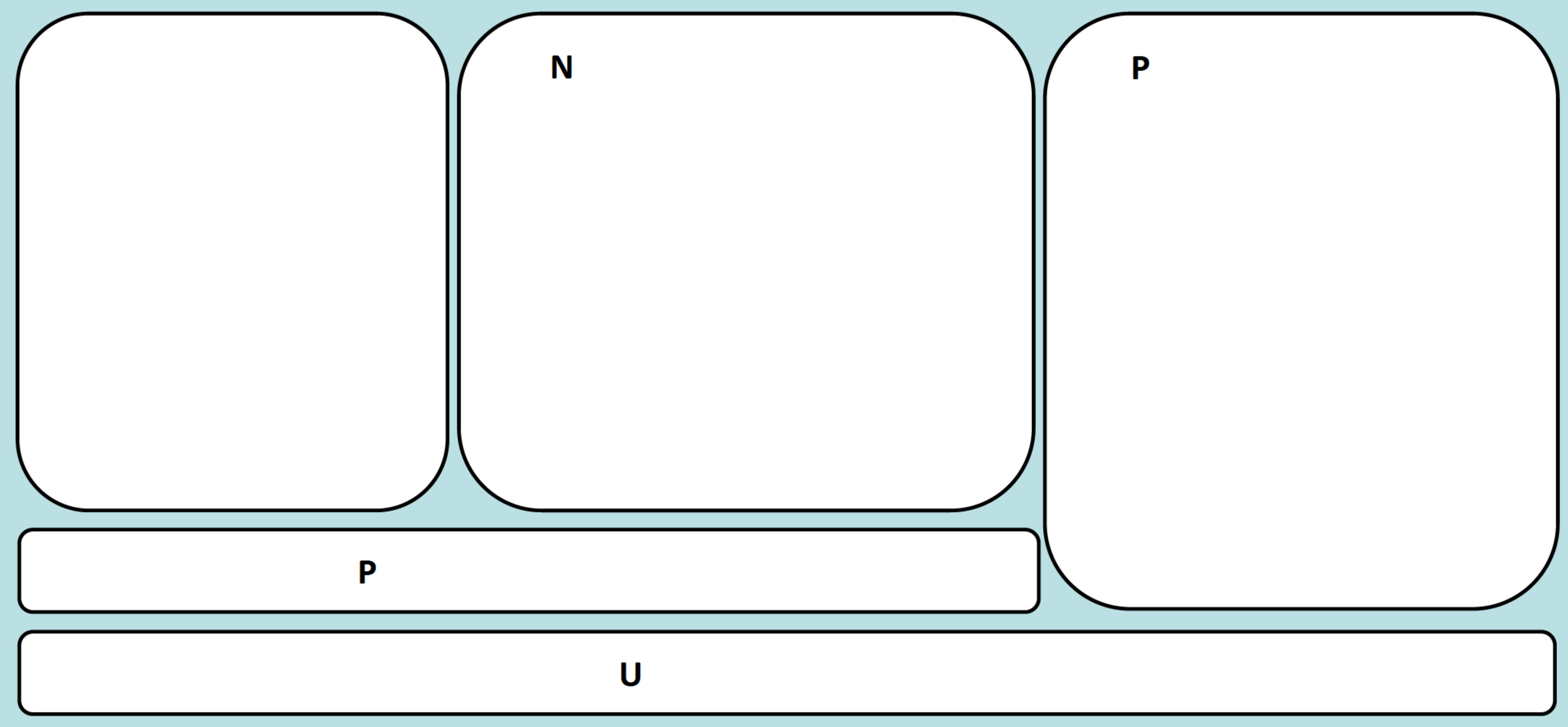
14. Bisson É. Surveillance des maladies à déclaration obligatoire au Québec: guide de saisie des données du registre central des maladies à déclaration obligatoire [Internet]. Québec: Bureau de surveillance épidémiologique; 2004 [cité 18 sept 2019]. Disponible sur: http://publications.msss.gouv.qc.ca/msss/fichiers/preventioncontrole/04-268-02W.pdf

SEROTYPE DISTRIBUTION OF INVASIVE STREPTOCOCCUS PNEUMONIAE STRAINS IN ≥ 5 YEARS OLD IN QUÉBEC, 2014-2018

D Page G Deceun nck P De Wals ( ) B e bv e *
n t tu nat o al de an é pub i ue du Qué ec abo a oi e de an é ub i ue du Québ c ai t Ann -d -Be ev e C nada Ce t e e e he che du ent e ho p ta e un ve i ai e de Qu bec QC C nada ns i ut n t on l de s nté p b iq e du Québec Di ct on d s sq es b o og ques t de a san é au t a a l Québec C nada

Background

T e Quebec pneumococ al su ei ance p og am is b sed on a s nt nel ne wo k o 20 hosp ta s ncl ding p diat c ho pi a s who send ll thei nva i e *S p eum niae* t ains to t e abo atoi e de anté p bl que u Québec (SPQ) St a ns om < 5 ea s o d p t ents and hose w th a peni i in m nimum nh bi o y co cent at on (MIC) ≥ 0 12 mg we e lso ubm ted by non sen inel ho pi a s Between anua y 2 14 a d Dec mbe 20 8 the p og am was modi ed to imp o e mon to ing o se ot pes Du ing his pe iod ll nvas ve *S pneumon ae* t ains we e eque ted to be send to he SPQ

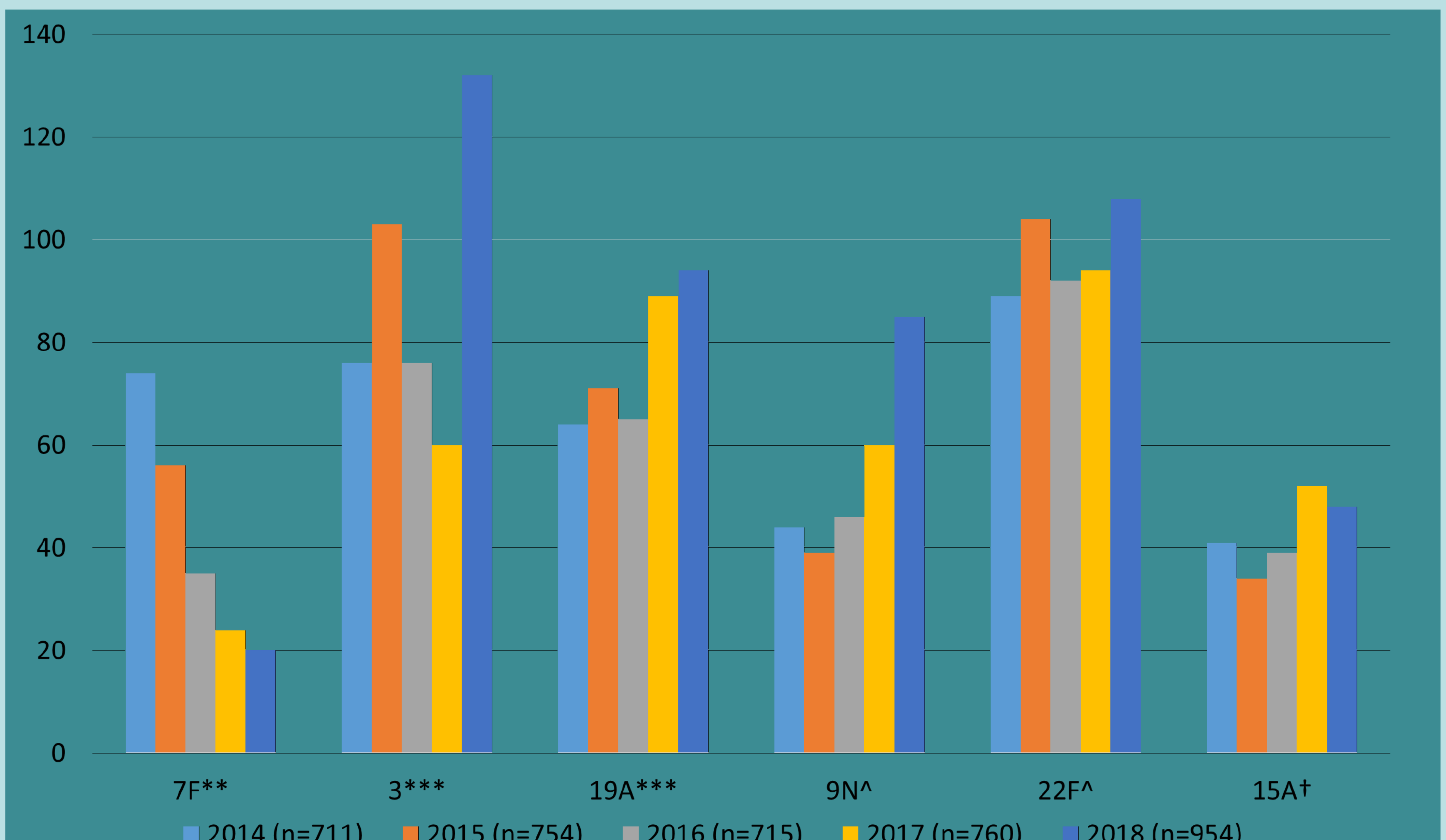


gu e 1 PD labo a o y su ve l ance co duct d n Qu bec between 2014 and 2018

Methods

A t tal o 3894 so ates o *S pne mon ae* st a ns om no ma y s e e c i ic l i es i ola ed om pa ie ts ≥ 5 yea s old between anua y 014 and Decembe 2018 we e ana yz d M l ip e i ola es co le ted w th n 14 days om he s me pat ent w th iden cal se o ypes we e coun ed once (1 t ain pat ent 14 d ys) Se o yp ng was done wi h the Quel ung ea t on si g a t se a om ta ens Se um In t tut (S I) e o yp ng was suc ess ul y done on 888 st ai s

Results



igu e 2 Di t bu ion o *S pn um niae* most equent e o ypes n ≥ 5 yea s o d o he 2 14- 2 18 e od
V V V V N

able 1 D st i ut on o *S pneumon ae* e o ypes in ≥ 5 y a s o d o the 2 14-2 18 pe od

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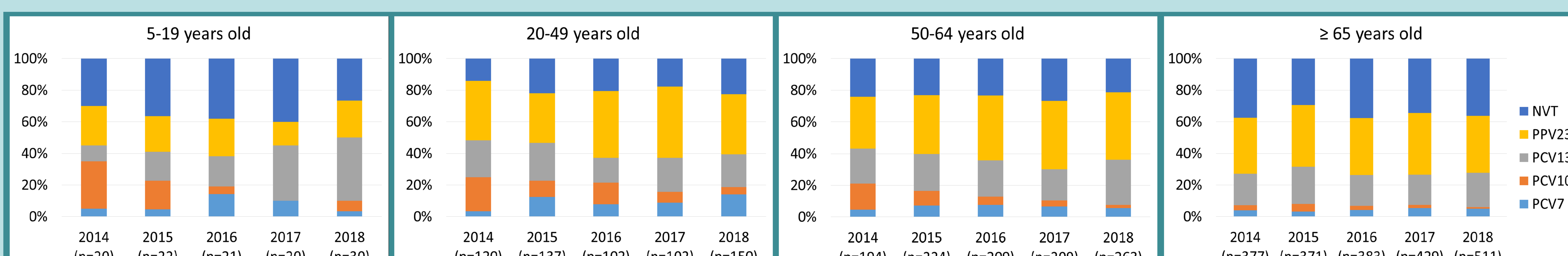

igu e 3 Di t ibu ion o *S pneumon ae* se types by a e g oup

Summary

n 014-2 18 the m st equent se ot pes we e 2 n 487 12 7%) 3 (n 447 11 0%) 19A n 383 9 8%) 9N (n 74 6 6%) 15A n 214 5 4%) a d 7 n 209 5 0%) Changes in acc ne- peci c se otype p o o t ons be we n 20 4 and 2018 we e s at st ca y ig i ic nt in a e g oups 5 19 yo (p 0 0159) 20- 9 yo p 0 000011) and 0-64 yo (p 0 0 0000014) Add t onal PCV10 e o ypes n age g oups 5-19 20 49 and 50 64 yo ec e sed wh le a di ion l CV13 se ot pes in 5-19 yo PCV7 speci c se o ypes and non-v cc ne e o ypes NVT) in 20 49 yo as w ll as ddi ion l PPV23 in 50 64 yo nc eas d

Conclusion

When co si e ng a l ge g oups mo t ases dete ted b long d to P V13 PPV23 and NVT The magn tu e o IPD educ i n due o PCV nt oduc i n va ies be we n count es ence ont nued su ei l nce s n ces a y to obse ve cha ges in se ot pe d st but on (2) The d st but on o vacc ne spe i ic e o ypes was va iab e be w en age g oups Due o e ent modi ca ion o va c ne ca enda in hi d en e tend d u ve lan e o i cu at ng se otypes s impo tant o ma nta n

References

1 De W ls P e ebv e B Ma kowski D ceun nck G De ay Dou i l - adet M t l mpact o 2 1 pneumoco cal con uga e va c ne p og am n the p o in e o Qu bec C nada V cc ne 2014 32 13) 150 -6
2 ei in DR aguc a EW oo JD nk Gel es R Puhan MA Che ian T et al Se o ype- peci c Changes n nv si e neum cocc l Di ease a te Pn umo occa Conju ate Va ci e nt oduc ion A Poo ed Ana ys s o Mu t ple Su ei ance i es V boud C éd t u P oS Med 20 3 1 (9) e10 1517

Acknowledgments

his wo k was a ia y uppo ed by P ze C nada A spe ial hanks o ll he cl n cal abo ato es o he p ov nce as we l s he SPQ nd NM

Institut national de santé publique
Québec
Laboratoire de santé publique du Québec

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SEROTYPE DISTRIBUTION OF INVASIVE *STREPTOCOCCUS PNEUMONIAE* STRAINS IN ≥ 5 YEARS OLD IN QUÉBEC, 2014-2018

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Background
In the province of Quebec, in a context of 13-valent pneumococcal conjugate vaccine (PCV13) use in children, all strains isolated in ≥ 5 yo patients with invasive pneumococcal disease (IPD) in 2014-2018 were requested to be sent to the LSPQ.

Methods
A total of 3894 strains were received and serotyped by Quellung reaction.

Results
The overall IPD rate was 10.0/100,000 person-years. Most frequent serotypes were 22F (n=487;12.5%), 3 (n=447;11.5%), 19A (n=383;9.8%), 9N (n=274;7.0%), 15A (n=214;5.5%) and 7F (n=209;5.4%). Over the period, serotype 7F decreased (from 10.4% to 2.1%) while proportions of serotype 3, 19A and non-vaccine serotypes remained stable (11.5%, 9.8% and 29.4% respectively). In the ≥ 65 yo group, IPD rate was 28.0/100 000 p.-y. In this age group, PCV13-serotypes represented 27.8% of cases and serotypes covered by the 23-valent pneumococcal polysaccharide (PPV23) vaccine (additional serotypes) represented 37.1% of cases.

Conclusions
Although PPV23 is offered to individuals ≥ 65 yo with 53% uptake (one dose), the proportion of serotypes included in this vaccine remains high. Trends in serotypes 3 and 19A will have to be monitored following the transition to the 10-valent vaccine for children in 2018.

Acknowledgments
This work was partially supported by Pfizer Canada.

Word count: 198/200

Abstract Topic: **B2. Disease Burden in Infants, Children/Youth, and Adults**

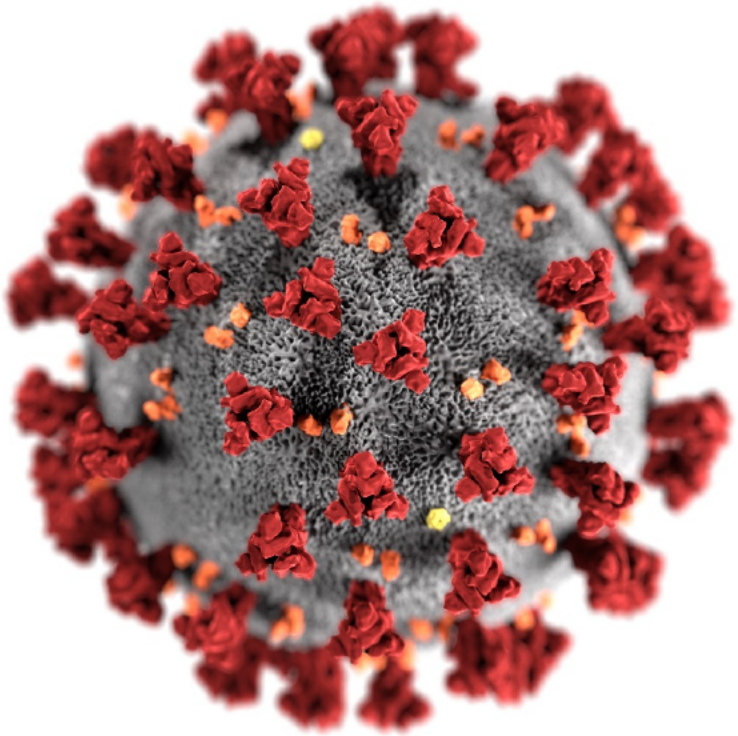
Keywords: serotype, surveillance, sentinel

COVID 19
CORONAVIRUS DISEASE

What Clinicians Need to Know About the Pfizer-BioNTech COVID-19 Vaccine

[redacted]

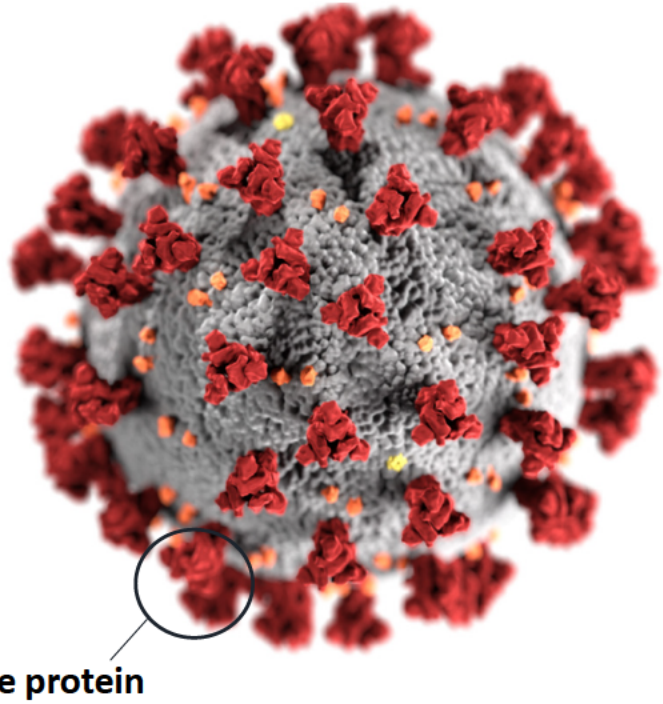
December 13, 2020



Pfizer-BioNTech COVID-19 Vaccine

Pfizer-BioNTech COVID-19 vaccine

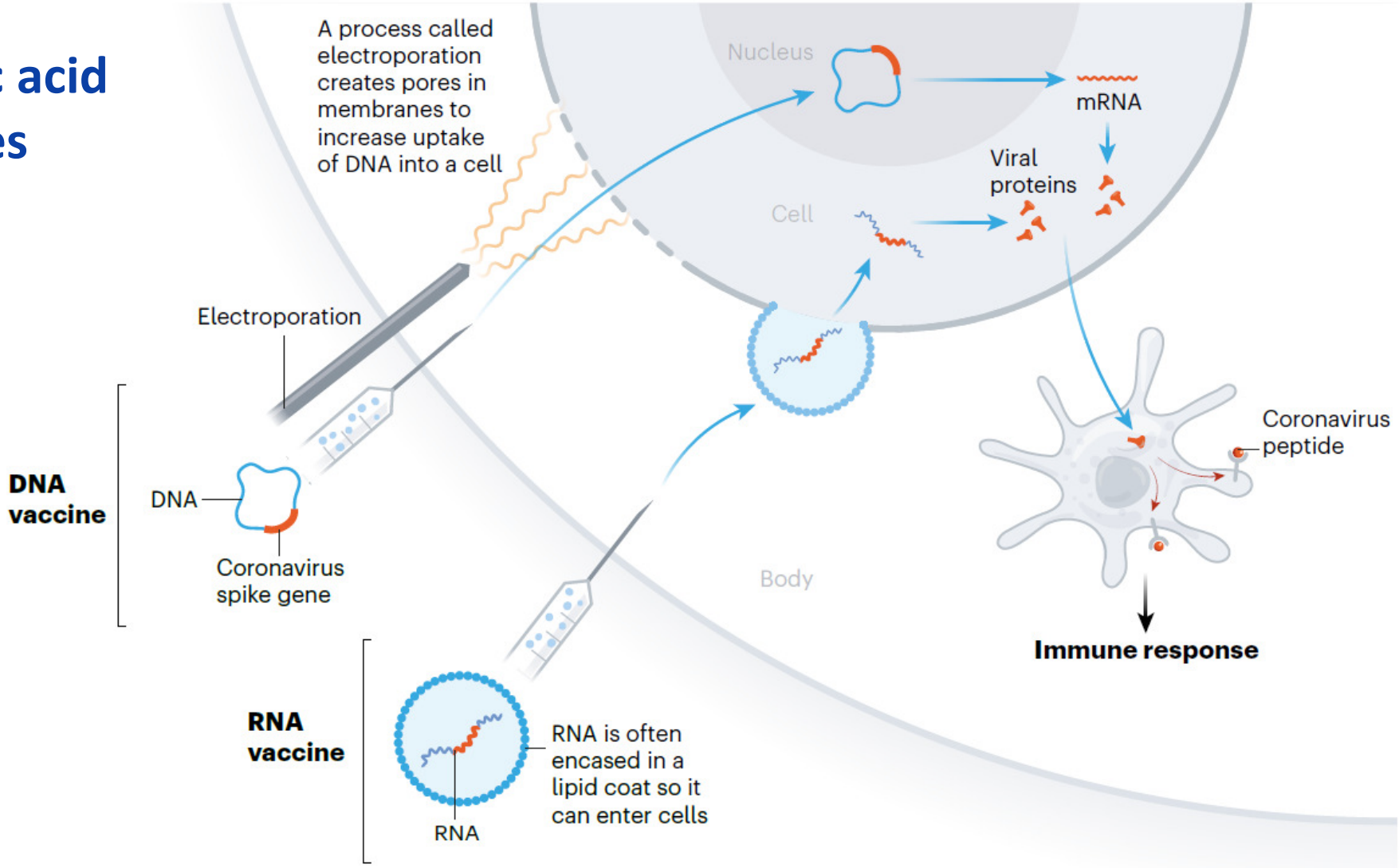
- Lipid nanoparticle-formulated mRNA vaccine encoding the spike protein
  - Spike protein: facilitates entry of virus into cells
- Vaccination induces antibodies that can block entry of SARS-CoV-2 into cells, thereby preventing infection
- FDA issued an Emergency Use Authorization on December 13, 2020 for use in persons aged ≥16 years



Explaining mRNA COVID-19 vaccines

- mRNA vaccines take advantage of the process that cells use to make proteins in order to trigger an immune response
  - Like all vaccines, COVID-19 mRNA vaccines have been **rigorously tested** for safety before being authorized for use in the United States
  - mRNA technology is **new, but not unknown**. They have been studied for more than a decade
  - mRNA vaccines **do not contain a live virus** and do not carry a risk of causing disease in the vaccinated person
  - mRNA from the vaccine never enters the nucleus of the cell and **does not affect or interact with a person's DNA**

Nucleic acid vaccines



Nature. Vol 580. April 30, 2020. https://media.nature.com/original/magazine-assets/d41586-020-01221-y/d41586-020-01221-y.pdf

Advisory Committee on Immunization Practices (ACIP) Recommendations

ACIP recommendations for use of COVID-19 vaccines

- On December 12, 2020, ACIP recommended use of the Pfizer-BioNTech COVID-19 vaccine in persons 16 years of age and older under the FDA's Emergency Use Authorization

- ACIP recommends that when a COVID-19 vaccine is authorized by FDA and recommended by ACIP, that 1) health care personnel and 2) residents of long-term care facilities be offered vaccination in the initial phase of the COVID-19 vaccination program

Vaccine Administration

Administration

- 2-dose series administered intramuscularly 3 weeks apart
- Administration of 2nd dose within 4-day grace period (e.g., day 17-21) considered valid
- If >21 days since 1st dose, 2nd dose should be administered at earliest opportunity (but no doses need to be repeated)
- Both doses are necessary for protection; efficacy of a single dose has not been systematically evaluated

Interchangeability with other COVID-19 vaccine products

- Pfizer-BioNTech COVID-19 vaccine not interchangeable with other COVID-19 vaccine products
  - Safety and efficacy of a mixed series has not been evaluated
- Persons initiating series with Pfizer-BioNTech COVID-19 vaccine should complete series with same product
- If two doses of different mRNA COVID-19 vaccine products inadvertently administered, no additional doses of either vaccine recommended at this time
  - Recommendations may be updated as further information becomes available or additional vaccine types authorized

Coadministration with other vaccines

- Pfizer-BioNTech COVID-19 vaccine should be administered alone with a minimum interval of 14 days before or after administration with any other vaccines
  - Due to lack of data on safety and efficacy of the vaccine administered simultaneously with other vaccines

- If Pfizer-BioNTech COVID-19 vaccine is inadvertently administered within 14 days of another vaccine, doses do not need to be repeated for either vaccine

Vaccination of Persons with Prior SARS-CoV-2 Infection or Exposure

Persons with a history of SARS-CoV-2 infection

- Vaccination should be offered to persons regardless of history of prior symptomatic or asymptomatic SARS-CoV-2 infection
  - Data from phase 2/3 clinical trials suggest vaccination safe and likely efficacious in these persons

- Viral or serologic testing for acute or prior infection, respectively, is not recommended for the purpose of vaccine decision-making

Persons with known current SARS-CoV-2 infection

- Vaccination should be deferred until recovery from acute illness (if person had symptoms) *and* criteria have been met to discontinue isolation

- No minimal interval between infection and vaccination

- However, current evidence suggests reinfection uncommon in the 90 days after initial infection, and thus persons with documented acute infection in the preceding 90 days may defer vaccination until the end of this period, if desired

https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html
https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html

Persons who previously received passive antibody therapy for COVID-19

- Currently no data on safety or efficacy of COVID-19 vaccination in persons who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment

- Vaccination should be deferred for at least 90 days to avoid interference of the treatment with vaccine-induced immune responses
  - Based on estimated half-life of therapies and evidence suggesting reinfection is uncommon within 90 days of initial infection

Persons with a known SARS-CoV-2 exposure

- **Community or outpatient setting:**
  - Defer vaccination until quarantine period has ended to avoid exposing healthcare personnel (HCP) or other persons during vaccination visit

- **Residents of congregate healthcare settings (e.g., long-term care facilities):**
  - May be vaccinated, as likely would not result in additional exposures. HCP are already in close contact with residents and should employ appropriate infection prevention and control procedures

- **Residents of other congregate settings (e.g., correctional facilities, homeless shelters)**
  - May be vaccinated, in order to avoid delays and missed opportunities for vaccination
  - Where feasible, precautions should be taken to limit mixing of these individuals with other residents or non-essential staff

https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html
https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html

Vaccination of Special Populations

Persons with underlying medical conditions

- Vaccine may be administered to persons with underlying medical conditions who have no contraindications to vaccination

- Phase 2/3 clinical trials demonstrate similar safety and efficacy profiles in persons with underlying medical conditions, including those that place them at increased risk for severe COVID-19, compared to persons without comorbidities

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Immunocompromised persons

- Persons with HIV infection, other immunocompromising conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19

- Data not currently available to establish safety and efficacy of vaccine in these groups

- These individuals may still receive COVID-19 vaccine unless otherwise contraindicated

- Individuals should be counseled about:
  - Unknown vaccine safety and efficacy profiles in immunocompromised persons
  - Potential for reduced immune responses
  - Need to continue to follow all current guidance to protect themselves against COVID-19

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Pregnant women

- There are no data on the safety of COVID-19 vaccines in pregnant women
  - Animal developmental and reproductive toxicity (DART) studies are ongoing
  - Studies in humans are ongoing and more planned

- mRNA vaccines and pregnancy
  - Not live vaccines
  - They are degraded quickly by normal cellular processes and don't enter the nucleus of the cell

- COVID-19 and pregnancy
  - Increased risk of severe illness (ICU admission, mechanical ventilation and death)
  - Might be an increased risk of adverse pregnancy outcomes, such as preterm birth

- If a woman is part of a group (e.g., healthcare personnel) who is recommended to receive a COVID-19 vaccine and is pregnant, she may choose to be vaccinated. A discussion with her healthcare provider can help her make an informed decision.

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancy-breastfeeding.html

Pregnant women

- Considerations for vaccination:
  - level of COVID-19 community transmission (risk of acquisition)
  - her personal risk of contracting COVID-19 (by occupation or other activities)
  - the risks of COVID-19 to her and potential risks to the fetus
  - the efficacy of the vaccine
  - the known side effects of the vaccine
  - the lack of data about the vaccine during pregnancy

- Pregnant women who experience fever following vaccination should be counseled to take acetaminophen as fever has been associated with adverse pregnancy outcomes

- Routine testing for pregnancy prior to receipt of a COVID-19 vaccine is not recommended.

Breastfeeding/Lactating women

- There are no data on the safety of COVID-19 vaccines in lactating women or the effects of mRNA vaccines on the breastfed infant or milk production/excretion

- mRNA vaccines are not considered live virus vaccines and are not thought to be a risk to the breastfeeding infant

- If a lactating woman is part of a group (e.g., healthcare personnel) who is recommended to receive a COVID-19 vaccine, she may choose to be vaccinated

Patient Vaccine Counseling

Reactogenicity

- Before vaccination, providers should counsel vaccine recipients about expected local and systemic post-vaccination symptoms

- Unless a person develops a contraindication to vaccination, they should be encouraged to complete the series even if they develop post-vaccination symptoms in order to optimize protection against COVID-19

- Antipyretic or analgesic medications may be taken for treatment of post-vaccination symptoms
  - Routine prophylaxis for the purposes of preventing symptoms is not recommended at this time, due to lack of information on impact of use on vaccine-induced antibody responses

Vaccine efficacy

- Two doses required to achieve high efficacy
  - Efficacy after 2nd dose: 95.0% (95% CI: 90.3%, 97.6%)

- Patients should be counseled on importance of completing the 2-dose series in order to optimize protection

Public health recommendations for vaccinated persons

- Protection from vaccine is not immediate; vaccine is a 2-dose series and will take 1 to 2 weeks following the second dose to be considered fully vaccinated

- No vaccine is 100% effective

- Given the currently limited information on how well the vaccine works in the general population; how much it may reduce disease, severity, or transmission; and how long protection lasts, vaccinated persons should continue to follow all current guidance to protect themselves and others, including:
  - Wearing a mask
  - Staying at least 6 feet away from others
  - Avoiding crowds
  - Washing hands often
  - Following CDC travel guidance
  - Following quarantine guidance after an exposure to someone with COVID-19
  - Following any applicable workplace or school guidance

https://www.cdc.gov/coronavirus/2019-ncov/index.html

Contraindications and Precautions

Contraindications and precautions

- Package insert:
  - Severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 vaccine is a contraindication to vaccination
  - Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of the vaccine

- Because of reports of anaphylactic reactions in persons vaccinated outside of clinical trials, the additional following guidance is proposed:
  - A severe allergic reaction to any vaccine or injectable therapy (intramuscular, intravenous, or subcutaneous) is a precaution to vaccination at this time
  - Vaccine providers should observe patients after vaccination to monitor for the occurrence of immediate adverse reactions:
    - Persons with a history of anaphylaxis: 30 minutes
    - All other persons: 15 mins

Algorithm for the triage of persons presenting for Pfizer-COVID-19 vaccine

	PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
CONDITIONS	**CONDITIONS** •Immunocompromising conditions •Pregnancy •Lactation **ACTIONS** •Additional counseling* •15-minute observation period	**CONDITIONS** •Moderate/severe acute illness **ACTIONS** •Risk assessment •Potential deferral of vaccination •15-minute observation period if vaccinated	**CONDITIONS** •None **ACTIONS** •N/A
ALLERGIES	**ALLERGIES** •History of food, pet, insect, venom, environmental, latex, etc., allergies •History of allergy to oral medications (including the oral equivalent of an injectable medication) •Non-serious allergy to vaccines or other injectables (e.g., no anaphylaxis) •Family history of anaphylaxis **ACTIONS** •15-minute observation period	**ALLERGIES** •History of severe allergic reaction (e.g., anaphylaxis) to another vaccine (not including Pfizer-BioNTech vaccine) •History of severe allergic reaction (e.g., anaphylaxis) to an injectable medication **ACTIONS:** •Risk assessment •Potential deferral of vaccination •30-minute observation period if vaccinated	**ALLERGIES** •History of severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech vaccine **ACTIONS** •Do not vaccinate

* See Special Populations section for information on patient counseling in these group

Interpretation of SARS-CoV-2 Test Results in Vaccinated Persons

SARS-CoV-2 tests

- **Viral tests:** Prior receipt of the Pfizer-BioNTech COVID-19 vaccine will not affect the results of SARS-CoV-2 nucleic acid amplification or antigen tests

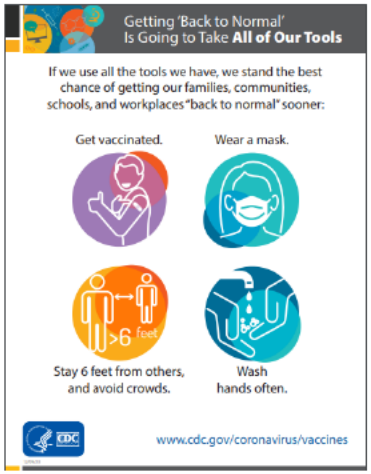
- **Antibody tests:**
  - Currently available antibody tests for SARS-CoV-2 assess IgM and/or IgG to spike or nucleocapsid proteins
  - Pfizer-BioNTech COVID-19 vaccine contains mRNA that encodes the spike protein; thus, a positive test for spike protein IgM/IgG could indicate either prior infection or vaccination
  - To evaluate for evidence of prior infection in an individual with a history of Pfizer-BioNTech COVID-19 vaccination, a test specifically evaluating IgM/IgG to the nucleocapsid protein should be used

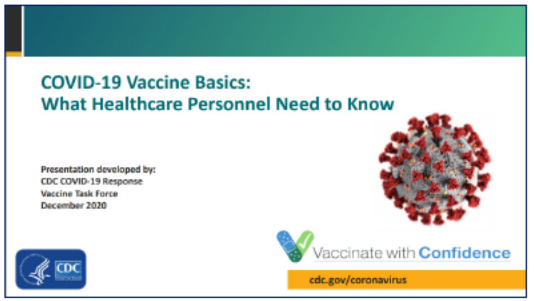
https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance

Clinical Resources

COVID-19 vaccine communication resources

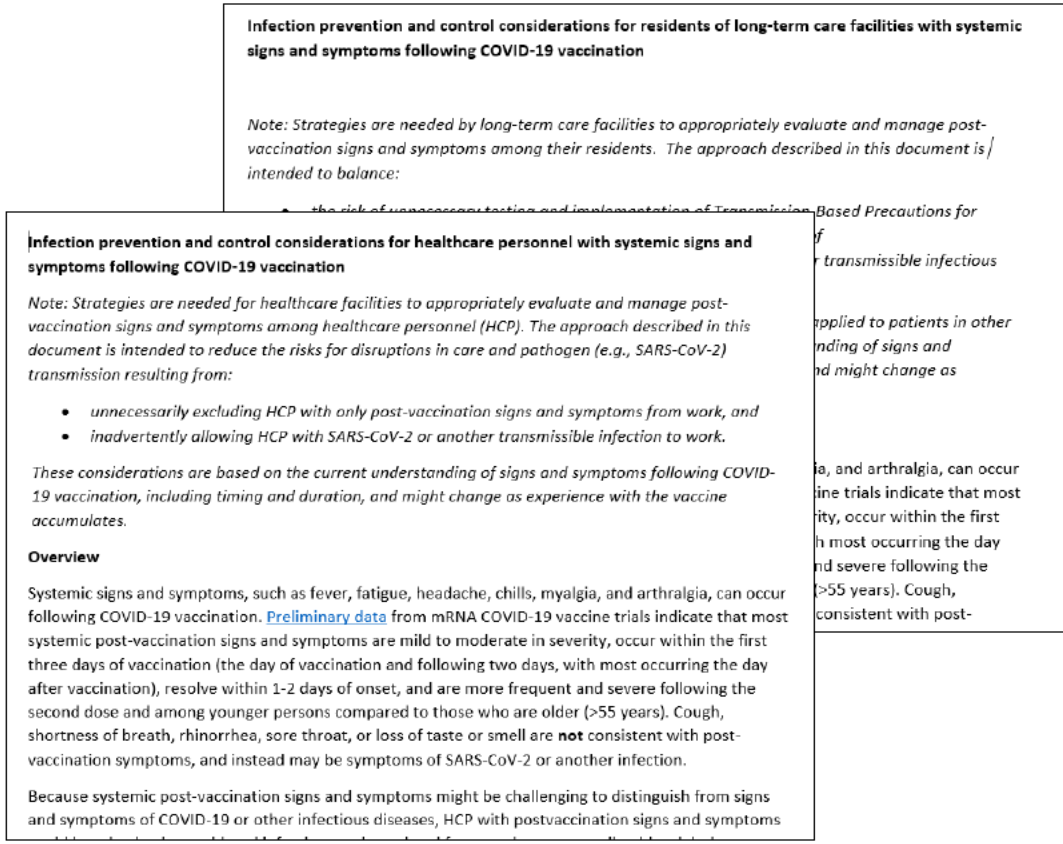
- Engaging in Effective COVID-19 Vaccine Conversations
  - https://www.cdc.gov/vaccines/covid-19/hcp/engaging-patients.htm
- Toolkit for Medical Centers, Clinics, and Clinicians
  - https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html
- More toolkits coming soon
  - Long-term care facilities
  - Health departments
  - Community-based organizations
  - Employers of essential workers





Infection prevention and control recommendations for persons with post-vaccination symptoms

- Healthcare personnel
- Long-term care facility residents



Infection prevention and control considerations for residents of long-term care facilities with systemic signs and symptoms following COVID-19 vaccination

Note: Strategies are needed by long-term care facilities to appropriately evaluate and manage post-vaccination signs and symptoms among their residents. The approach described in this document is intended to balance:

Infection prevention and control considerations for healthcare personnel with systemic signs and symptoms following COVID-19 vaccination

Note: Strategies are needed for healthcare facilities to appropriately evaluate and manage post-vaccination signs and symptoms among healthcare personnel (HCP). The approach described in this document is intended to reduce the risks for disruptions in care and pathogen (e.g., SARS-CoV-2) transmission resulting from:

- *unnecessarily excluding HCP with only post-vaccination signs and symptoms from work, and*
- *inadvertently allowing HCP with SARS-CoV-2 or another transmissible infection to work.*

These considerations are based on the current understanding of signs and symptoms following COVID-19 vaccination, including timing and duration, and might change as experience with the vaccine accumulates.

Overview

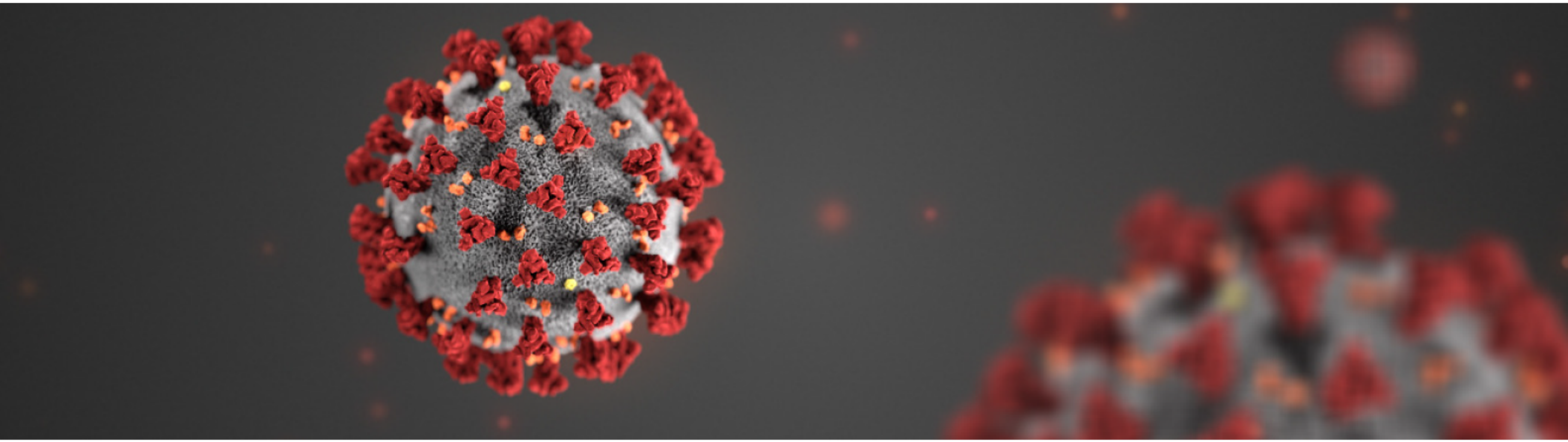
Systemic signs and symptoms, such as fever, fatigue, headache, chills, myalgia, and arthralgia, can occur following COVID-19 vaccination. Preliminary data from mRNA COVID-19 vaccine trials indicate that most systemic post-vaccination signs and symptoms are mild to moderate in severity, occur within the first three days of vaccination (the day of vaccination and following two days, with most occurring the day after vaccination), resolve within 1-2 days of onset, and are more frequent and severe following the second dose and among younger persons compared to those who are older (>55 years). Cough, shortness of breath, rhinorrhea, sore throat, or loss of taste or smell are **not** consistent with post-vaccination symptoms, and instead may be symptoms of SARS-CoV-2 or another infection.

Because systemic post-vaccination signs and symptoms might be challenging to distinguish from signs and symptoms of COVID-19 or other infectious diseases, HCP with postvaccination signs and symptoms

https://www.cdc.gov/vaccines/covid-19/index.html

FDA EUA resources

- FDA COVID-19 EUA
  - https://www.fda.gov/media/144412/download
- FDA COVID-19 Information
  - https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19
- FDA EUA Guidance
  - https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covid19euas



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Vaccines and Related Biological Products Advisory Committee Meeting
December 17, 2020

FDA Briefing Document

Moderna COVID-19 Vaccine

Sponsor:
ModernaTX, Inc.

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Glossary

AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ARDS	acute respiratory distress syndrome
CBRN	chemical, biological, radiological, or nuclear
CDC	Centers for Disease Control and Prevention
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
hACE2	human angiotensin converting enzyme 2
HHS	Health and Human Services
HIV	human immunodeficiency virus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern respiratory syndrome
mRNA	messenger RNA
NAAT	nucleic acid amplification-based test
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. Executive Summary

On November 30, 2020, ModernaTX (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational COVID-19 vaccine (mRNA-1273) intended to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine is based on the SARS-CoV-2 spike glycoprotein (S) antigen encoded by RNA and formulated in lipid nanoparticles (LNPs). The proposed use under an EUA is for active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is 2 doses, 100 µg each, administered 1 month apart.

The EUA request includes safety and efficacy data from an ongoing Phase 3 randomized, double-blinded and placebo-controlled trial of mRNA-1273 in approximately 30,400 participants. The primary efficacy endpoint is the reduction of incidence of COVID-19 among participants without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days post-dose 2. In an interim analysis conducted using a data cutoff of November 7, 2020, a total of 27,817 participants randomized 1:1 to vaccine or placebo with a median 7 weeks of follow-up post-dose 2 were included in the per-protocol efficacy analysis population of participants without evidence of SARS-CoV-2 infection prior to vaccination. Efficacy in preventing confirmed COVID-19 occurring at least 14 days after the second dose of vaccine was 94.5.0% (95% CI 86.5%, 97.8%) with 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. Subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across age groups, genders, racial and ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19. Secondary efficacy analyses suggested benefit of the vaccine in preventing severe COVID-19 (11 protocol-defined severe COVID-19 cases in the placebo group vs. 0 cases in the vaccine group), in preventing COVID-19 following the first dose, and in preventing COVID-19 in individuals with prior SARS-CoV-2 infection, although available data for some of these outcomes did not allow for firm conclusions. Efficacy data from the final scheduled analysis of the primary efficacy endpoint (data cutoff of November 21, 2020, with a median follow-up of >2 months post-dose 2) demonstrated a VE of 94.1% (95% CI 89.3%, 96.8%), with 11 COVID-19 cases in the vaccine group and 185 COVID-19 cases in the placebo group and was consistent with results obtained from the interim analysis. The VE in this analysis when stratified by age group was 95.6% (95% CI: 90.6%, 97.9%) for participants 18 to <65 years of age and 86.4% (95% CI: 61.4%, 95.5%) for participants ⩾65 years of age. A final secondary efficacy analysis also supported efficacy against protocol-defined severe COVID-19, with 30 cases in the placebo group vs. 0 cases in the vaccine group.

Safety data from a November 11, 2020 interim analysis of approximately 30,350 participants ≥18 years of age randomized 1:1 to vaccine or placebo with a median of 7 weeks of follow-up after the second dose supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA. These safety data are the primary basis of FDA's safety review. On December 7, 2020, the Sponsor submitted additional follow-up data from these participants with a cutoff of November 25, 2020, which represents a median of 9 weeks (>2 months) of follow-up post-dose 2. Key safety data from this later submission, including death, other serious adverse events, and unsolicited adverse events of interest were independently verified and confirmed not to change the safety conclusions from the interim safety analysis.

The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and

chills (43.4%); severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose 2 than after dose 1, and were generally less frequent in participants ⩾65 years of age as compared to younger participants. Among unsolicited adverse events of clinical interest, which could be possibly related to vaccine, using the November 25, 2020 data cutoff, lymphadenopathy was reported as an unsolicited event in 173 participants (1.1%) in the vaccine group and 95 participants (0.63%) in the placebo group. Lymphadenopathy (axillary swelling and tenderness of the vaccination arm) was a solicited adverse reaction observed after any dose in 21.4% of vaccine recipients <65 years of age and in 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups, respectively. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the safety population. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

With the exception of more frequent, generally mild to moderate reactogenicity in participants <65 years of age, the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment.

This meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is being convened to discuss and provide recommendations on whether, based on the totality of scientific evidence available, the benefits of the mRNA-1273 COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health and, as of December 11, 2020, has caused more than 71 million cases of COVID-19 and claimed the lives of more than 1.6 million people worldwide. In the United States, more than 16 million cases have been reported to the Centers for Disease Control and Prevention (CDC), with over 296,000 deaths. Confirmed cases and mortality continue to rise globally. On January 31, 2020, the U.S. Secretary of Health and Human Services (HHS) declared a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS. Following the World Health Organization's declaration of the novel coronavirus pandemic on March 11, 2020, the U.S.

President declared a national emergency in response to COVID-19 on March 13, 2020. Vaccines to protect against COVID-19 are critical to mitigate the current SARS-CoV-2 pandemic and to prevent future disease outbreaks.

SARS-CoV-2 is a novel, zoonotic coronavirus that emerged in late 2019 in patients with pneumonia of unknown cause.[1] The virus was named SARS-CoV-2 because of its similarity to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV, a lineage B betacoronavirus).[2] SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus sharing more than 70% of its sequence with SARS-CoV, and ~50% with the coronavirus responsible for Middle Eastern respiratory syndrome (MERS-CoV).[3] The SARS-CoV-2 spike glycoprotein (S), which is the main target for neutralizing antibodies, binds to its receptor human angiotensin converting enzyme 2 (hACE2) to initiate infection.[4] SARS-CoV-2 is the cause of COVID-19, an infectious disease with respiratory and systemic manifestations. Disease symptoms vary, with many persons presenting with asymptomatic or mild disease and some progressing to severe respiratory tract disease including pneumonia and acute respiratory distress syndrome (ARDS), leading to multiorgan failure and death.

In an attempt to prevent the spread of disease and to control the pandemic, numerous COVID-19 vaccine candidates are in development. These vaccines are based on different platforms including mRNA and DNA technologies and include viral vectored, subunit, inactivated, and live-attenuated vaccines. Most COVID-19 candidate vaccines express the spike protein or parts of the spike protein, i.e., the receptor binding domain, as the immunogenic determinant.

2.2 EUA Request for the Moderna COVID-19 Vaccine mRNA-1273

ModernaTX, Inc. (Sponsor) is developing a vaccine to prevent COVID-19 that is based on the pre-fusion stabilized SARS-CoV-2 spike glycoprotein (S) antigen encoded by mRNA and formulated in a lipid nanoparticle (LNP). The Moderna COVID-19 Vaccine (also referred to as mRNA-1273) is a 2-dose series of 100-µg intramuscular injections administered 1 month apart. The vaccine is supplied as a multi-dose vial (10 doses) containing a frozen suspension -25º to -15ºC) of mRNA-1273 that must be thawed prior to administration. The vaccine does not contain a preservative.

A Phase 3 randomized and placebo-controlled trial using mRNA-1273 in approximately 30,000 participants is currently ongoing to evaluate the vaccine's safety and efficacy. A prespecified interim efficacy analysis from 27,817 participants using a data cutoff date of November 7, 2020, demonstrated vaccine efficacy (VE) of 94.5% (95% CI: 86.5%, 97.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. At the time of this interim analysis, the median efficacy follow-up was 7 weeks post completion of the 2-dose series. Safety data from a November 11, 2020, interim analysis with a median of 7 weeks follow-up after the second dose of vaccine were reported to demonstrate an acceptable tolerability profile with no significant safety concerns. On November 30, 2020, ModernaTX submitted an EUA request to FDA, based on the interim analyses described above, for use of mRNA-1273 to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

On December 7, 2020, the Sponsor submitted an amendment to the EUA request with additional accrued safety data on all participants with a median of 2 months (9 weeks) follow-up after the second dose, using a data cutoff date of November 25, 2020, and data from the prespecified final efficacy analysis using a data cutoff of November 21, 2020, which met the median follow-up of 2 months after dose 2 and demonstrated vaccine efficacy of 94.1% (95%

CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 occurring at least 14 days after the second dose. Although the complete datasets and analyses from the primary efficacy analysis and associated safety analyses submitted on December 7, 2020, have not been independently verified by the FDA to the same extent as the data for the interim efficacy analyses and associated safety analyses submitted on November 30, 2020, based on comprehensive independent review of the data from the interim analysis, and the consistency of findings across the two analysis time points, FDA considers that the totality of available data are sufficient to support an evaluation of this product for EUA.

2.3 U.S. Requirements to Support Issuance of an EUA for a Biological Product

Based on the declaration by the Secretary of HHS that the COVID-19 pandemic constitutes a public health emergency with a significant potential to affect national security or the health and security of United States citizens living abroad, FDA may issue an EUA after determining that certain statutory requirements are met (section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb-3)).[5]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2, or to mitigate a serious or life-threatening disease or condition caused by an FDA-regulated product used to diagnose, treat, or prevent a disease or condition caused by SARS-CoV-2.
- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

If these criteria are met, under an EUA, FDA can allow unapproved medical products (or unapproved uses of approved medical products) to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by threat agents. FDA has been providing regulatory advice to COVID-19 vaccine manufacturers regarding the data needed to determine that a vaccine's benefit outweigh its risks. This includes demonstrating that manufacturing information ensures product quality and consistency along with data from at least one phase 3 clinical trial demonstrating a vaccine's safety and efficacy in a clear and compelling manner.

In the event an EUA is issued for this product, it would still be considered unapproved and would continue under further investigation (under an Investigational New Drug Application). Licensure of a COVID-19 vaccine will be based on review of additional manufacturing, efficacy, and safety data, providing greater assurance of the comparability of licensed product to product tested in the clinical trials, greater assurance of safety based on larger numbers of vaccine recipients who have been followed for a longer period of time, and additional information about efficacy that addresses, among other questions, the potential for waning of protection over time.

2.4 Alternatives for Prevention of COVID-19

No vaccine or other medical product is FDA approved for prevention of COVID-19. On December 11, 2020, FDA issued an EUA for the Pfizer-BioNTech COVID-19 vaccine for active immunization for prevention of COVID-19 due to SARS-CoV-2 in individuals 16 years of age and older. However, the Pfizer-BioNTech COVID-19 vaccine is not an approved product, and furthermore is not available in quantity sufficient to vaccinate all persons in the U.S. for whom the vaccine is authorized for use. On October 22, 2020, FDA approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalization. Several other therapies are currently available under emergency use authorization, but not FDA approved, for treatment of COVID-19. Thus, there is currently no adequate, approved, and available alternative for prevention of COVID-19.

2.5 Applicable Guidance for Industry

Risk and benefit considerations are unique for COVID-19 vaccines, given that an EUA may be requested to allow for a vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people. FDA published in October 2020 guidance for industry entitled "Emergency Use Authorization for Vaccines to Prevent COVID-19" describing FDA's current recommendations regarding the manufacturing, nonclinical, and clinical data and information needed under section 564 of the FD&C Act to support the issuance of an EUA for an investigational vaccine to prevent COVID-19, including a discussion of FDA's current thinking regarding the circumstances under which an EUA for a COVID-19 vaccine would be appropriate.[6]

2.6 Safety and Effectiveness Information Needed to Support an EUA

Effectiveness data

Issuance of an EUA requires a determination that the known and potential benefits of the vaccine outweigh the known and potential risks. For a preventive COVID-19 vaccine to be potentially administered to millions of individuals, including healthy individuals, data adequate to inform an assessment of the vaccine's benefits and risks and support issuance of an EUA would include meeting the prespecified success criteria for the study's primary efficacy endpoint, as described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" (i.e., a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%).[7]

Safety data

An EUA request for a COVID-19 vaccine should include all safety data accumulated from studies conducted with the vaccine, with data from Phase 1 and 2 focused on serious adverse events, adverse events of special interest, and cases of severe COVID-19 among study participants. Phase 3 safety data should include characterization of reactogenicity (common and expected adverse reactions shortly following vaccination) in a sufficient number of participants from relevant age groups and should include a high proportion of enrolled participants (numbering well over 3,000) followed for serious adverse events and adverse events of special interest for at least one month after completion of the full vaccination regimen. The Phase 1 and 2 safety data likely will be of a longer duration than the available safety data from the Phase 3 trial at the time of submission of an EUA request and thus, are intended to complement the available data from safety follow-up from ongoing Phase 3 studies.

Phase 3 Follow-up

Data from Phase 3 studies should include a median follow-up duration of at least 2 months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile. From a safety perspective, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate postvaccination period. Adverse events considered plausibly linked to vaccination generally start within 6 weeks of vaccine receipt.[8] Therefore, a 2-month follow-up period may allow for identification of potential immune-mediated adverse events that began within 6 weeks of vaccination. From the perspective of vaccine efficacy, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived. The EUA request should include a plan for active follow-up for safety (including deaths, hospitalizations, and other serious or clinically significant adverse events) among individuals administered the vaccine under an EUA in order to inform ongoing benefit-risk determinations to support continuation of the EUA.

2.7 Continuation of Clinical Trials Following Issuance of an EUA for a COVID-19 Vaccine

FDA does not consider availability of a COVID-19 vaccine under EUA, in and of itself, as grounds for immediately stopping blinded follow-up in an ongoing clinical trial or grounds for offering vaccine to all placebo recipients. To minimize the risk that use of an unapproved vaccine under EUA will interfere with long-term assessment of safety and efficacy in ongoing trials, it is critical to continue to gather data about the vaccine even after it is made available under EUA. An EUA request should therefore include strategies that will be implemented to ensure that ongoing clinical trials of the vaccine are able to assess long-term safety and efficacy (including evaluating for vaccine-associated enhanced respiratory disease and decreased effectiveness as immunity wanes over time) in sufficient numbers of participants to support vaccine licensure. These strategies should address how ongoing trial(s) will handle loss of follow-up information for study participants who choose to withdraw from the study in order to receive the vaccine under an EUA.

FDA is aware that some COVID-19 vaccine developers may wish to immediately unblind their trials upon issuance of an EUA in order to rapidly provide vaccine to trial participants who received placebo. Regardless of when vaccination of placebo recipient would occur, there may be advantages to maintaining blinding in a crossover design that provides vaccine to previous placebo recipients and placebo to previous vaccine recipients. Such strategies would impact collection of longer-term placebo-controlled safety data and evaluation of the duration of vaccine efficacy. Ethical and scientific issues associated with offering vaccination to placebo recipients have been discussed in recent statements and articles.[9-11]

2.8 Previous Meetings of the VRBPAC to Discuss Vaccines to Prevent COVID-19

On October 22, 2020, the VRBPAC met in open session to discuss, in general, the development, authorization, and/or licensure of vaccines to prevent COVID-19. No specific application was discussed at this meeting. Topics discussed at the meeting included:

- FDA's approach to safety and effectiveness, and chemistry, manufacturing and control (CMC) data as outlined in the respective guidance documents
- Considerations for continuation of blinded Phase 3 clinical trials if an EUA has been issued for an investigational COVID-19 vaccine

- Studies following licensure and/or issuance of an EUA for COVID-19 vaccines to:
    - Further evaluate safety, effectiveness and immune markers of protection
    - Evaluate the safety and effectiveness in specific populations.

On December 10, 2020, the VRBPAC met in open session to discuss the EUA request of the Pfizer-BioNTech COVID-19 Vaccine for the prevention of COVID-19 in individuals 16 years of age older. Topics discussed at the meeting but not voted upon included Pfizer's plan for continuation of blinded, placebo-controlled follow-up in ongoing trials in the event that the vaccine is made available under EUA and gaps in plans for further evaluation of vaccine safety and effectiveness in populations that receive the Pfizer-BioNTech Vaccine under an EUA. The committee voted in favor of a determination that, based on the totality of scientific evidence available, the benefits of the proposed vaccine outweigh its risks for use in individuals 16 years of age and older.

3. Topics for VRBPAC Discussion

The Vaccines and Related Biological Products Advisory Committee will convene on December 17, 2020, to discuss and provide recommendations on whether based on the totality of scientific evidence available, the benefits of the Moderna COVID-19 Vaccine outweigh its risks for use in individuals 18 years of age and older. The Committee will also discuss what additional studies should be conducted by the vaccine manufacturer following issuance of the EUA to gather further data on the safety and effectiveness of this vaccine.

4. Moderna COVID-19 Vaccine (mRNA-1273)

4.1 Vaccine Composition, Dosing Regimen

The Moderna COVID-19 Vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine contains a synthetic messenger ribonucleic acid (mRNA) encoding the pre-fusion stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.

The Moderna COVID-19 Vaccine is provided as a frozen suspension [stored between -25º to -15ºC (-13º to 5ºF)] multi-dose vial containing 10 doses. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 mL each) can be withdrawn from each vial. Vials can be stored refrigerated between 2° to 8°C (36° to 46°F) for up to 30 days prior to first use. Unopened vials may be stored between 8° to 25°C (46° to 77°F) for up to 12 hours. After the first dose has been withdrawn, the vial should be held between 2° to 25°C (36° to 77°F) and discarded after 6 hours.

The Moderna COVID-19 Vaccine, mRNA-1273 (100 µg) is administered intramuscularly as a series of two doses (0.5 mL each), given 28 days apart.

FDA has reviewed the CMC data submitted to date for this vaccine and has determined that the CMC information is consistent with the recommendations set forth in FDA's Guidance on Emergency Use Authorization for Vaccines to Prevent COVID-19. FDA has determined that the Sponsor has provided adequate information to ensure the vaccine's quality and consistency for authorization of the product under an EUA.

4.2 Proposed Use Under EUA

The proposed use of the vaccine under an EUA is for the prevention of COVID-19 in adults 18 years of age and older.

5. FDA Review of Clinical Safety and Effectiveness Data

5.1 Overview of Clinical Studies

Data from three ongoing clinical studies were included in the EUA request, which are summarized in Table 1 below. Study mRNA-1273-P301 is a multi-center, Phase 3 randomized, blinded, placebo-controlled safety, immunogenicity, and efficacy study that is the focus of the EUA review. Study mRNA1273-P201 is a Phase 2 dose-confirmation study that explored 2 dose levels of mRNA-1273 and will not be discussed in detail. Study 20-0003 is a Phase 1 open label, dose-ranging, first-in-human study of mRNA-1273 and will also not be discussed in detail. A brief summary of the P201 and 20-0003 study designs and results to date is found in Appendix A, page 53.

Table 1. Clinical Trials Submitted in Support of Efficacy and Safety Determinations of the Moderna COVID-19 Vaccine mRNA-1273

Study Number	Type of Study (Efficacy, Safety, Nonclinical)	Participants randomized (N)	Study Design & Type of Control	Test Product(s); Dosing Regimens	Study Status
P301	Efficacy, Safety	30418	A Phase 3, randomized, stratified, observer-blind, placebo-controlled study	mRNA-1273 100 µg	Ongoing-vaccine efficacy demonstrated at the 1st interim analysis
P201	Safety, Immunogenicity	600	A Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study	mRNA-1273 50ug,100µg	Ongoing-Day 57 primary analysis have completed
20-0003*	Safety, Immunogenicity	120	A Phase 1 Open-label dose-ranging study	mRNA-1273 25ug 50ug,100ug 250ug	Ongoing-Day 119 (25ug, 100ug, 250ug), Day 57 (50ug)

*Sponsor: Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health

5.2 Study mRNA-1273-P301

5.2.1 Design

Study mRNA-1273-P301 is an ongoing randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of mRNA-1273 administered in 2 doses 28 days apart in adults 18 years of age and older. The study took place in 99 sites in the United States. Participants (N=30,351) were randomized 1:1 to receive intramuscular injections of either 100 µg of mRNA-1273 vaccine (n=15,181) or placebo

(n=15,170) on Day 1 and Day 29. Participants were stratified by age and health risk into one of three groups: 18 to <65 years of age and not at risk for progression to severe COVID-19, 18 to <65 years of age and at risk for progression to severe COVID-19, and ≥65 years of age, with the latter two groups consisting of 41.4% of the study population. Participants were considered at risk for progression to severe COVID-19 if they had underlying comorbidities including diabetes, chronic lung disease, severe obesity, significant cardiovascular disease, liver disease, or infection with HIV. The study included 24,907 (82.1%) participants considered at occupational risk for acquiring SARS-CoV-2 infection, of whom 7,613 (25.1%) were healthcare workers. Other essential workers were also represented. The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).

Symptoms of COVID-19 experienced by participants during post-vaccination follow-up prompted an unscheduled illness visit and nasopharyngeal (NP) swab. NP samples were tested for SARS CoV-2 at a central laboratory using a reverse transcription-polymerase chain reaction (RT-PCR) test (Viracor; FDA authorized under EUA), or other sufficiently validated nucleic acid amplification-based test (NAAT). The central laboratory NAAT result is used for the case definition, unless it is not possible to test the sample at the central laboratory.

The case-driven study design required 151 COVID-19 cases to trigger the final scheduled efficacy analysis. Two interim analysis timepoints were pre-specified; the first upon accrual of 53 cases and the second upon accrual of 106 cases. The expected duration of study participation is approximately 25 months.

Primary Efficacy Endpoint

The primary efficacy endpoint was efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1). The primary analysis was based on the Per-Protocol Set, defined as all randomized, baseline SARS-CoV-2 negative participants who received planned doses per schedule and have no major protocol deviations. For the primary efficacy endpoint, the case definition for a confirmed COVID-19 case was defined as:

- At least TWO of the following systemic symptoms: Fever (≥38ºC), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), or
- At least ONE of the following respiratory signs/ symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; and
- NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Vaccine efficacy was defined as the percent reduction (mRNA-1273 vs. placebo) in the hazard of the primary endpoint, i.e. VE =1 – Hazard Ratio (HR). A stratified Cox proportional hazard (PH) model using Efron's method to handle ties and with treatment group as the independent variable was used to estimate the HR, where the same stratification factor used for randomization was applied. The primary objective would be met if the null hypothesis of H0: VE ≤30% is rejected at any of the interim or primary analyses at the respective significance level.

The final scheduled efficacy analysis of the primary endpoint was planned when a total of 151 adjudicated cases occurring at least 14 days after the second injection had been accrued. In addition, two interim analyses were planned when 35% (53 cases) and 70% (106 cases) of the

total target number of cases had been accrued. The Lan-DeMets spending function was used for approximating O'Brien-Fleming efficacy bounds to preserve the overall Type I error rate at a one-sided α =0.025, yielding nominal one-sided α of 0.0002, 0.0073, and 0.0227 at the first and second interim and the primary analyses, respectively. As conducted, the first and only interim analysis in the study occurred at 95 adjudicated cases of the primary endpoint, where the null hypothesis of H0: VE ≤30% was evaluated at a one-sided alpha of 0.0047.

Secondary Efficacy Endpoints

Secondary endpoints based on the Per-Protocol Set included the VE of mRNA-1273 to prevent the following:

- Severe COVID-19 (as defined below)
- COVID-19 based on a less restrictive definition of disease (defined below) occurring at least 14 days after the second dose of vaccine
- Death due to COVID-19
- COVID-19 occurring at least 14 days after the first dose of vaccine (including cases that occurred after the second dose)

One additional secondary endpoint was based on the Full Analysis Set (FAS): VE of mRNA-1273 to prevent COVID-19 occurring at least 14 days after the second dose, regardless of prior SARS-CoV-2 infection.

One of the secondary efficacy endpoints assessed COVID-19 as defined by a less restrictive definition: a positive NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) for SARS-CoV-2 by RT-PCR **and** one of the following systemic symptoms:

- fever (temperature ≥38ºC), or
- chills,
- cough,
- shortness of breath or difficulty breathing,
- fatigue,
- muscle aches or body aches,
- headache,
- new loss of taste or smell,
- sore throat,
- nasal congestion or rhinorrhea,
- nausea or vomiting, or diarrhea

Another secondary endpoint assessed cases of severe COVID-19, defined as a case of confirmed COVID-19 plus at least one of the following:

- Clinical signs at rest indicative of severe systemic illness (RR ≥30 breaths per minute, HR ≥125 beats per minute, SpO2≤93% on room air at sea level, or PaO2/FiO2<300 mm Hg);
- Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an ICU;
- Death

Vaccine efficacy of secondary endpoints was estimated from the Cox proportional-hazards model when the primary endpoint reached statistical significance. Estimates based on the Per-Protocol Set were presented with nominal two-sided 95% confidence intervals.

Analysis Populations

For the purposes of analysis, the following populations are defined:

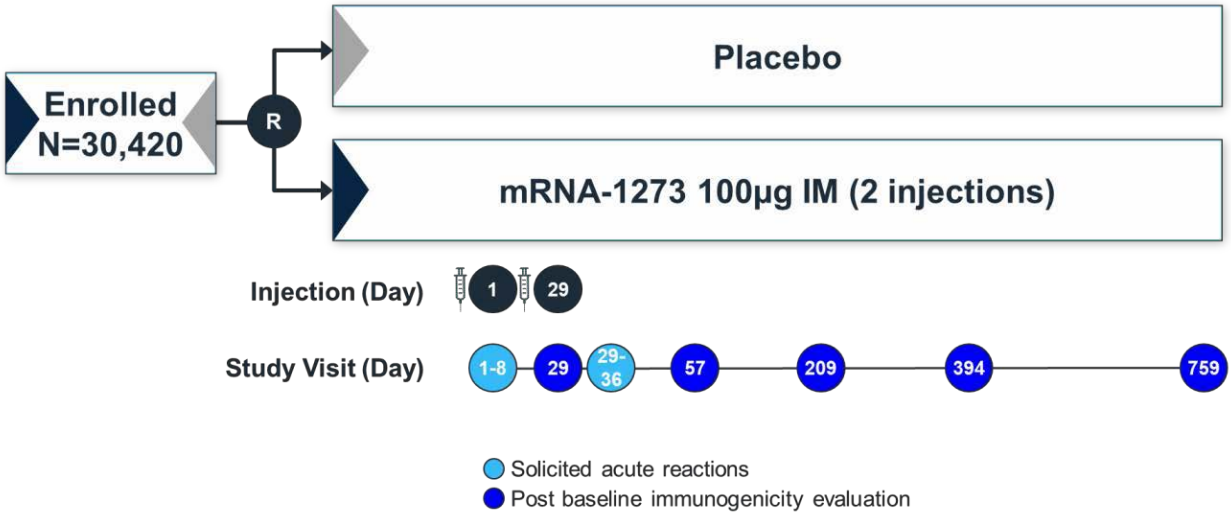
Table 2. Efficacy Set Definitions

Population	Description
Randomized	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set	All randomized participants who received at least one dose of Investigational Product (IP).
mITT Set	All participants in the FAS who had no immunologic or virologic evidence of prior COVID-19 (i.e., negative NP swab test at Day 1 and/or bAb against SARS-CoV-2 nucleocapsid below limit of detection [LOD] or lower limit of quantification [LLOQ]) at Day 1 before the first dose of IP.
Per Protocol Set	All participants in the mITT Set who received planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.
Safety Set	All randomized participants who received at least one dose of IP.
Solicited Safety Set	All randomized participants who received at least one dose of IP and contributed any solicited adverse reaction data.

Evaluation of Safety

The primary safety objective for all phases was to describe the safety of mRNA-1273 after 1 or 2 doses. In all studies, participants recorded local reactions, systemic events, and antipyretic/pain medication usage from Day 1 through Day 7 after each dose. Unsolicited adverse events (AEs) are collected from dose 1 to 28 after the last dose and medically attended adverse events (MAAEs) and serious AEs (SAEs) from dose 1 to the end of the study. Figure 1 below shows the study safety monitoring plan.

Figure 1. Safety Monitoring Plan, Study 301



Safety assessments included the following:

- Solicited local and systemic adverse reactions (AR) that occurred during the 7 days following each dose (i.e., the day of vaccination and 6 subsequent days). Solicited ARs were recorded daily using eDiaries.
- Unsolicited AEs observed or reported during the 28 days following each dose (i.e., the day of vaccination and 27 subsequent days). Unsolicited AEs are those not included in the protocol-defined solicited AR.
- AEs leading to discontinuation from vaccination and/or study participation from Day 1 through Day 759 or withdrawal from the study.
- Medically Attended Adverse Events (MAAE) from Day 1 through Day 759 or withdrawal from the study.
- Serious Adverse Events (SAEs) from Day 1 through Day 759 or withdrawal from the study.
- Abnormal vital sign measurements.
- Physical examination findings.
- Pregnancy and accompanying outcomes.

Safety laboratory evaluations were not assessed in Study P301 but were collected in the phase 2 Study P201. See Appendix A on page 53.

Potential COVID-19 illnesses and their sequelae were not to be reported as AEs, with the exception of illnesses that met regulatory criteria for seriousness and were not confirmed to be COVID-19. Such illnesses were evaluated and reported as SAEs.

Monitoring for risk of vaccine-enhanced disease was performed by an unblinded team supporting the Data Monitoring Committee that reviewed cases of severe COVID-19 as they were received and reviewed AEs at least weekly for additional potential cases of severe COVID-19. The stopping rule was triggered when the 1-sided probability of observing the same or a more extreme case split was 5% or less when the true incidence of severe disease was the same for vaccine and placebo participants.

The table below shows the Phase 3 safety analyses populations that were used to determine the proportions of study participants who experienced adverse events, including solicited adverse reactions after each dose, unsolicited adverse events, medically attended adverse events, and serious adverse events.

Table 3. Safety Set Definitions

Population	Description
Randomized Set	All participants who are randomized, regardless of the participants treatment status in the study.
Safety Set	All randomized participants who received at least one dose of investigational product. The safety set was used for all analyses of safety except solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set	All randomized participants who received at least one dose of investigational product and contributed any solicited adverse reaction data. The solicited safety set was used for the analyses of solicited adverse reactions. Participants were included in the treatment group corresponding to the investigational product they received.
Solicited Safety Set-1st Injection	All randomized participants who received the 1st dose and provided any solicited reaction data.

Population	Description
Solicited Safety Set-2nd Injection	All randomized participants who received the 2nd dose and provided any solicited reaction data.

5.2.2 FDA Assessment of Phase 3 Follow-Up Duration

As of the interim analysis cutoff (November 7, 2020, for efficacy, November 11, 2020, for safety), the proportion of participants across groups who received one dose of vaccine or placebo was 100%, and the proportion of participants who received two doses was 91.9% (92.1% vaccine, 91.7% placebo). The median follow-up after dose 2 was 7 weeks across groups. (For participants who did not receive a second dose of vaccine or placebo, follow-up after dose 2 was zero. Among participants who received dose 2, the median follow-up after the second dose was 50.0 days.) The proportion of participants with at least 1 month of follow-up after dose 2 was 76.7% (77.2% vaccine, 76.2% placebo) and with at least 2 months follow-up after dose 2 was 25.3% (25.7% vaccine, 24.9% placebo). FDA has completed its independent validation and evaluation of the datasets from which the Sponsor's interim safety and efficacy analyses were derived.

A second safety data cutoff was performed on November 25, 2020, and final efficacy analysis performed with a data cutoff of November 21, 2020, when 196 primary endpoint cases accrued. These data include a median follow-up of 2 months (9 weeks) for both efficacy and safety. The proportion of participants with at least 1 month of follow-up after dose 2 was 87.9% (88.2% vaccine, 87.7% placebo) and with at least 2 months follow-up after dose 2 was 53.6% (53.8% vaccine, 53.5% placebo). The Sponsor submitted analyses from the final efficacy analysis (Tables, Figures and Listings) on December 4, 2020, and safety analyses (Tables, Figures and Listings) on December 7, 2020, for FDA review under the EUA. Datasets were also submitted on December 7, 2020 and validated by FDA by December 8, 2020. The review of the second dataset submission for the final scheduled efficacy analysis and safety data through November 25, 2020, was not as comprehensive as that of the interim efficacy data and safety data first submitted in support of the EUA. However, preliminary assessments of safety and efficacy data and analyses from second data cutoff do not demonstrate any notable differences compared with the efficacy and safety analyses from November 7, 2020, and November 11, 2020, respectively, and key safety and efficacy data (e.g., the primary analysis, cases of severe COVID-19, and serious adverse events) from the December 7, 2020, submission were verified. FDA therefore considers the totality of submitted data to satisfy the expectation of a median of 2 months follow-up after completion of the full vaccination regimen.

5.2.3 Participant Disposition and Inclusion in Analysis Populations

Disposition tables are presented below in Table 4 (Per-Protocol Set) and Table 5 (Safety Set). The proportion of participants excluded from the Per-Protocol Set was balanced between treatment groups, with the majority of those excluded due to positive or unknown baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow-up, and these and other analysis population exclusions were generally balanced between treatment groups. In the per protocol population, 26.3% of vaccine recipients and 25.7% of placebo recipients completed at least 2 months follow-up after dose 2.

Table 4. Efficacy Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Full Analysis Set	15180 (99.8)	15170 (99.7)	30350 (99.8)
Modified Intent-to-Treat Set	14312 (94.1%)	14370 (94.5%)	28682 (94.3)
Participants excluded from PP set	1274 (8.4%)	1327 (8.7%)	2601 (8.6%)
Randomized but received no Investigational Product (IP)	28 (0.2%)	40 (0.3%)	68 (0.2%)
Baseline SARS-CoV-2 status was positive or not known	868 (5.7%)	800 (5.3%)	1668 (5.5)
Received IP other than what the participant was randomized to	5 (<0.1)	7 (<0.1)	12 (<0.1)
Discontinued study or study vaccine without receiving the second dose	136 (0.9)	203 (1.3)	339 (1.1)
Did not receive second dose of IP	144 (0.9)	155 (1.0)	299 (1.0)
Received vaccine out of window	81 (0.5)	98 (0.6)	179 (0.6)
Major protocol deviation	12 (<0.1)	24 (0.2)	36 (0.1)
Per Protocol Set	13934 (91.6)	13883 (91.3)	27817 (91.4)
Completed 1 dose**	13934 (100)	13883 (100)	27817 (100)
Completed 2 doses**	13218 (94.9)	13164 (94.8)	26382 (94.8)
Completed at least 7 weeks follow-up after dose 2**	7293 (52.3)	7304 (52.6)	14597 (52.5)
Completed at least 2 months follow-up after dose 2**	3669 (26.3)	3568 (25.7)	7237 (26.0)
Discontinued from Study**	24 (0.2)	34 (0.2)	58 (0.2)
Reason for Discontinuation**			
Adverse Event	0	0	0
Death	0	1 (<0.1)	1 (<0.1)
Withdrawal by Participant	18 (0.1)	22 (0.2)	40 (0.1)
Lost to Follow-up	2 (<0.1)	9 (<0.1)	11 (<0.1)
Protocol Deviation	0	0	0
Physician Decision	2 (<0.1)	0	2 (<0.1)
Other	2 (<0.1)	2 (<0.1)	4 (<0.1)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2
[a] EUA request (interim analysis): November 11, 2020 cutoff
*Percentage based on number of participants in the Safety Set
**Percentage based on number of participants in the Per-Protocol Set

Based on the November 11, 2020 safety data cutoff, an overview of participant disposition is presented in the table below. The proportion of randomized participants who discontinued from the study was 0.9% (288 participants) across study groups, with a greater number in the placebo group (168) compared with the vaccine group (120). The most frequently reported reason was withdrawal of consent (67 participants in the vaccine group, 120 in the placebo group). In addition, 51 participants were lost to follow-up (20 in the vaccine group, 31 in the placebo group). In the vaccine group, 3 participants withdrew due to an adverse event (<0.1%, including 1 participant who withdrew due to a SAE) and 3 participants died during the study. In the placebo group, no participants withdrew due to an adverse event, and 4 participants died during the study.

Table 5. Safety Analysis Population Study Disposition[a], mRNA-1273-P301

Disposition	Vaccine Group (N=15208) n (%)	Placebo Group (N=15210) n (%)	Total (N=30418) n (%)
Randomized	15208	15210	30418
Completed 1 dose	15180 (99.8)	15170 (99.7)	30350 (99.8)
Completed 2 doses	13982 (91.9)	13916 (91.5)	27898 (91.7)
Exposed (Safety Set)	15184	15166	30350 (99.8)
Discontinued from Study	120 (0.8)	168 (1.1)	288 (0.9)
Reason for Discontinuation			
Adverse Event	3 (<0.1)	0	3 (<0.1)
Death	3 (<0.1)	4 (<0.1)	7 (<0.1)
Withdrawal by Participant	67 (0.4)	120 (0.8)	187 (0.6)
Lost to Follow-up	20 (0.1)	31 (0.2)	51 (0.2)
Protocol Deviation	1 (<0.1)	1 (<0.1)	2 (<0.1)
Physician Decision	17 (0.1)	2 (<0.1)	19 (<0.1)
Other	9 (<0.1)	10(<0.1)	19 (<0.1)
Completed ≥1 month f/up*	14354 (94.5)	14345 (94.6)	28700 (94.6)
Completed ≥2 months f/up*	12021 (79.2)	11974 (79.0)	23995 (79.1)
Completed ≥1 month f/up after dose 2*	11717 (77.2)	11559 (76.2)	23276 (76.7)
Completed ≥2 months f/up after dose 2*	3894 (25.7)	3773 (24.9)	7667 (25.3)

Source: Sponsor's Table 14.1.1.1.1.1, Table 4.1.2.1, Table 14.1.1.1.3.2, Table 14.1.6.2.
[a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.4 Demographics and Other Baseline Characteristics

The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions. The protocol-specified risk factors were those conditions that placed an individual at increased risk for severe complications of COVID-19 and were selected based on CDC recommendations[12] from March 2020. These conditions included the following:

- Chronic lung disease (e.g., emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis) or moderate to severe asthma
- Significant cardiac disease (e.g., heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension)
- Severe obesity (body mass index ≥40 kg/m2)
- Diabetes (Type 1, Type 2 or gestational)
- Liver disease
- HIV infection

There was a similar distribution of demographic characteristics between the treatment groups as well as between the all randomized population, Full Analysis Set, and the Per-Protocol Set.

Table 6. Demographic Characteristics[a], Per-Protocol Set

Characteristic	Vaccine Group (N=13934) n (%)	Placebo Group (N=13883) n (%)	Total (N=27817) n (%)
Sex			
Female	6661 (47.8)	6514 (46.9)	13175 (47.4)
Male	7273 (52.2)	7369 (53.1)	14642 (52.6)
Age (years)			
Mean (SD)	51.6 (15.45)	51.5 (15.55)	51.6 (15.50)
Median	53.0	52.0	53.0
Min, max	18, 95	18, 95	18, 95
Age- subgroups (years)			
18 to <65	10407 (74.7)	10384 (74.8)	20791 (74.7)
65 and older	3527 (25.3)	3499 (25.2)	7026 (25.3)
Race			
American Indian or Alaska Native	107 (0.8)	110 (0.8)	217 (0.8)
Asian	616 (4.4)	684 (4.9)	1300 (4.7)
Black or African American	1369 (9.8)	1338 (9.6)	2707 (9.7)
Native Hawaiian or Other Pacific Islander	33 (0.2)	30 (0.2)	63 (0.2)
White	11078 (79.5)	11005 (79.3)	22083 (79.4)
Other	298 (2.1)	293 (2.1)	591 (2.1)
Ethnicity			
Hispanic or Latino	2783 (20.0)	2769 (19.9)	5552 (20.0)
Not Hispanic or Latino	11019 (79.1)	10987 (79.1)	22006 (79.1)
Race and Ethnicity			
Non-Hispanic white	8858 (63.6)	8755 (63.1)	17613 (63.3)
Communities of color	5054 (36.3)	5102 (36.7)	10156 (36.5)
Occupational Risk*	11397 (81.8)	11408 (82.2)	22805 (82.0)
Healthcare worker	3541 (25.4)	3531 (25.4)	7072 (25.4)
High Risk Condition**			
No high risk condition	11820 (77.9)	11788 (77.7)	23608 (77.8)
One high risk condition present	3116 (22.4)	3075 (22.1)	6191 (22.3)
Two or more high risk conditions present	561 (4.0)	554 (4.0)	1115 (4.0)
Age and Health Risk for Severe COVID-19***			
18 to <65 years and not at risk	8309 (59.6)	8323 (60.0)	16632 (59.8)
18 to <65 years and at risk	2098 (15.1)	2061 (14.8)	4159 (15.0)
≥65 years	3527 (25.3)	3499 (25.2)	7026 (25.3)

Source: Sponsor's Table14.1.3.4.2. [a] EUA request (interim analysis): November 11, 2020 data cutoff.
Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.
[**] High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
[***] Age and health risk for severe COVID-19 is used as stratification factor for randomization.

The demographic characteristics among vaccine and placebo participants in the safety population were similar. There were no significant imbalances in demographic and other baseline characteristics between the per-protocol population and the safety population, with median 7-week follow-up.

Table 7. Demographic Characteristics[a], Safety Set

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Sex			
Female	7255 (47.8)	7100 (46.8)	14355 (47.3
Male	7929 (52.2)	8065 (53.2)	15995 (52.7)
Age (years)			
Mean (SD)	51.4 (15.50)	51.3 (15.60)	51.4 (15.55)
Median	53.0	52.0	52.0
Min, max	18, 95	18, 95	18, 95
Age – Subgroups (years)			
≥18 to <65	11414 (75.2)	11415 (75.3)	22830 (75.2)
65 and older	3770 (24.8)	3750 (24.7)	7520 (24.8)
Race			
American Indian or Alaska Native	110 (0.7)	120 (0.8)	230 (0.8)
Asian	653 (4.3)	732 (4.8)	1385 (4.6)
Black or African American	1562 (10.3)	1528 (10.1)	3090 (10.2)
Native Hawaiian or other Pacific islander	34 (0.2)	32 (0.2)	66 (0.2)
White	12032 (79.2)	11990 (79.1)	24023 (79.2)
Other	321 (2.1)	315 (2.1)	636 (2.1)
Multiracial	315 (2.1)	319 (2.1)	634 (2.1)
Ethnicity			
Hispanic or Latino	3121 (20.6)	3112 (20.5)	6234 (20.5)
Not Hispanic or Latino	11920 (78.5)	11914 (78.6)	23834 (78.5)
Race and Ethnicity			
Non-Hispanic White	9534 (62.8)	9458 (62.4)	18992 (62.6)
Communities of color	5624 (37.0)	5680 (37.5)	11305 (37.2)
Occupational Risk*	12420 (81.8)	12487 (82.3)	24907 (82.1)
Healthcare worker	3787 (24.9)	3826 (25.2)	7613 (25.1)
High Risk Condition**			
One high risk condition present	3360 (22.1)	3382 (22.3)	6742 (22.2)
No high risk condition	11824 (77.9)	11783 (77.7)	23608 (77.8)
Age and Health Risk for Severe COVID-19***			
≥18 to <65 years and not at risk	8889 (58.5)	8884 (58.6)	17773 (58.6)
≥18 to <65 years and at risk	2530 (16.7)	2534 (16.7)	5065 (16.7)
≥65 years	3765 (24.8)	3747 (24.7)	7512 (24.8)

Characteristic	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Baseline SARS CoV-2 status****			
Negative	14316 (94.3%)	14366 (94.7)	26862 (94.5%)
Positive	341 (2.2%)	334 (2.2%)	675 (2.2%)
Missing	527 (3.5%)	465 (3.5%)	993 (3.3%)

Source: Sponsor's Table 14.1.3.2.2 [a] EUA request (interim analysis): November 11 2020 cutoff.
* Occupational risk includes: Healthcare Workers, Emergency Response, Retail/Restaurant Operations, Manufacturing and Production Operations, Warehouse Shipping and Fulfillment centers, Transportation and Delivery Services, Border Protection and Military Personnel, and Personal care and in-home services, Hospitality and Tourism Workers, Pastoral, Social or Public Health Workers, Educators and Students.**
**High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary fibrosis, and cystic fibrosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human immunodeficiency virus (HIV) infection

The following table provides the proportions of participants randomized to each of the protocol-specified strata based on presence or absence of protocol-defined risk factors for severe COVID-19 disease, including age ⩾65 years. The presence of these risk factors was assessed at screening via review of the participants medical history. The protocol specified that at least 25% (and up to 50%) of enrolled participants were to be either ⩾65 years of age or 18 through <65 years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff, ~25% of participants were age ⩾65 years, and 16.7% of participants were age 18 to <65 years with a protocol-defined risk factor. The remainder of participants (58.6%) were age 18 to <65 years without risks. The proportions of participants in each of these three strata randomized to vaccine or placebo are shown in the table below.

Table 8. Protocol-Defined Risk for Severe COVID-19 Disease, Safety Seta

Participants Risk Categories	Vaccine Group (N=15184) n (%)	Placebo Group (N=15165) n (%)	Total (N=30350) n (%)
Without Any Protocol Risk for Severe COVID-19	11824 (77.9)	11783 (77.7)	23608 (77.8)
With Any Protocol Risk for Severe COVID-19	3360 (22.1)	3382 (22.3)	6742 (22.2)
Chronic Lung Disease	707 (4.7)	741 (4.9)	1448 (4.8)
Significant Cardiac Disease	742 (4.9)	741 (4.9)	1483 (4.9)
Severe Obesity	986 (6.5)	978 (6.4)	1964 (6.5)
Diabetes	1427 (9.4)	1431 (9.4)	2858 (9.4)
Liver Disease	100 (0.7)	96 (0.6)	196 (0.6)
HIV Infection	90 (0.6)	86 (0.6)	176 (0.6)

Source: Sponsor's Table 14.1.3.2.2. [a] EUA request (interim analysis): November 11, 2020 cutoff

5.2.5 Vaccine Efficacy

Interim Primary Efficacy Analysis

The interim primary efficacy analysis was based on the Per-Protocol Set, which consisted of all participants with negative baseline SARS-CoV-2 status (i.e., negative RT-PCR for SARS-CoV-2 at Day 1 and/or negative serology against SARS-CoV-2 nucleocapsid) and who received 2 doses of investigational product per schedule with no major protocol deviations. The primary efficacy endpoint was vaccine efficacy (VE) in preventing protocol defined COVID-19 occurring at least 14 days after dose 2. Cases were adjudicated by a blinded committee. The primary

efficacy success criterion would be met if the null hypothesis of VE ≤30% was rejected at the O'Brien Fleming boundary at either the interim or primary analysis. The efficacy analysis presented is based on the data at the first pre-specified interim analysis timepoint consisting of 95 adjudicated cases. As shown in Table 9, in participants ≥18 years of age, there were 5 COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group, with a VE of 94.5%, a lower bound of the 95% CI of 86.5%, and a one-sided p-value of <0.0001 for testing H0: VE ≤30%, which met the pre-specified success criterion. In participants ≥65 years of age in the Per-Protocol Set, there were no COVID-19 cases in the vaccine group and 15 COVID-19 cases in the placebo group.

Table 9. Interim Analysis[a] for Primary Efficacy Endpoint, COVID-19 Starting 14 Days After the 2nd Dose, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*	Met Predefined Success Criterion**
All participants	5 (<0.1) 1.840	90 (0.6) 33.365	94.5% (86.5%, 97.8%)	Yes
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)	NA
65 and older	0 / 3527	15 / 3499 (0.4) 21.046	100%	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1.
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the 2nd dose. All potential COVID-19 cases starting 14 days after the 2nd dose in the clinical database as of 07-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (07-Nov-2020 is the data cutoff date for efficacy). One case (in the placebo group) was assessed as a case by the adjudication committee but did not meet case definition based on statistical analysis plan (participant had body aches, nasal congestion, rhinorrhea, which were not protocol defined symptoms).
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/placebo) and 95% CI from the stratified Cox proportional hazard model.
**The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary: the one-sided nominal alpha of 0.0049 based on 95 cases using the Lan-DeMets O'Brien-Fleming spending function.

There were an additional 18 COVID-19 cases which met the protocol-defined primary efficacy endpoint but were not able to be adjudicated in time for the interim analysis. Of these 18 cases, one was in the vaccine group, and 17 were in the placebo group. Vaccine efficacy for the primary efficacy endpoint including these unadjudicated cases was similar to the results presented above.

Interim Subgroup Analyses of Vaccine Efficacy

Subgroup analyses for the primary efficacy endpoint include VE based on age, sex, race and ethnicity, risk factor, and baseline SARS-CoV-2 status and provide additional information on the applicability of these results across the general population. In general, VE among the subgroups are similar to the VE seen in the overall study population. The small number participants and cases in some subgroups, such as participants ≥75 years of age and participants in certain racial subgroups, limits the interpretability of the individual VE results, but are displayed for completeness.

Table 10. Subgroup Analyses of Vaccine Efficacy[a], COVID-19 14 Days After Dose 2 Per Adjudication Committee Assessments, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Age (years)			
18 to <65	5 / 10407 (<0.1) 2.504	75 / 10384 (0.7) 37.788	93.4% (83.7%, 97.3%)
65 to <75	0 / 2904	12/ 2823 (0.4) 20.883	100%
75 and older	0 / 623	3 / 676 (0.4) 21.726	100%
Age and risk for severe COVID-19**			
18 and <65 and not at risk	4 / 8309 (<0.1) 2.524	57 / 8323 (0.7) 36.034	93.0% (80.8%, 97.5%)
18 and <65 and at risk	1 / 2098 (<0.1) 2.428	18 / 2061 (0.9) 44.673	94.6% (59.4%, 99.3%)
≥65	0 / 3527	15 / 3499 (0.4) 21.046	100%
Sex			
Female	3 / 6661 (<0.1) 2.271	45 / 6514 (0.7) 34.991	93.5% (79.2%, 98.0%)
Male	2 / 7273 (<0.1) 1.433	45 / 7369 (0.6) 31.883	95.5% (81.5%, 98.9%)
Race and Ethnicity			
Non-Hispanic white	5 / 8858 (<0.1) 2.657	70 /8755 (0.8) 37.721	93.0% (82.6%, 97.2%)
Communities of color	0 / 5054	20 / 5102 (0.4) 23.892	100%
Ethnicity			
Hispanic or Latino	0 / 2783	12 / 2769 (0.4) 26.346	100%
Not Hispanic or Latino	5 / 11019 (<0.1) 2.243	77 / 10987 (0.7) 34.729	93.6% (84.1%, 97.4%)
Race			
American Indian or Alaska Native	0 / 107	0 / 110	
Asian	0 / 616	3 / 684 (0.4) 26.549	100%
Black or African American	0 / 1,369	4 / 1338 (0.3) 18.566	100%
Native Hawaiian or Other Pacific Islander	0 / 33	0 / 30	
White	5 /11078 (<0.1) 2.215	80 / 11005 (0.7) 35.821	93.8% (84.8%, 97.5%)
Multiple	0 / 293	1 / 304 (0.3)	100%

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Other	0 / 298	2 / 293 (0.7) 45.645	100%

Source: Sponsor's Table 14.2.2.1.1.6.1.1, Table 14.2.2.1.1.6.3.1, Table 4.2.2.1.1.6.7.1, Table 14.2.2.1.1.6.10.1, Table 14.2.2.1.1.6.4.1, Table 14.2.2.1.1.6.2.1, Table 14.2.2.1.1.6.5.1, Table 14.2.2.1.1.6.6.1
[a] EUA request (interim analysis): November 7, 2020 data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
At risk for severe COVID-19 due to comorbidity, regardless of age. High risk is defined as patients who meet at least one of the following criteria (protocol-defined): Chronic lung disease (eg, emphysema and chronic bronchitis, idiopathic pulmonary f brosis, and cystic f brosis) or moderate to severe asthma; Significant cardiac disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension); Severe obesity (body mass index ≥40 kg/m2); Diabetes (Type 1, Type 2 or gestational); Liver disease; Human Immunodeficiency Virus (HIV) infection
**used as stratification factor for randomization

The demographics of the participants with confirmed COVID-19 cases contributing to the primary efficacy analysis are displayed below in Table 11.

Table 11. Demographic Characteristics[a], Participants With COVID-19 Starting 14 Days After Dose 2, Per Adjudication Committee Assessments, Per-Protocol Set

Characteristic	Vaccine (N[a] =5) N[b] (%)	Placebo (N[a] =90) N[b] (%)	Total (N[a] =95) N[b] (%)
Sex			
Female	3 (60)	45 (50)	48 (50.5)
Male	2 (40)	45 (50)	47 (49.5)
Age group			
18 to <65 years	5 (100)	75 (83.3)	80 (84.2)
≥65 to <75 years	0	12 (13.3)	12 (12.6)
≥75 years	0	3 (3.3)	3 (3.2)
Race			
American Indian or Alaska Native	0	0	0
Asian	0	3 (3.3)	3 (3.2)
Black or African American	0	4 (4.4)	4 (4.2)
Native Hawaiian or Other Pacific Islander	0	0	0
White	5 (100)	80 (88.9)	80 (84.2)
Multiracial	0	1 (1.1)	1 (1.1)
Other	0	2 (2.2)	2 (2.1)
Ethnicity			
Hispanic or Latino	0	12 (13.3)	12 (12.6)
Not Hispanic or Latino	5 (100)	77 (85.6)	82 (86.3)
Not reported	0	1 (1.1)	1 (1.1)
At risk for severe COVID-19			
Yes	1 (20)	24 (26.7)	25 (26.3)
No	4 (80)	66 (73.3)	70 (73.7)

[a] N = number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations. [a] EUA request (interim analysis): November 07 2020 efficacy data cutoff. [a] EUA request (interim analysis): November 07 2020 cutoff.
[b] n = Number of participants with the specified characteristic.

Only 2.2% of participants had evidence of prior infection at study enrollment, and there was only one COVID-19 case starting 14 days after dose 2 reported from this subgroup, which was in a participant in the placebo group. There is insufficient data to conclude on the efficacy of the vaccine in previously infected individuals.

Table 12. Vaccine Efficacy by Baseline SARS-CoV-2 Status[a]: First COVID-19 From 14 Days After Dose 2 Per Adjudication Committee Assessment, Full Analysis Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.

Additional subgroup analyses of the interim primary efficacy analysis were conducted to evaluate the vaccine efficacy, by risk factor for severe COVID-19. VE point estimates were consistent with the efficacy observed for the overall study population, though interpretation of the results is limited by small numbers of participants and cases.

Table 13. Vaccine Efficacy by Risk Factor: First COVID-19 Occurrence From 14 Days After Dose 2, Per Adjudication Committee Assessment, Per-Protocol Set

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI $\geq$40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

[a] EUA request (interim analysis): November 7, 2020 efficacy data cutoff
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented for subgroups for which the lower bound was not evaluable by the statistical methods used for the analysis.
** Post hoc analysis.

Interim Secondary Efficacy Analyses

Severe COVID-19 Cases

All 11 cases of severe COVID-19 at least 14 days after second dose as assessed by the adjudication committee were in the placebo group. Of these 11 participants, 5 had risk factors for severe COVID-19 and 6 did not. Three severe COVID-19 cases resulted in hospitalization and 8 did not. Nine of these cases met the severe COVID-19 case definition based on low oxygen saturation ≤93% on room air without any other severe disease criteria. One participant had low oxygen saturation as well as systolic blood pressure <90 mmHg. One participant had low oxygen saturation and missing data on whether other criteria were met. The vaccine efficacy of this secondary efficacy endpoint is shown in Table 14.

Table 14. Severe COVID-19 Cases Starting 14 Days After Second Dose Based on Adjudication Committee Assessment, Per-Protocol Set

	Vaccine Group N=13934 Cases n (%)	Placebo Group N=13883 Cases n (%) Incidence rate per 1,000 person-years	Vaccine Efficacy (VE) % (95% CI)*
Severe COVID-19	0	11 (<0.1); 4.072	100%

[a] EUA request (interim analysis): Novemer 07 2020 efficacy data cutoff.
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo) and 95% CI from the stratified Cox proportional hazard model. The VE 95% confidence interval is not presented when the lower bound was not evaluable by the statistical methods used for the analysis.

One participant in the mRNA-1273 group, a participant >65 years of age who had risk factors for severe COVID-19, was hospitalized due to oxygen saturation of 88% on room air 2 months after receiving the second dose of vaccine. There was a verbal report of a positive SARS-CoV-2 RT-PCR test 3 days prior to hospitalization; however, NP swab collected during hospitalization was negative for SARS-CoV-2. Due to absence of a confirmed RT-PCR result at the time of data snapshot, this case was not referred for adjudication and not captured. The pre-hospitalization RT-PCR result was later reported to be positive from an external CLIA-certified laboratory and may represent a severe COVID-19 case with hospitalization in the vaccine group.

There were 4 additional severe COVID-19 cases which met the protocol-defined severe COVID-19 endpoint but were not able to be adjudicated in time for the interim analysis. All 4 cases were in the placebo group.

Other Secondary Efficacy Endpoints

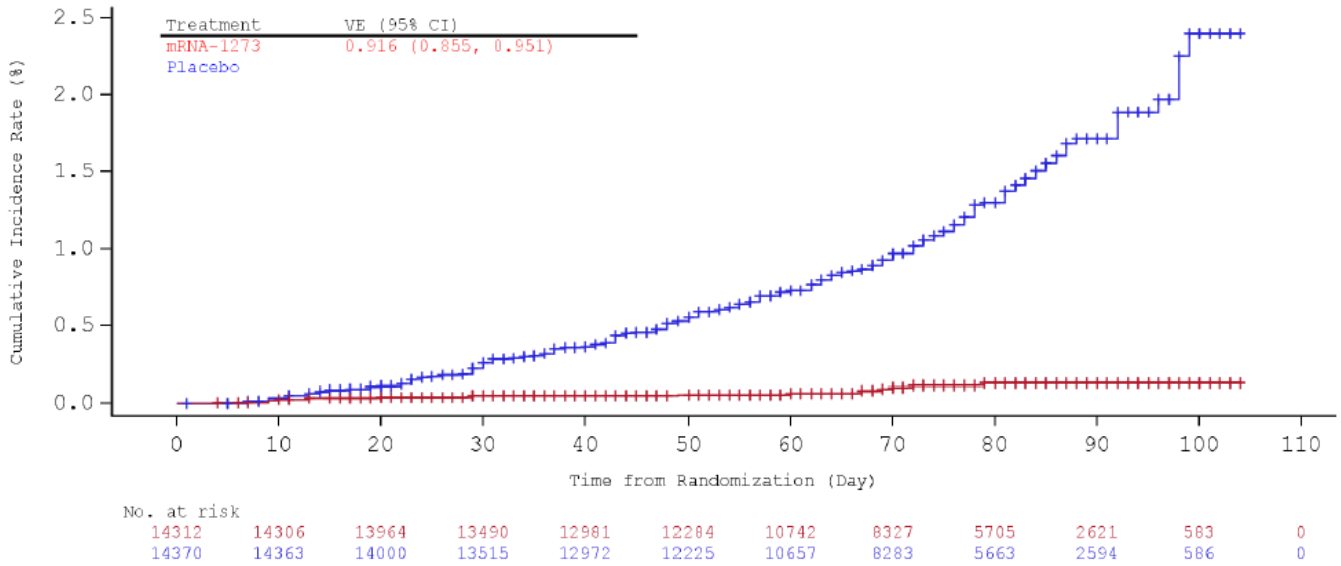
The secondary efficacy endpoint of VE of mRNA-1273 for the prevention of COVID-19 disease based on a less restrictive definition of COVID-19 disease from 14 days after dose 2 showed similar case splits and VE to the primary efficacy endpoints described above. Efficacy against COVID-19 occurring at least 14 days after the first dose of vaccine, including cases that occurred after the second dose, was also similar to the primary endpoint. There were no deaths due to COVID-19 at the time of the interim analysis to enable an assessment of vaccine efficacy against death due to COVID-19.

Cumulative Incidence Curves – Interim Efficacy Analysis

Based on the cumulative incidence curve for cases in the mITT efficacy population after randomization (same as date of dose 1), COVID-19 cases appear to have occurred similarly at low rates for both the mRNA-1273 and placebo groups until around Day 14 after dose 1. The

curves then diverge, with more cases accumulating in the placebo group than the mRNA-1273 group.

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Additional Interim Efficacy Analyses

Additional analyses were done to assess efficacy against COVID-19 after one dose of mRNA-1273. In participants in the mITT set who only received one dose of the vaccine at the time of the interim analysis, VE after one dose was 80.2% (95% CI 55.2%, 92.5%). These participants had a median follow-up time of 28 days (range: 1 to 108 days). The small, non-random sample and short median follow-up time limits the interpretation of these results. There appears to be some protection against COVID-19 disease following one dose; however, these data do not provide sufficient information about longer term protection beyond 28 days after a single dose.

Table 15. Vaccine Efficacy[a] of mRNA-1273 to Prevent COVID-19 From Dose 1 by Time Period in Participants Who Only Received One Dose, mITT Set

First COVID-19 Occurrence After Dose 1	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.5)	39/1079 (96.7)	80.2% (55.2%, 92.5%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.8% (-53.6%, 86.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (68.8%, 99.1%)

Surveillance time in person years for given endpoint across all participants within each group at risk for the endpoint
* VE is calculated as 1-ratio of incidence rates (mRNA-1273/Placebo). The 95% CI of VE is calculated using the exact method conditional upon the total number of cases, adjusting for person-years
**Participants who were not at risk (cases or censored at prior time period) are excluded from this analysis
[a] Based on interim analysis: Novemer 7, 2020 efficacy data cutoff.

A similar analysis was conducted to look at vaccine efficacy against severe COVID-19 after one dose. In participants in the mITT group who received only one vaccine, 2 participants in the mRNA-1273 group and 4 participants in the placebo group developed severe COVID-19. Both participants in the vaccine group met the case definition for severe COVID-19 based on oxygen saturation ≤93% on room air. These results should be interpreted cautiously given the small sample size and case number and the short follow-up duration.

Table 16. Vaccine Efficacy[a] of mRNA-1273 to Prevent Severe COVID-19 After Dose 1 in Participants Who Only Received One Dose in mITT Set

	Vaccine Group N=996 Case n (%)	Control Group N=1079 Case n (%)	Vaccine Efficacy (95% CI)
Number of participants with severe COVID-19 starting after dose 1	2 (0.2)	4 (0.4)	42.6% (-300.8, 94.8)

[a] Based on interim analysis : EUA request (interim efficacy analysis): November 7, 2020 efficacy data cutoff.

Final Scheduled Efficacy Analysis

Data from the final scheduled efficacy analysis were submitted as an amendment to the EUA request on December 7, 2020. Analyses of efficacy endpoints beyond those presented below have not been independently verified by the FDA. The median efficacy and safety follow-up for participants in the study at of the time of the final scheduled efficacy analysis (November 21, 2020 efficacy data cutoff) was 9 weeks. Vaccine efficacy against COVID-19 starting 14 days after the second dose was 94.1% (95% CI 89.3%, 96.8%) and was consistent with results obtained from the interim analysis. The VE in participants ≥65 years of age appears to be lower than in younger adults 18 to <65 years (86.4% compared to 95.6%) and lower than observed in the interim analysis (100% based on a total of 15 cases).

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Source: Sponsor's Table 14.2.2.1.1.1.1, Table 14.2.2.1.1.6.1.1
COVID-19: symptomatic COVID-19 requiring positive RT-PCR result and at least 2 systemic symptoms or 1 respiratory symptom. Cases starting 14 days after the second dose. All potential COVID-19 cases starting 14 days after the second dose in the clinical database as of 21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy). One case (in the vaccine group) was adjudicated as a COVID-19 case by the committee but did was meet the case definition per statistical analysis plan due to documented symptoms and positive PCR being more than 14 days apart.
21-Nov-2020 have been sent to adjudication committee, and have been adjudicated for this analysis (21-Nov-2020 is the data cutoff date for efficacy).
* Incidence rate is defined as the number of participants with an event divided by the number of participants at risk and adjusted by person-years (total time at risk) in each treatment group. The 95% CI is calculated using the exact method (Poisson distribution) and adjusted by person-years.
**VE and 95% CI from the stratified Cox proportional hazard model
***The one-sided p-value is <0.0001 from the stratified Cox proportional hazard model to test the null hypothesis of VE ≤30%, achieving the pre-specified efficacy boundary.
[1] Percentage based on number of participants in the 18 to <65 years of age group.
[2] Percentage based on number of participants in the ≥65 years of age group.

Severe COVID-19 Cases

In the primary efficacy analysis, there were an additional 19 cases of severe COVID-19 (one of which resulted in death from COVID-19), for a total of 30 severe COVID-19 cases starting 14 days after dose 2, per adjudication committee assessment. All 30 cases were in the placebo group. Nine of the total 30 severe COVID-19 cases resulted in hospitalization. Of the 19 additional severe cases since the interim analysis, 12 cases met the severe case definition due to low oxygen saturation ≤93% with no other criteria met. The remaining participants met the definition based on the following reasons: death (1 participant), ARDS requiring ECMO (1 participant), low oxygen saturation and renal and neurologic dysfunction (1 participant), low oxygen saturation and low blood pressure (2 participants), need for high flow oxygen (1 participant), low blood pressure only (1 participants). The COVID-19 case which resulted in death was in a 54-year-old participant with diabetes. The possible severe COVID-19 case in a mRNA-1273 vaccine recipient described with the interim efficacy analysis (negative SARS-CoV-2 PCR per the study central laboratory but reported positive PCR per a CLIA-certified external lab) is not included in the per-protocol analysis below.

Table 18. Secondary Efficacy Analysis, Severe COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Severe Cases 14 Days After Dose 2 Based on Adjudication Committee Assessments	Vaccine Group N=13934 Cases n (%) (Incidence rate per 1,000 person-years)	Placebo Group N=13883 Cases n (%) (Incidence rate per 1,000 person-years)	Vaccine Efficacy (VE) % (95% CI)*
All participants	0	30 (0.2) 9.138	100%

[a] EUA request (primary analysis): November 21, 2020 efficacy data cutoff.

Efficacy Summary

The data from the planned interim efficacy analysis, with a cutoff date of November 7, 2020, and median follow-up for efficacy of 7 weeks post-dose 2, met the prespecified success criteria established in the study protocol. Efficacy of the vaccine to prevent COVID-19 occurring at least 14 days after dose 2 was 94.5%, (95% CI 86.5%; 97.8%) in participants without prior evidence of SARS-CoV-2 infection. VE was >93% in the group of participants with or without prior infection, although interpretation of data in participants with positive SARS-CoV-2 status at baseline is limited by the small sample size and case numbers in this subgroup. Efficacy outcomes across demographic subgroups were consistent with the efficacy seen in the overall study population. All 11 cases of severe COVID-19 occurring 14 days after the second dose

were in the placebo group, although one severe COVID-19 may have occurred in the vaccine group but did not meet criteria for the protocol-specified case definition. Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose 1 was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose 1 and before dose 2, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine, because the numbers of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison.

Data from a final efficacy analysis (data cutoff November 21, 2020) was submitted as an amendment after the initial EUA request. The FDA has not independently verified the complete efficacy data from this dataset, beyond those analyses presented above. The final scheduled efficacy analysis on the primary endpoint, demonstrating a VE point estimate of 94.1% (95% CI: 89.3%, 96.8%), appear to align with the data obtained from the interim analysis, except for a lower efficacy observed in participants ≥65 years of age compared to that in younger adults 18 to <65 years of age and compared to the efficacy estimate from the interim analysis.

5.2.6 Safety

The safety analyses presented in this review are largely derived from the November 11, 2020 dataset that was the basis for the November 30, 2020 EUA request. FDA has not independently verified the complete safety dataset and analyses from the cutoff date of November 25, 2020. However, all new deaths, SAEs, unsolicited adverse events of interest, and pregnancies were reviewed using the cutoff date of November 25, 2020. No additional safety concerns were raised based on the additional data reviewed by FDA or analyses presented by the Sponsor. The safety analyses from the November 25, 2020 cutoff date, as presented by the Sponsor, appear to align with results from the interim analysis in terms of overall rates and types of solicited and unsolicited adverse events.

Adverse events were reported in a higher proportion of vaccine recipients than placebo recipients, and this imbalance was driven by reactogenicity (solicited AEs) reported in the 7 days following each dose of vaccine. The proportions of participants with SAEs, death, and withdrawals due to adverse events were balanced across the study groups. Overall, rates of AEs were lower in participants with baseline positive SARS-CoV-2 status compared with those with baseline negative SARS-CoV-2 status. The tables below provide an overview of the rates of AEs by treatment groups and baseline SARS-CoV-2 status.

Table 19. Participants Reporting at Least One Adverse Event, Among All Participants and by Baseline SARS-COV2 Status (Safety Set)[a]

Adverse Event Type	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set	**N=15176**	**N=15162**
Solicited adverse reactions after any injection	14338/15176 (94.5)	9027/15162 (59.5)
Baseline SARS-COV-2 negative	13566/14309 (94.8%)	8576/14363 (59.7)
Baseline SARS-COV-2 positive	279 /340 (82.1%)	151/334 (45.2)
Solicited local adverse reaction	13,962/15176 (92.0)	4,381/15161 (28.9)
Baseline SARS-COV-2 negative	13211/14309 (92.3)	4147/14362 (28.9)
Baseline SARS-COV-2 positive	268/340 (78.8)	74/334 (22.2)
Grade 3 solicited injection site reaction[a]	1386/15176 (9.1)	143/15161 (0.9)
Baseline SARS-COV-2 negative	1307/14309 (9.1)	131/14362 (0.9)
Baseline SARS-COV-2 positive	23/340 (6.8)	5/334 (1.5)
Solicited systemic adverse reaction	12553/15176 (82.7)	8032/15,162 (53.0)
Baseline SARS-COV-2 negative	11893/14309 (83.1)	7628/14363(53.1)
Baseline SARS-COV-2 positive	237/340 (69.7)	137/334 (41.0)
Grade 3 or 4 solicited systemic adverse reaction	2,501/15,176 (16.5)	560/15,162 (3.7)
Baseline SARS-COV-2 negative	2383/14309 (16.7)	529/14363 (3.7)
Baseline SARS-COV-2 positive	37/340 (10.9)	13/334 (3.9)
Safety Set	**N=15184**	**N=15165**
Unsolicited adverse event up to 28 days after any injection	3325/15184 (21.9)	2949/15165 (19.4)
Baseline SARS-COV-2 negative	3204/14316 (22.4)	2846/14366 (19.8)
Baseline SARS-COV-2 positive	49/341 (14.4)	56/334 (16.8)
Unsolicited adverse event	3283/15184 (21.6)	2902/15165 (19.1)
Grade 3 unsolicited adverse event	187/15184 (1.2)	148/15165 (1.0)
Related** unsolicited adverse events	1127/15184 (7.4)	609/15165 (4.0)
Baseline SARS-COV-2 negative	1095/14316 (7.6)	585/14366 (4.1)
Baseline SARS-COV-2 positive	16/341 (4.7)	14/334 (4.2)
Related** Grade 3 unsolicited adverse event	69/15184 (0.5)	28/15165 (0.2)
Medically attended adverse Event	1215/15184 (8.0)	1276/15165 (8.4)
Baseline SARS-COV-2 negative	1167/14316 (8.2)	1243/14366 (8.7)
Baseline SARS-COV-2 positive	19/341 (5.6)	18/334 (5.4)
Related** medically attended adverse events	122/15184 (0.8)	73/15165 (0.5)
Baseline SARS-COV-2 negative	118/14316 (0.8)	68/14366 (0.5)
Baseline SARS-COV-2 positive	0/341	5/334 (1.5)
Serious adverse event	82/15184 (0.5)	86/15165 (0.6)
Baseline SARS-COV-2 negative	79/14316 (0.6)	82/14366 (0.6)
Baseline SARS-COV-2 positive	0/341	3/334 (0.9)
Related** serious adverse event	5/15184 (<0.1)	4/15165 (<0.1)
Baseline SARS-COV-2 negative	5/14316 (<0.1)	4/14366 (<0.1)
Baseline SARS-COV-2 positive	0/341	0/334
Death*	4/15184 (<0.1)	4/15165 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	41/15184 (0.3)	71/15165 (0.5)
Baseline SARS-COV-2 negative	34/14316 (0.2)	68/14366 (0.5)
Baseline SARS-COV-2 positive	4/341 (1.2)	3/334 (0.9)

Source**:** Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7

[a] There were no reports of Grade 4 injection site adverse reactions

[a] EUA request (interim analysis)-November 11, 2020

**Related as assessed by investigator

In subgroup analyses of adults ≥65 years of age, rates of solicited reactions (any, Grade 3 or higher) and all other unsolicited adverse events (AEs) (all and related) were comparable to those observed in all participants. Table 20 below summarizes AEs in participants ≥65 years of age, irrespective of baseline serostatus (as less than 1% of ≥65-year-olds were seropositive at baseline).

Table 20. Adverse Events Among Adults ≥65 Years of Age (Safety Set)[a]

Participants Reporting at Least One	Vaccine Group n/N (%)	Placebo Group n/N (%)
Solicited Safety Set		
Solicited adverse reactions after any injection	3497/3766 (92.9)	2010/3750 (53.6)
Solicited local adverse reaction	3337/3766 (88.6)	859/3750 (22.9)
Grade 3 solicited local adverse reaction	279/3766 (7.4)	66/3750 (1.8)
Solicited systemic adverse reaction	2922/3766 (77.6)	1754/3750 (46.8)
Grade 3 or 4 solicited systemic adverse reaction	444/3766 (11.8)	119/3750 (3.2)
Safety Set		
Unsolicited Adverse Event up to 28 days after any	872/3770 (23.1)	734/3750 (19.6)
Related** unsolicited adverse events	261/3770 (6.9)	138/3750 (3.7)
Medically Attended Adverse Event	336/3770 (8.9)	376/3750 (10.0)
Related** medically attended adverse events	22/3770 (0.6)	13/3750 (0.3)
Serious Adverse Event	36/3770 (1.0)	42/3750 (1.1)
Related** serious adverse event	2/3770 (<0.1)	1/3750 (<0.1)
Death	1/3768 (<0.1)	2/3752 (<0.1)
Related** deaths	0	0
AE leading to discontinuation of the vaccine	12/3770 (0.3)	17/3750 (0.5)
Related** AE leading to discontinuation of the vaccine	3/3370 (<0.1)	4/3750 (0.1)

Source: Sponsor's Table 14.3.1.1.3, Table 14.3.1.7.1, Table 14.3.1.7.3, Table 14.3.1.7.7. [a] EUA request (interim analysis)-November 11 2020. Data provided in response to Information Request (IR),- received December 7 2020
**Related as assessed by investigator

Solicited Adverse Reactions

Solicited local and systemic adverse reactions with onset within 7 days after each dose were assessed across groups and are presented in the tables below stratified by age (18 to 64 years; ≥65 years) for all participants. Solicited adverse reactions (AR) were recorded daily by study participants using eDiaries and included the assessment of local injection site reactions (pain, erythema, swelling, and lymphadenopathy) and systemic reactions (fever, headache, fatigue, myalgia, arthralgia, chills, and nausea/vomiting).

Local Adverse Reactions

Solicited local AR were reported by the majority of vaccine recipients and at higher rates than placebo recipients. Vaccine recipients reported higher rates of local reactions after dose 1 than dose 2. The proportions of participants reporting any local AR were 84.2% and 88.8% after dose 1 and dose 2 in vaccine recipients, compared to 19.8% and 18.8% after dose 1 and dose 2 in placebo recipients, respectively. The proportions reporting at least one grade 3 local AR were 3.5% and 7.0% after dose 1 and dose 2, respectively in vaccine recipients and 0.5% after any dose in placebo recipients. There were no reports of Grade 4 local reactions after any dose across groups. The majority of vaccine recipients (57.6%) reported onset of local AR on Day 1 while at home, and the median duration was 2 days after dose and 3 days after dose 2.

Overall across both age cohorts, the most frequently reported local AR was pain, reported by 83.7% vs 19.8% of vaccine/placebo recipients after the first dose (2.8% vs 0.4% reported as Grade 3) and 88.4% vs 17.0% of vaccine/placebo recipients after dose 2 (4.1% vs 0.3% reported as Grade 3). The median durations for pain were 2 days and 3 days after dose 1 and dose 2, respectively. The highest rates of pain were in participants 18 to <64 years after dose 2, with 90.1% reporting any pain and 4.6% reporting Grade 3 pain.

Axillary lymphadenopathy (vaccination arm) was the second most frequently reported local AR overall. It was reported in 10.2% vs 4.8% of vaccine/placebo recipients after dose 1 and 14.0% vs 3.9% of vaccine/placebo recipients after dose 2 respectively. Grade 3 axillary lymphadenopathy was reported in 0.3% vs 0.2% vaccine/placebo recipients after dose 1 and in 0.5% vs 0.1% of vaccine/placebo recipients after dose 2. The median duration after dose 1 was 1 day and after dose 2 was 2 days. The highest rates of axillary lymphadenopathy were reported by participants 18 to 64 years of age after dose 2, with 16.0% reporting any severity lymphadenopathy and 0.4% reporting Grade 3 lymphadenopathy.

Local reactions that persisted beyond 7 days after any dose were reported by both vaccine recipients and placebo recipients. Local reactions that persisted were reported by 3.7% of vaccine recipients and 1.3% of placebo recipients across both age cohorts. In the younger age cohort, 4.2% of vaccine recipients and 1.4% of placebo recipients reported a local reaction that persisted beyond 7 days, of which 0.6% of vaccine recipients and <0.1% of placebo recipients reported a Grade 3 reaction that persisted. In the older age cohort, 2.3% of vaccine recipients compared to 1.1% of placebo recipients reported a local reaction that persisted, including 0.5% of vaccine recipients, and <0.1% of placebo recipients reporting Grade 3 local reactions. Frequently reported local reactions persisting beyond 7 days in the younger age cohort in vaccine/placebo recipients were pain (1.5%/0.6%) and axillary lymphadenopathy (2.5%/0.7%), and in the older age cohort pain (1.2%/0.6%) and erythema (0.7%/<0.1%).

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain[a]	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema[b] (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling[b] (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Lymphadenopathy[c]	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)

Source: Sponsor's Table 14.3.1.1.4, Table 14.3.1.1.5
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose
[a] EUA request (interim analysis)-November 11 2020
Note: Adverse reaction data were collected on the electronic diary (eDiary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Table 22. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain[a]	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema[b] (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling[b] (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Lymphadenopathy[c]	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)
Grade 3	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5]
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
[a] EUA request (interim analysis)-November 11 2020.
Note: Adverse reaction data were collected on the electronic diary by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n= # of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N.
a: Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
b: Erythema and Swelling/Induration- Grade 3: >100mm/>10cm; Grade 4: necrosis/exfoliative dermatitis
c: Axillary Swelling/Tenderness collected as solicited local adverse reaction (i.e. lymphadenopathy: localized axillary swelling or tenderness ipsilateral to the vaccination arm) - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization
Note: No grade 4 solicited local adverse reactions were reported.

Systemic Adverse Reactions

Solicited systemic AR were reported for the majority of vaccine recipients and at higher rates than for placebo recipients. Vaccine recipients had higher rates of systemic reactions after the second dose than the first dose. The proportions of vaccine and placebo participants reporting systemic AR were as follows: reporting any grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2, and reporting Grade 3 was 2.9% vs. 2.0% after dose 1 and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a Grade 4 systemic reaction (mainly fever > 104 ºF). The majority of vaccine recipients reported onset of systemic AR while at home either on Day 1 (33.7%) or on Day 2 (37.0%), and the median duration after any dose was 2 days.

Overall, the most frequently reported systemic AR was fatigue, reported by 68.5% of vaccine recipients and 36.1% of placebo recipients. After any dose, Grade 3 fatigue was reported by 9.6% of vaccine participants and 1.3% of placebo recipients. Grade 4 fatigue was reported by 1 participant in the vaccine group and none in the placebo group. After dose 1, any/Grade 3 fatigue was reported by 37.2%/1.0% of vaccine recipients and after dose 2 any/Grade 3 fatigue was reported by 65.2%/9.7% of vaccine recipients. The median duration for fatigue in vaccine recipients was 2 days after any dose. The highest rates of fatigue were reported by participants 18 to 64 years after the 2nd dose, with 67.6% reporting any fatigue, 10.6% reporting Grade 3, and 1 participant reporting Grade 4 (after Dose 1).

Rates of other solicited systemic AR were: headache 63.0% vaccine group vs. 36.5% placebo group; myalgia 59.6% vaccine group vs. 20.1% placebo group; arthralgia 44.8% vaccine group vs. 17.2% placebo group; and chills 43.4% vaccine group vs. 9.5% placebo group. The rates of Grade 3 AR were: headache 5.5% vaccine group vs. 2.2% placebo group; myalgia 8.6% vaccine group vs. 0.6% placebo group; arthralgia 5.1% vaccine group vs. 0.5% placebo group; and chills 1.3% vaccine group vs. 0.2% of placebo group. The median duration was 1 day after dose 1 and 1 to 2 days after dose 2. The highest rates of solicited reactions were observed in participants 18 to 64 years after dose 2 and included the following: headache 62.8% (5.0% reported Grade 3), myalgia 61.3% (10.0% Grade 3), arthralgia 45.2% (5.8% Grade 3), and chills 45.8% (1.5% Grade 3). There was one vaccine recipient in the younger age cohort who also reported Grade 4 arthralgia after dose 1.

Fever was reported after any dose by 14.8% of vaccine participant and 0.6% of placebo recipients. Fever was reported after dose 1 in 0.8% of vaccine recipients and 15.6% of vaccine recipients after dose 2. Grade 3 (≥102.1 ºF) was reported by <0.1% (11 participants) of vaccine recipients after Dose 1 and 1.3% (186 participants) of vaccine recipients after dose 2. Grade 4 (≥104.0 ºF) fever were reported by 4 vaccine recipients after dose 1 and 11 vaccine recipients after dose 2. In participants 18 to 64 years after dose 2, any fever, Grade 3 fever, and Grade 4 fever were reported in 1,806 participants (17.4%), 168 participants (1.6%), and 10 participants (<0.1%), respectively.

Systemic reactions persisting longer than 7 days were reported in both age cohorts of vaccine and placebo recipients after any dose. In the vaccine group, 11.9% of participants reported a solicited reaction that persisted beyond 7 days compared to 9.5% of placebo participants. In the younger age cohort, 9.8% of vaccine recipients and 8.9% of placebo recipients reported a systemic reaction that persisted beyond 7 days; and 2.0% of vaccine recipients and 1.2% of placebo recipients reported Grade 3 or 4 systemic reaction that persisted beyond 7 days. In the older age cohort, 9.4% of vaccine recipients and 8.1% of placebo recipients reported a systemic reaction that persisted; 1.7% of vaccine recipients (63 participants) and 0.8% of placebo

recipients (31 participants) reported a Grade 3 or 4 reaction that persisted. The most frequently reported systemic reactions that persisted beyond 7 days in vaccine recipients/placebo recipients 18 to 64 years were fatigue (5.7%/5.0%), headache (4.8%/4.0%), myalgia (2.7%/2.7%), and arthralgia (2.6%/2.8%); in the older cohort were fatigue (5.8%/4.5%), arthralgia (3.7%/3.8%), myalgia (2.9%/2.7%), and headache (2.8%/2.7%).

Fever persisted beyond 7 days in 7 vaccine recipients and 4 placebo recipients, all of whom were in the younger age cohort. There were 2 vaccine recipients who reported grade 3 fever that persisted, and none in the placebo group.

Table 23. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18-64 years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3	363/11405 (3.2)	248/11406 (2.2)	1801/10358 (17.4)	215/10320 (2.1)
Grade 4	5/11405 (<0.1)	4/11406 (<0.1)	10/10358 (<0.1)	2/10320 (<0.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3	10/11403 (<0.1)	1/11404 (<0.1)	168/10352 (1.6)	1/10315 (<0.1)
Grade 4	4/11403 (<0.1)	4/11404 (<0.1)	10/10352 (<0.1)	2/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3	120/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Grade 4	1/11401 (<0.1)	0	0	0
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357 (6.1)	1312/10316 (12.7)
Grade 3	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3	47/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Grade 4	1/11401 (<0.1)	0	0	0
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis)-November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ⩾39.0 – ⩽40.0°C or ⩾102.1 – ⩽104.0° F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Table 24. Frequency of Solicited Systemic Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age ≥65 Years, Solicited Safety Set*[a]

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Any Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3	84/3761 (2.2)	63/3748 (1.7)	387/3589 (10.8)	58/3549 (1.6)
Grade 4	0	0	2/3589 (<0.1)	1/3549 (<0.1)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3	1/3760 (<0.1)	1/3748 (<0.1)	18/3587 (0.5)	0
Grade 4	0	2/3748 (<0.1)	1/3587 (<0.1)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)

Adverse Reaction	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3	4/3761 (0.1)	4/3745 (0.1)	10/3587 (0.3)	3/3549 (<0.1)
Grade 4	0	0	1/3587 (<0.1)	0
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

Source: Sponsor's Tables 14.3.1.1.4 and 14.3.1.1.5
[a] EUA request (interim analysis) November 11 2020
*Safety Analyses Set: all randomized participants who received ≥1 vaccine or control dose.
Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicitated adverse reactions.
n=# of participants with specified reaction
N = number of exposed participants who submitted any data for the event, percentages are based on n/N a: Fever - Grade 3: ≥39.0 – ≤40.0°C or ≥102.1 – ≤104.0°F; Grade 4: >40.0°C >104.0°F
b: Headache – Grade 3: Significant; any use of Rx pain reliever or prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
c: Fatigue, Myalgia, Arthralgia – Grade 3: Significant; prevents daily activity; Grade 4: Requires E.R. visit or hospitalization
d: Nausea/Vomiting – Grade 3: Prevents daily activity, requires outpatient intravenous hydration; Grade 4: Requires E.R. visit or hospitalization for hypotensive shock
e: Chills – Grade 3: Prevents daily activity and requires medical intervention; Grade 4: Requires E.R. visit or hospitalization

Unsolicited AEs

Unsolicited AEs from the November 11, 2020 data cutoff include safety data from participants who had at least 1 month of follow-up after dose 2 (76.7% of all participants) those who had at least 2 months of follow-up after dose 2 (25.3% of all participants). The median study duration following dose 2 was 7 weeks across study groups. Table 25 below shows unsolicited AEs reported through the first data cutoff. Treatment emergent adverse events (AEs) were defined as any event that occurred during the study and was not present before exposure (study vaccine or placebo), any event that occurred during the study and was not present before exposure, or any event already present that worsened after exposure. The following unsolicited adverse events were specified in the protocol:

- Unsolicited AEs observed or reported during the 28 days following each vaccine or placebo dose
- AEs leading to discontinuation from vaccination and/or study participation through Day 759 (study completion) or withdrawal from the study
- Serious adverse events and medically attended adverse events through Day 759 (study completion) or withdrawal from study

Determination of severity for all unsolicited AE were made by the investigators based on medical judgement and definitions of severity as mild, moderate, or severe.

The overall proportions of participants who reported an unsolicited adverse event were generally similar, with numerically slightly higher rates of unsolicited AEs in the vaccine group compared to placebo group for some categories of unsolicited nonserious AEs.

Table 25. Summary of Unsolicited AEs Regardless of Relationship to the Investigational Vaccine, Through 28 Days After Any Vaccination, Study 301, Safety Set

Event Type	Nov 11 Dataset[a] mRNA-1273 (N=15184) n (%)	Nov 11 Dataset[a] Placebo (N=15165) n (%)	Nov 25 Dataset[b] mRNA-1273 (N=15185) n (%)	Nov 25 Dataset[b] Placebo (N=15166) n (%)
All unsolicited AEs	3325 (21.9)	2949 (19.4)	3632 (23.9)	3277 (21.6)
Medically-attended	1215 (8.0)	1276 (8.4)	1372 (9.0)	1465 (9.7)
Severe unsolicited AEs	216 (1.4)	190 (1.3)	234 (1.5)	202 (1.3)
Leading to discontinuation from study vaccine	41 (0.3)	71 (0.5)	50 (0.3)	80 (0.5)
Serious	82 (0.5)	86 (0.6)	93 (0.6)	89 (0.6)
Death	2 (<0.1)	3 (<0.1)	2 (<0.1)	3 (<0.1)

Source:
Abbreviation: AE = adverse event.
Note: An AE is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure. Percentages were based on the number of safety participants.
[a] EUA request (interim analysis)-November 11 2020
[b] Primary efficacy analysis-November 25, 2020

Unsolicited Adverse Events

The table below shows rates of unsolicited AEs that occurred within 28 days of any vaccination and at rates of ≥1% in the vaccine group through the November 11, 2020 data cutoff. The proportion of vaccine recipients who reported an unsolicited AE was 21.9% (3325 participants) compared to 19.4% of placebo participants. A higher frequency of unsolicited adverse events was reported in the vaccine group compared to placebo group and was primarily attributed to local and systemic reactogenicity following vaccination.

Table 26. Unsolicited Adverse Events Occurring in ≥1% of Vaccine Group Participants, by MedDRA Primary System Organ Class and Preferred Term (Safety Analysis Set)[a]

System Organ Class Preferred Term	Vaccine N=15184 n (%) Any	Vaccine N=15184 n (%) Severe	Placebo N=15165 n (%) Any	Placebo N=15165 n (%) Severe
Infections and infestations	521 (3.4)	13 (<0.1)	621 (4.1)	25 (0.2)
Vascular disorders	149 (1.0)	28 (0.2)	138 (0.9)	39 (0.3)
Nervous system disorders	624 (4.1)	27 (0.2)	552 (3.6)	21 (0.1)
Headache	435 (2.9)	19 (0.1)	409 (2.7)	13 (<0.1)
Respiratory, thoracic and mediastinal disorders	480 (3.2)	8 (<0.1)	522 (3.4)	9 (<0.1)
Cough	148 (1.0)	1 (<0.1)	143 (0.9)	1 (<0.1)
Oropharyngeal pain	137 (0.9)	1 (<0.1)	184 (1.2)	3 (<0.1)
Gastrointestinal disorders	426 (2.8)	14 (<0.1)	387 (2.6)	16 (0.1)
Diarrhea	178 (1.2)	2 (<0.1)	147 (1.0)	1 (<0.1)
Skin and subcutaneous tissue disorders	213 (1.4)	4 (<0.1)	158 (1.0)	2 (<0.1)
Musculoskeletal and connective tissue disorders	586 (3.9)	24 (0.2)	521 (3.4)	18 (0.1)
Arthralgia	174 (1.1)	10 (<0.1)	152 (1.0)	2 (<0.1)
Myalgia	172 (1.1)	11 (<0.1)	138 (0.9)	0

System Organ Class Preferred Term	Vaccine N=15184 n (%)	Vaccine N=15184 n (%)	Placebo N=15165 n (%)	Placebo N=15165 n (%)
General disorders and administration site	894 (5.9)	43 (0.3)	560 (3.7)	13 (<0.1)
Fatigue	344 (2.3)	12 (<0.1)	307 (2.0)	7 (<0.1)
Injection site pain	147 (1.0)	6 (<0.1)	49 (0.3)	1 (<0.1)
Injury, poisoning and procedural complications	238 (1.6)	16 (0.1)	262 (1.7)	13 (<0.1)

Source: Sponsor's Tables 14.3.1.8.1 and 14.3.1.17.1
n (%)=number (percentage) of participants reporting the adverse event at least once
[a] EUA request (interim analysis): Novemer 11, 2020 data cutoff.

Unsolicited AEs considered related by the investigator to study vaccination were reported by 7.4% of vaccine recipients and 4.0% of placebo recipients. The proportion of participants who reported severe unsolicited AEs was 1.4% following any vaccine dose (275 participants) and 1.3% following any placebo dose (225 participants). The most frequently reported severe AEs that occurred in greater numbers of vaccine than placebo recipients were headache, myalgia, arthralgia, injection site erythema, and injection site pain (Table 26).

Medically attended adverse events (MAAE) from dose 1 through 28 day following any dose were reported for 8.0% of participants in the vaccine group (1,839 events in 1,215 participants) and 8.4% of those in the placebo group (1,837 events in 1,276 participants). The majority of these events were considered not related to study vaccinations and were primarily attributed to local and systemic reactogenicity following vaccinations.

FDA conducted standard MedDRA queries (SMQs) using FDA-developed software to evaluate for constellations of unsolicited adverse events with onset following dose 1 through the November 11, 2020 cutoff. The SMQs were conducted on adverse event Preferred Terms that could represent various conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune disorders. FDA assessment of additional safety data accrued through the November 25, 2020 cutoff is ongoing, though specific SMQ of adverse events of clinical interest were assessed.

A SMQ evaluating lymphadenopathy-related events (including injection site lymphadenopathy, lymph node pain, and lymphadenitis) through the November 25, 2020 data cut demonstrated a numerical imbalance across study groups, with 1.1% of vaccine recipients (191 events in 173 vaccine recipients) compared to 0.63% of placebo recipients (109 events in 95 participants) reporting such events in the Safety Set. The rates reported in the older cohort (≥65 years) were 0.74% (28 events in 28 participants) in vaccine recipients compared to 0.35% (16 events in 13 participants) in placebo recipients. The rates reported in the younger cohort (18-64 years) were 1.3% (163 events in 145 participants) in vaccine recipients and 0.72% (93 events in 82 participants) in placebo recipients. These events support a plausible relationship to study vaccination and were also reported in the evaluation of solicited local adverse reactions. Local axillary swelling/tenderness was reported in approximately 19% of participants during the 7 days following any dose in the Solicited Safety Set. The median duration following any dose was 1 to 2 days, and <1% reported Grade 3 axillary swelling/tenderness.

A SMQ evaluating hypersensitivity-related adverse events through the November 25, 2020 data cutoff demonstrated a numerical imbalance across study groups, with 1.5% of vaccine recipients (258 events in 233 participants) and 1.1% of placebo recipients (185 events in 166 participants) reporting such events in the Safety Set. In the older cohort (age ≥65 years) which

comprised 24.8% of the Safety Set, the rates of hypersensitivity were 1.8% (74 events in 68 participants) in vaccine recipients and 1% (45 events in 38 participants) in placebo recipients. In the younger age cohort (18-64 years), the rates were 1.5% (184 events in 165 participants) in vaccine recipients compared to 1.1% (140 events in 128 participants). Overall, the most frequently reported AEs in the hypersensitivity SMQ were injection site rash (0.24% vaccine, 0.01% placebo), injection site urticaria (0.1% vaccine, 0% placebo), and rash maculo-papular (0.07% vaccine, 0.01% placebo). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

A query of specific adverse events of clinical interest in the Safety Set through November 25, 2020 demonstrated a small imbalance in the number of participants reporting Bell's palsy (facial paralysis), with 3 vaccine recipients and 1 placebo recipient reporting this MAAE. One case of Bell's palsy in the vaccine group was considered a SAE; a 67-year-old female with diabetes was hospitalized for stroke due to new facial paralysis 32 days after vaccination. This case was reported as resolving. Another Bell's palsy case in the vaccine group occurred 28 days after vaccination in a 30-year-old female who reported an upper respiratory infection 27 days prior to onset of her facial paralysis. This case was reported as resolved. An additional case of Bell's palsy in the vaccine group was reported with the primary analysis safety data (November 25, 2020 data cutoff) and occurred 22 days after vaccination in a 72-year-old female; this event was still ongoing at the time of safety report. The case in the placebo group, reported as resolving, occurred 17 days post injection in a 52-year-old-male. Causality assessment is confounded by predisposing factors in these participants. However, considering the temporal association and biological plausibility, a potential contribution of the vaccine to the manifestations of these events of facial palsy cannot be ruled out. FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events, including other neurologic, neuro-inflammatory, and thrombotic events, that would suggest a causal relationship to the Moderna COVID-19 vaccine.

Immediate Adverse Events

Immediate solicited reactions occurring within 30 minutes of vaccination were infrequent and there does not appear to be an imbalance between the treatment groups. Review of unsolicited AEs that occurred within 30 minutes of vaccination demonstrated comparable rates across study groups (0.6% vaccine, 0.6% placebo), and none of the events reported in the vaccine group were considered serious.

Study Withdrawals due to an Adverse Event (Safety Set)

Adverse events that led to discontinuation of vaccination were reported in 0.3% in the vaccine group and 0.5% in the placebo group. Following the November 25, 2020 cutoff, 4 participants were withdrawn from the study due to an adverse event (2 vaccine recipients and 2 placebo recipients). The two AEs reported in the vaccine group were acute pancreatitis and road traffic accident, and the two AEs reported in the placebo group were incarcerated hernia and duodenal ulcer hemorrhage. FDA's review of data through this latter time point is ongoing.

Serious Adverse Events

Deaths

As of December 3, 2020, 13 deaths were reported (6 vaccine, 7 placebo). Two deaths in the vaccine group were in participants >75 years of age with pre-existing cardiac disease; one

participant died of cardiopulmonary arrest 21 days after dose 1, and one participant died of myocardial infarction 45 days after dose 2. Another two vaccine recipients were found deceased at home, and the cause of these deaths is uncertain: a 70-year-old participant with cardiac disease was found deceased 57 days after dose 2, and a 56-year-old participant with hypertension, chronic back pain being treated with opioid medication died 37 days after dose 1 (The official cause of death was listed as head trauma). One case was a 72-year-old vaccine recipient with Crohn's disease and short bowel syndrome who was hospitalized for thrombocytopenia and acute kidney failure due to obstructive nephrolithiasis 40 days after dose 2 and developed complications resulting in multiorgan failure and death. One vaccine recipient died of suicide 21 days after dose 1. The placebo recipients died from myocardial infarction (n=3), intra-abdominal perforation (n=1), systemic inflammatory response syndrome in the setting of known malignancy (n=1), COVID-19 (n=1), and unknown cause (n=1). These deaths represent events and rates that occur in the general population of individuals in these age groups.

Non-fatal Serious Adverse Events

Among participants who received at least one dose of vaccine or placebo (N=30,351), the proportion of participants who reported at least one SAE from dose 1 to the primary analysis cutoff date (November 25, 2020) was 1% in the mRNA-1273 group and 1% in the placebo group. The most common SAEs occurring at higher rates in the vaccine group than the placebo group were myocardial infarction (0.03% in vaccine group, 5 cases vs. 3 cases in placebo group), cholecystitis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group), and nephrolithiasis (0.02% in vaccine group, 3 cases vs. 0 cases in placebo group). The small numbers of cases of these events do not suggest a causal relationship. The most common SAEs occurring at higher rates in the placebo arm than the vaccine arm, aside from COVID-19 (0.1% in placebo group), were pneumonia (0.05% in placebo group) and pulmonary embolism (0.03% in placebo group). Occurrence of other SAEs, including cardiovascular SAEs, were otherwise balanced between treatment groups.

As of November 25, 2020, 7 SAEs (4.8%) in the mRNA-1273 group and 5 (3.3%) in the placebo group were assessed by the investigator as related to study vaccination (Table 27). Of the 7 SAEs in the mRNA-1273 group, the Sponsor assessed 4 as related and 3 as unrelated to the vaccine.

Table 27. SAEs Considered Related by Investigator

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Intractable nausea and vomiting	1	65 F; history of headaches and severe nausea requiring hospitalization	Resolved	Yes/Yes
mRNA-1273	Facial swelling	1	46 F; dermal filler cosmetic injection 6 months prior	Resolved	Yes/Yes
mRNA-1273	Facial swelling	2	51 F; dermal filler cosmetic injection 2 weeks prior	Resolved	Yes/Yes
mRNA-1273	Rheumatoid arthritis	14	57 M; hypothyroid	Unresolved	Yes/Yes
mRNA-1273	Dyspnea with exertion, peripheral edema	8	66 F; diabetes, hypertension	Resolving	Yes/No

Investigational Product	SAE	Onset (days after last dose)	Demographics/ Risk factors	Resolution	Related per Investigator/ Moderna
mRNA-1273	Autonomic dysfunction	24	46 F; hypothyroid; possible sinus infection	Unresolved	Yes/No
mRNA-1273	B-cell lymphocytic lymphoma	31	75 F; history of metastatic lung cancer, breast cancer	Unresolved	Yes/No
Placebo	Polymyalgia rheumatica	15	83 M; chronic low back pain	Resolving	Yes/Yes
Placebo	Facial swelling, paresthesia, anxiety	7	41 F; dental procedure 2 weeks prior	Resolved	Yes/No
Placebo	Procedural hemorrhage	16	52 M; aortic stenosis, hyperlipidemia; aspirin intake	Resolved	Yes/No
Placebo	Pulmonary embolism	24	59 M; smoking	Unresolved	Yes/No
Placebo	Pneumonia and myocardial infarction	29	70 M; coronary artery disease, chronic kidney disease, diabetes	Resolved	Yes/No

There was one event of lip angioedema 2 days after vaccination in a 29-year-old female participant in the vaccine group which was classified as medically significant but not considered an SAE. The participant has a history of dermal filler injection in the lips (unknown how long prior to vaccination). She reported having a similar reaction after receipt of an influenza vaccine in the past. Taken in context with the SAEs of facial swelling which occurred in 2 participants who had previous history of cosmetic filler injections, it is possible the localized swelling in these cases is due to an inflammatory reaction from interaction between the immune response after vaccination and the dermal filler. This phenomenon has been reported after natural infection (e.g., after an influenza-like illness).

In FDA's opinion following review of the narratives, 3 SAEs are considered likely related, including the one report of intractable nausea/vomiting and 2 reports of facial swelling. The possibility that the vaccine contributed to the SAE reports of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction cannot be excluded. The vaccine was unlikely to have contributed to the other SAEs assessed by the investigator as related. As described in detail in a previous section, there was one report of Bell's palsy in the vaccine arm which occurred 32 days after vaccination; both the investigator and the Sponsor assessed this event as unrelated to the study vaccine, but in FDA's assessment a causal relationship cannot be definitively excluded.

Subgroup Analyses

There were no specific safety concerns identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection, and occurrence of solicited, unsolicited, and serious adverse events in these subgroups were generally consistent with the overall study population.

Pregnancies

Study participants of childbearing potential were screened for pregnancy prior to each vaccination, with a positive test resulting in exclusion or discontinuation from study vaccination. The study is collecting outcomes for all reported pregnancies that occur after vaccination, or

before vaccination and not detected by pre-vaccination screening tests. Thirteen pregnancies were reported through December 2, 2020 (6 vaccine, 7 placebo). Study vaccination occurred prior to the last menstrual period (LMP) in 5 participants (2 vaccine, 3 placebo), within 30 days after LMP in 5 participants (2 vaccine, 3 placebo), >30 days after LMP in 2 participants (1 vaccine, 1 placebo), and date of LMP not known in 1 participant (1 vaccine, 0 placebo). Unsolicited AEs related to pregnancy include a case of spontaneous abortion and a case of elective abortion, both in the placebo group. One participant in the placebo group is lost to follow-up. Pregnancy outcomes are otherwise unknown at this time.

A combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in rats was submitted to FDA on December 4, 2020. FDA review of this study concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention.

Safety Summary

The information provided by the Sponsor was adequate for review and to make conclusions about the safety of the mRNA-1273 vaccine in the context of the proposed indication and population for intended use under EUA. The number of participants in the Phase 3 safety population (N=30,350; 15,184 vaccine,15,165 placebo) meets the expectations described in FDA's Guidance on Development and Licensure of Vaccines to Prevent COVID-19 for efficacy. The initial EUA request was based on data from the pre-specified interim analysis (November 11, 2020 data cutoff) with a median follow-up duration of 7 weeks after dose 2; this interim analysis data is the primary basis of this EUA review and conclusions. Data and analyses from a November 25, 2020 data cut with a median duration of at least 2 months follow-up after completion of the 2-dose primary vaccination series was submitted as an amendment to the EUA request on December 7, 2020. The FDA has not independently verified the complete safety data from the primary analysis, aside from all new deaths (including those reported through December 3, 2020) and SAEs. No new safety concerns have been identified. The rates and types of solicited adverse reactions and unsolicited adverse events are unlikely to change significantly with an additional 2 weeks of follow-up. The totality of the data package submitted in the EUA request meets the Agency's expectations on the minimum duration of follow-up.

Local site reactions and systemic solicited events after vaccination were frequent and mostly mild to moderate. The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%); 0.2% to 9.7% were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in adults ≥65 years of age as compared to younger participants. Among adverse events of clinical interest, lymphadenopathy was reported in 173 participants (1.14%) in the vaccine group and 95 participants (0.63%) in the placebo group. There was a numerical imbalance in hypersensitivity adverse events across study groups, with 1.5% of vaccine recipients and 1.1% of placebo recipients reporting such events in the Safety Set. There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine. Throughout the safety follow-up period to date, there has been three reports of Bell's palsy in the vaccine group and one in the placebo group. Currently available information is insufficient to determine a causal relationship with the vaccine. There were no other notable patterns or numerical imbalances between treatment groups for specific categories of adverse events (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-

1273.

As of December 3, 2020, there were a total of 13 deaths reported in the study (6 vaccine, 7 placebo). These deaths represent events and rates that occur in the general population of individuals in these age groups. The frequency of non-fatal serious adverse events was low and without meaningful imbalances between study arms (1% in the mRNA-1273 group and 1% in the placebo group). The most common SAEs in the vaccine group which were numerically higher than the placebo group were myocardial infarction (0.03%), cholecystitis (0.02%), and nephrolithiasis (0.02%), although the small numbers of cases of these events do not suggest a causal relationship. The most common SAEs in the placebo arm which were numerically higher than the vaccine arm, aside from COVID-19 (0.1%), were pneumonia (0.05%) and pulmonary embolism (0.03%).

6. Sponsor's Plans for Continuing Blinded, Placebo-Controlled Follow-Up

ModernaTX expects that participants, including approximately 25% who are healthcare workers, may request unblinding to receive mRNA-1273 or another vaccine potentially available under EUA external to the trial. More extensive participant-driven crossover would be expected to alter the composition of the trial population, with greatly increased participant dropout due to a large proportion of participants belonging to priority vaccination groups desiring to be vaccinated with vaccine made available under EUA. ModernaTX is evaluating the opportunity to amend the protocol to proactively reconsent participants who received placebo to be offered mRNA-1273 vaccination and to remain in the trial, enabling ModernaTX to continue to collect the relevant safety and effectiveness data over the entire two years of follow-up while increasing the likelihood of retaining participants on trial. Adverse events among those vaccinated within the trial will be captured, regardless of the treatment group to which the participants were originally allocated, over the entire follow-up period of 24 months.

7. Pharmacovigilance Activities

The Sponsor submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with the Moderna COVID-19 Vaccine. The Sponsor identified vaccine-associated enhanced disease (which includes but is not limited to vaccine-associated enhanced respiratory disease) and anaphylactic reactions (including anaphylaxis) as important potential risks. Use in the pediatric population, use in pregnant and breast-feeding women, immunogenicity in participants with immunosuppression, concomitant administration with non-COVID vaccines, long-term safety and long-term effectiveness are areas the Sponsor identified as missing information.

The Sponsor will conduct both passive and active surveillance activities for continued vaccine safety monitoring. Passive surveillance activities will include submitting spontaneous reports of the following events to the Vaccine Adverse Event Reporting System (VAERS) within 15 days:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

The Sponsor will also conduct periodic aggregate review of safety data and proposed to submit periodic safety reports at quarterly intervals, or at another interval specified by FDA. FDA has

requested that periodic reports be submitted monthly. Each periodic safety report is required to contain descriptive information which includes:

- A narrative summary and analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age groups, special populations (e.g., pregnant women), and adverse events of special interest
- Newly identified safety concerns in the interval
- Actions taken since the last report because of adverse experiences (e.g., changes made to Vaccination Provider fact sheets, changes made to studies or studies initiated)

Sponsor studies will include completion of long-term follow-up from ongoing clinical trials as well as the following three planned surveillance studies.

- Pregnancy Cohort: The Sponsor plans to establish a passive pregnancy registry to monitor vaccination during pregnancy within populations expected to receive the vaccine under EUA, and to submit a protocol for FDA review and approval.

- Active Follow-up for Safety: This study is an active safety surveillance activity conducting retrospective analyses of medical and pharmacy claims data to address three objectives; estimation of background rates of 23 prespecified adverse events of special interest (AESI), descriptive analyses of observed versus expected rates, and self-controlled risk interval analyses that will be conducted if certain criteria are met from the descriptive analyses. The planned study duration is through December 2022.

- Real World Effectiveness Study: This study is a prospective cohort study to be conducted at Kaiser Permanente Southern California to evaluate vaccine effectiveness in preventing the following outcomes: laboratory confirmed and clinical COVID-19 infection, hospitalization, and mortality for COVID-19. Vaccinated participants will receive Moderna COVID-19 Vaccine between January 1, 2021 and December 31, 2021, and the comparator group will be age matched, unvaccinated KPSC members. The planned study duration is through December 31, 2023.

FDA will provide feedback on these studies after further review of protocols once submitted by the Sponsor.

Reporting to VAERS and ModernaTX, Inc.

Providers administering the Moderna COVID-19 Vaccine must report to VAERS (as required by the National Childhood Vaccine Injury Act) and to ModernaTX the following information associated with the vaccine of which they become aware:

- Vaccine administration errors whether or not associated with an adverse event
- Serious adverse events (irrespective of attribution to vaccination)
- Cases of Multisystem Inflammatory Syndrome in adults
- Cases of COVID-19 that result in hospitalization or death

Additional VAERS Reporting

An additional source of VAERS reports will be through a program administered by the CDC known as v-safe. V-safe is a smartphone-based opt-in program that uses text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow-up to anyone who reports

medically significant (important) adverse events. Responses indicating missed work, inability to do normal daily activities, or that the recipient received care from a doctor or other healthcare professional will trigger the VAERS Call Center to reach out to the participant and collect information for a VAERS report, if appropriate.

8. Benefit/Risk Assessment in the Context of Proposed Indication and Use Under EUA

8.1 Known Benefits

The known benefits among recipients of the proposed vaccine relative to placebo are:

- Reduction in the risk of confirmed COVID-19 occurring at least 14 days after the second dose of vaccine
- Reduction in the risk of confirmed severe COVID-19 occurring at least 14 days after the second dose of vaccine

The 2-dose vaccination regimen was highly effective in preventing PCR-confirmed COVID-19 occurring at least 14 days after receipt of the second dose. Secondary efficacy analyses showed consistency with outcomes in the primary efficacy analysis; the vaccine was effective in preventing COVID-19 using a less restrictive definition of the disease and considering all cases starting 14 days after the first injection. Efficacy findings in the interim analysis were also consistent across various subgroups, including racial and ethnic minorities, participants ages 65 years and older, and those at risk for severe COVID-19 disease due to obesity, diabetes, cardiac disease, liver disease, chronic lung disease, mild to severe asthma, and infection with HIV, although the efficacy estimate in participants ages 65 years and older was slightly lower in the primary efficacy analysis.

8.2 Unknown Benefits/Data Gaps

Duration of protection

As the interim and final analyses have a limited length of follow-up, it is not possible to assess sustained efficacy over a period longer than 2 months.

Effectiveness in certain populations at high-risk of severe COVID-19

Although the proportion of participants at high risk of severe COVID-19 is adequate for the overall evaluation of safety in the available follow-up period, the subsets of certain groups such as immunocompromised individuals (e.g., those with HIV/AIDS) are too small to evaluate efficacy outcomes.

Effectiveness in individuals previously infected with SARS-CoV-2

Limited data suggest that individuals with prior SARS-CoV-2 infection can be at risk of COVID-19 (i.e., re-infection) and may benefit from vaccination. Regarding the benefit of the mRNA-1273 for individuals with prior infection with SARS-CoV2, participants with a known history of SARS-CoV-2 infection were excluded from the Phase 3 study, and there was only one case of COVID-19 among study participants with positive SARS-COV-2 infection status at baseline. Thus, the study was not designed to assess the benefit in individuals with prior SARS-CoV-2 infection.

Effectiveness in pediatric populations

No efficacy data are available from participants ages 17 years and younger.

Future vaccine effectiveness as influenced by characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections

The study enrollment and follow-up occurred during the period of July 27, 2020 to November 21, 2020, in sites across the United States. The evolution of the pandemic characteristics, such as increased attack rates, increased exposure of subpopulations, as well as potential changes in the virus infectivity, antigenically significant mutations to the S protein, and/or the effect of co-infections may potentially limit the generalizability of the efficacy conclusions over time. Continued evaluation of vaccine effectiveness following issuance of an EUA and/or licensure will be critical to address these uncertainties.

Vaccine effectiveness against asymptomatic infection

Data are limited to assess the effect of the vaccine in preventing asymptomatic infection as measured by detection of the virus and/or detection of antibodies against non-vaccine antigens that would indicate infection rather than an immune response induced by the vaccine. Additional evaluations will be needed to assess the effect of the vaccine in preventing asymptomatic infection, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against long-term effects of COVID-19 disease

COVID-19 disease may have long-term effects on certain organs, and at present it is not possible to assess whether the vaccine will have an impact on specific long-term sequelae of COVID-19 disease in individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 should translate to overall prevention of COVID-19-related sequelae in vaccinated populations, though it is possible that asymptomatic infections may not be prevented as effectively as symptomatic infections and may be associated with sequelae that are either late-onset or undetected at the time of infection (e.g., myocarditis). Additional evaluations will be needed to assess the effect of the vaccine in preventing long-term effects of COVID-19, including data from clinical trials and from the vaccine's use post-authorization.

Vaccine effectiveness against mortality

A larger number of individuals at high risk of COVID-19 and higher attack rates would be needed to confirm efficacy of the vaccine against mortality. However, non-COVID vaccines (e.g., influenza) that are efficacious against disease have also been shown to prevent disease-associated death.[13-16] Benefits in preventing death should be evaluated in large observational studies following authorization.

Vaccine effectiveness against transmission of SARS-CoV-2

Data are limited to assess the effect of the vaccine against transmission of SARS-CoV-2 from individuals who are infected despite vaccination. Demonstrated high efficacy against symptomatic COVID-19 may translate to overall prevention of transmission in populations with high enough vaccine uptake, though it is possible that if efficacy against asymptomatic infection were lower than efficacy against symptomatic infection, asymptomatic cases in combination with reduced mask-wearing and social distancing could result in significant continued transmission. Additional evaluations including data from clinical trials and from vaccine use post-authorization will be needed to assess the effect of the vaccine in preventing virus shedding and transmission, in particular in individuals with asymptomatic infection.

8.3 Known Risks

The vaccine elicited increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days. The most common solicited adverse reactions were pain at injection site (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Adverse reactions characterized as reactogenicity were generally mild to moderate; 0.2% to 9.7% of these events were reported as severe, with severe solicited adverse reactions being more frequent after dose 2 than after dose 1 and generally less frequent in older adults (≥65 years of age) as compared to younger participants. Among reported unsolicited adverse events, lymphadenopathy occurred much more frequently in the vaccine group than the placebo group and is plausibly related to vaccination. The number of participants reporting hypersensitivity-related adverse events was numerically higher in the vaccine group compared with the placebo group (258 events in 233 participants [1.5%] vs. 185 events in 166 participants [1.1%]). There were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.

Serious adverse events, while uncommon (1.0% in both treatment groups), represented medical events that occur in the general population at similar frequency as observed in the study. Of the 7 SAEs in the mRNA-1273 group that were considered as related by the investigator, FDA considered 3 as related: intractable nausea and vomiting (n=1), facial swelling (n=2). For the serious adverse events of rheumatoid arthritis, peripheral edema/dyspnea with exertion, and autonomic dysfunction, a possibility of vaccine contribution cannot be excluded. For the event of B-cell lymphoma, an alternative etiology is more likely. An SAE of Bell's palsy occurred in a vaccine recipient, for which a causal relationship to vaccination cannot be concluded at this time.

No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

8.4 Unknown Risks/Data Gaps

Safety in certain subpopulations

There are currently insufficient data to make conclusions about the safety of the vaccine in subpopulations such as children less than 18 years of age, pregnant and lactating individuals, and immunocompromised individuals.

FDA review of a combined developmental and perinatal/postnatal reproductive toxicity study of mRNA-1273 in female rats concluded that mRNA1273 given prior to mating and during gestation periods at dose of 100 µg did not have any effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention

Adverse reactions that are very uncommon or that require longer follow-up to be detected

Following authorization of the vaccine, use in large numbers of individuals may reveal additional, potentially less frequent and/or more serious adverse events not detected in the trial safety population of approximately 30,000 participants over the period of follow-up at this time. Active and passive safety surveillance will continue during the post-authorization period to detect new safety signals.

Although the safety database revealed an imbalance of cases of Bell's palsy (3 in the vaccine group and 1 in the placebo group), causal relationship is less certain because the number of cases was small and not more frequent than expected in the general population. Further signal detection efforts for these adverse events will be informative with more widespread use of the vaccine.

Vaccine-enhanced disease

Available data do not indicate a risk of vaccine-enhanced disease, and conversely suggest effectiveness against severe disease within the available follow-up period. However, risk of vaccine-enhanced disease over time, potentially associated with waning immunity, remains unknown and needs to be evaluated further in ongoing clinical trials and in observational studies that could be conducted following authorization and/or licensure.

9. References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine.* 2020;382(8):727-733.
2. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2.
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England).* 2020;395(10224):565-574.
4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020;181(2):271-280.e278.
5. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb–3 and 360bbb-3b. (2011).
6. FDA. Guidance for Industry: Emergency Use Authorization for Vaccines to Prevent COVID-19. October 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-vaccines-prevent-covid-19.
7. FDA. Guidance for Industry: Development and Licensure of Vaccines to Prevent COVID-19. June 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19.
8. National Vaccine Injury Compensation Program. Vaccine Injury Table, Revised and Effective March 21, 2017. https://www.hrsa.gov/sites/default/files/hrsa/vaccine-compensation/vaccine-injury-table.pdf.
9. International Coalition of Medicines Regulatory Authorities. Statement on continuation of vaccine trials. http://www.icmra.info/drupal/en/covid-19/statement_on_continuation_of_vaccine_trials. 2020.
10. Krause PR, Fleming TR, Longini IM, et al. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. *The New England journal of medicine.* 2020.
11. Wendler D, Ochoa J, Millum J, Grady C, Taylor HA. COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science.* 2020:eabf5084.
12. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html.
13. Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group, the. Historical Comparisons of Morbidity and Mortality for Vaccine-Preventable Diseases in the United States. *JAMA.* 2007;298(18):2155-2163.
14. Verhees RAF, Dondorp W, Thijs C, Dinant GJ, Knottnerus JA. Influenza vaccination in the elderly: Is a trial on mortality ethically acceptable? *Vaccine.* 2018;36(21):2991-2997.
15. Flannery B, Reynolds SB, Blanton L, et al. Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014. 2017;139(5):e20164244.
16. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;69(11):1845-1853.

10. Appendix A. Phase 1 and 2 Studies

Study DMID Protocol 20-0003

Study Design

DMID Protocol 20-0003 is an ongoing Phase 1, open-label, first-in-human, dose-ranging study to evaluate the safety and immunogenicity of mRNA-1273 in healthy adults 18 years of age and older. A total of 120 participants without risk factors for progression to severe COVID-19 were enrolled into one of 10 age and dose cohorts to receive 2 injections of 25 µg, 50 µg, 100 µg, or 250 µg of mRNA-1273 given 28 days apart. The study included 60 participants 18 through 55 years of age, 30 participants 56 through 70 years of age, and 30 participants 71 years and older. Participants will be followed safety and immunogenicity for 12 months after last vaccination.

Study Objectives/Endpoints Relevant to the EUA

The immunogenicity objectives are to evaluate the binding antibody (bAb) concentrations for spike IgG as measured by ELISA and neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination. The study also evaluated T-cell responses elicited by the mRNA-1273 vaccine as assessed by an intracellular cytokine stimulation assay. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study, and all results were descriptive.

Study Results

The study showed a dose response in participants across all age groups as measured by both binding and neutralizing antibodies after 2 doses. There was a comparable response between the 100-µg and 250-µg dose groups, and both were greater compared to the 25-µg group. The bAb and nAb levels seen after 2 doses of 100 µg or 250 µg of mRNA-1273 were similar in magnitude compared to those seen in pooled convalescent sera from patients recovered from COVID-19. All dose levels elicited CD4+ T-cell responses that were strongly biased toward expression of Th1 cytokines, with minimal Th2 cytokine expression. This Th1-dominant profile was clinically reassuring in terms of risk of developing vaccine-induced disease. These results, along with the interim safety data showing a lower incidence of reactogenicity in the 100ug group compared to the 250ug group, led to the selection of the 100ug dose to advance to Phase 2 and 3. Preliminary safety data from this Phase 1 study show a similar profile to that observed in the Phase 3 study. No SAEs or severe COVID-19 cases have been reported from this study as of November 16, 2020.

Study mRNA-1273-P201

Study Design

Study mRNA-1273-P201 is an ongoing phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273 in healthy adults 18 years and older. The study enrolled 600 participants, consisting of 300 participants 18 to <55 years old and 300 participants 55 years and older, who

were randomized equally to receive either 2 doses of 50ug of mRNA-1273, 100ug of mRNA-1273, or saline placebo given 28 days apart. Participants will be followed for safety and immunogenicity for 12 months post last vaccination.

Study Objectives/Endpoints Relevant to the EUA
The immunogenicity objectives are to evaluate the immunogenicity of 2 doses of mRNA-1273 at the 2 dose levels (50 µg and 100 µg) administered 28 days apart as assessed by level of bAb and by nAb titers at baseline and at various time points after vaccination. All participants are followed for solicited adverse reactions through 7 days post each vaccination. Unsolicited AEs are collected through 28 days after each vaccination. All SAEs and medically attended adverse events are collected through the end of the study.

Statistical Analysis

No formal statistical hypothesis was tested in this study and all results were descriptive.

Study Results

The immune response as assessed by bAb and nAb after 2 doses were comparable in the 50-µg and 100-µg dose groups, with an overall geometric mean fold rise (GMFR)>20-fold in bAB as measured by ELISA and >50-fold in nAb as measured by microneutralization assay at 28 days post-dose 2. In the 100-µg dose group, the older age cohort (≥55 years) had slightly lower bAb response when compared to the younger age cohort (18 to <55 years) at 28 days post-dose 2, but the nAb response was similar between both age groups

Safety profile was similar to that reported in the Phase 3 study. Laboratory evaluations (including complete blood count, liver function tests, kidney functions tests, and coagulation studies) were conducted for participants ≥55 years of age (N=100) at baseline and at 1 month after the second dose (Day 29, Day 57). According to narratives that the Sponsor provided to FDA on December 6, 2020, there were 2 participants in the 100-µg group who experienced Grade 3 decreases in hemoglobin (Grade 0 reported at baseline), but both Grade 3 values were within normal range and not clinically significant. The overall event rates were not provided.

As of December 6, 2020, there were 3 SAEs reported in the vaccine group: a 65-year-old participant with community acquired pneumonia 25 days after vaccination, a 72-year-old participant with arrhythmia after being struck by lightning 28 days after vaccination, and an 87-year-old participant with worsening of chronic bradycardia 45 days after vaccination. On FDA review of the narratives, none of these SAEs are assessed as related. There were no cases of severe COVID-19 reported in the study.

Review Your Publication Report

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Request Information

Request ID	
Project Title	WI203144 Serotype monitoring of S. pneumoniae invasive strains in adult population in the province of Quebec_ a 3 years study evaluation.
Study Type	Clinical
Principal Investigator First Name	Brigitte
PI Middle Name	
Principal Investigator Last Name	Lefebvre
Project Start Date	11/20/2015
Project End Date	11/04/2020

Publication Follow Up

* indicates required field

* Was your planned publication published?	No, publication is still pending
Estimate the date you expect publication(s) to be in the public domain.	12/01/2023

SUBMIT SAVE ONLY

Technical Questions

Update

OMICRON VARIANT (B.1.1.529)

December 8, 2021

Pfizer BIONTECH

This Slide Presentation Includes Forward-looking Statements

This press release contains “forward-looking statements” of BioNTech within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, statements concerning: BioNTech’s efforts to combat COVID-19; the collaboration between BioNTech and Pfizer including the program to develop a COVID-19 vaccine and COMIRNATY (COVID-19 Vaccine, mRNA) (BNT162b2) (including the potential of a Omicron-specific COVID-19 vaccine candidate, the potential timing for the development of a Omicron-specific COVID-19 vaccine candidate, the testing of BNT162b2 against the Omicron variant, the effectiveness of a third booster dose of BNT162b2 to induce protection against Omicron-induced COVID-19 disease, and the timing for assessment of the effectiveness of a variant-specific COVID-19 vaccine, qualitative assessments of available data, potential benefits, expectations for clinical trials, the anticipated timing of regulatory submissions, regulatory approvals or authorizations and anticipated manufacturing, distribution and supply); our expectations regarding the potential characteristics of BNT162b2 or variant-specific COVID-19 vaccine candidates in our clinical trials and/or in commercial use based on data observations to date; the ability of BNT162b2 to prevent COVID-19 caused by the Omicron and other emerging virus variants; the expected time point for additional readouts on efficacy data of BNT162b2 in our clinical trials; the nature of the clinical data, which is subject to ongoing peer review, regulatory review and market interpretation; the risk of further widespread use of our vaccine will lead to new information about efficacy, safety, or other developments, including the risk of additional adverse reactions, some of which may be serious; decisions by regulatory authorities that may impact labeling or marketing, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of our vaccine, including development of products or therapies by other companies; the timing for submission of data for, or receipt of, any marketing authorization or Emergency Use Authorization; our contemplated shipping and storage plan, including our estimated product shelf life at various temperatures; disruptions in the relationships between us and our collaboration partners, clinical trial sites or other third-parties; risks related to the availability of raw materials to manufacture a vaccine; challenges related to our vaccine’s formulation, two-dose and booster schedule and attendant storage, distribution and administration requirements, including risks related to storage and handling after delivery by BioNTech and third-party providers; and the ability of BioNTech to supply the quantities of BNT162 or variant-specific COVID-19 vaccine candidates to support clinical development and market demand, including our production estimates for 2021. Any forward-looking statements in this press release are based on BioNTech current expectations and beliefs of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements.

For a discussion of these and other risks and uncertainties, see BioNTech’s Annual Report as Form 20-F for the Year Ended December 31, 2020, filed with the SEC on March 30, 2021, which is available on the SEC’s website at www.sec.gov. All information in this press release is as of the date of the release, and BioNTech undertakes no duty to update this information unless required by law.

Safety Information

AUTHORIZED USE IN THE U.S.:
The Pfizer-BioNTech COVID19 Vaccine is authorized for use under an Emergency Use Authorization (EUA) for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 5 years of age and older.

IMPORTANT SAFETY INFORMATION FROM U.S. FDA EMERGENCY USE AUTHORIZATION PRESCRIBING INFORMATION:

- Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with known history of a severe allergic reaction (eg, anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 Vaccine
- Appropriate medical treatment used to manage immediate allergic reactions must be immediately available in the event an acute anaphylactic reaction occurs following administration of Pfizer-BioNTech COVID-19 Vaccine
- Monitor Pfizer-BioNTech COVID-19 Vaccine recipients for the occurrence of immediate adverse reactions according to the Centers for Disease Control and Prevention guidelines (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/managing-anaphylaxis.html)
- Reports of adverse events following use of the Pfizer-BioNTech COVID-19 Vaccine under EUA suggest increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. The decision to administer the Pfizer-BioNTech COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances
- Syncope (fainting) may occur in association with administration of injectable vaccines, in particular in adolescents. Procedures should be in place to avoid injury from fainting
- Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the Pfizer-BioNTech COVID-19 Vaccine
- The Pfizer-BioNTech COVID-19 Vaccine may not protect all vaccine recipients
- In clinical studies, adverse reactions in participants 16 years of age and older included pain at the injection site (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), fever (14.2%), injection site swelling (10.5%), injection site redness (9.5%), nausea (1.1%), malaise (0.5%), and lymphadenopathy (0.3%), following administration of the primary series
- In a clinical study, adverse reactions in adolescents 12 through 15 years of age included pain at the injection site (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), lymphadenopathy (0.8%), and nausea (0.4%), following administration of primary series
- In a clinical study, adverse reactions in adults 18 through 55 years of age following administration of a booster dose were pain at the injection site (83.0%), fatigue (63.7%), headache (48.4%), muscle pain (39.1%), chills (29.1%), joint pain (25.3%), lymphadenopathy (5.2%), nausea (0.7%), decreased appetite (0.3%), rash (0.3%), and pain in extremity (0.3%)
- Following administration of the Pfizer-BioNTech COVID-19 Vaccine, the following have been reported outside of clinical trials:
    - severe allergic reactions, including anaphylaxis, and other hypersensitivity reactions, diarrhea, vomiting, and pain in extremity (arm) and syncope
    - myocarditis and pericarditis
- Additional adverse reactions, some of which may be serious, may become apparent with more widespread use of the Pfizer-BioNTech COVID-19 Vaccine
- Available data on Pfizer-BioNTech COVID-19 Vaccine administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy
- Data are not available to assess the effects of Pfizer-BioNTech COVID-19 Vaccine on the breastfed infant or on milk production/excretion
- There is no information on the co-administration of the Pfizer-BioNTech COVID-19 Vaccine with other vaccines.
- An overall review of adverse reactions reported in the study following the Pfizer-BioNTech COVID-19 Vaccine heterologous booster dose did not identify any new safety concerns, as compared with adverse reactions reported following a Pfizer-BioNTech COVID-19 Vaccine primary series doses or homologous booster dose
- Vaccination providers must report Adverse Events in accordance with the Fact Sheet to VAERS online at https://vaers.hhs.gov/reportevent.html. For further assistance with reporting to VAERS call 1-800-822-7967. The reports should include the words "Pfizer-BioNTech COVID-19 Vaccine EUA" in the description section of the report
- Vaccination providers should review the Fact Sheet for Information to Provide to Vaccine Recipients/Caregivers and Mandatory Requirements for Pfizer-BioNTech COVID-19 Vaccine Administration Under Emergency Use Authorization
- Before administration of Pfizer-BioNTech COVID-19 Vaccine, please see Emergency Use Authorization (EUA) Fact Sheet for Healthcare Providers Administering Vaccine (Vaccination Providers) including Full EUA Prescribing Information available at www.cvdvaccine-us.com

Pfizer BIONTECH

Safety Information

COMIRNATY® ▼(COVID-19 mRNA Vaccine) has been granted conditional marketing authorisation by the European Medicines Agency to prevent coronavirus disease 2019 (COVID-19) in people from 5 years of age. EMA's human medicines committee (CHMP) has completed its rigorous evaluation of COMIRNATY®, concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available.

Important safety information

Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with a known hypersensitivity to the active substance or to any of the excipients listed

Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself. It is important that precautions are in place to avoid injury from fainting

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals

The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY® may be lower in immunosuppressed individuals.

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials

As with any vaccine, vaccination with COMIRNATY® may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.

Comirnaty has no or negligible influence on the ability to drive and use machines. However, some of side effectsm mentioned below, may temporarily affect the ability to drive or use machines.

In clinical studies, the most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age

In clinical trials, the most frequent adverse reactions in participants 18 to 55 years of age who received a booster were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

The overall safety profile of COMIRNATY® in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older. The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%)

There is limited experience with use of COMIRNATY® in pregnant women. Administration of COMIRNATY® in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

It is unknown whether COMIRNATY® is excreted in human milk.

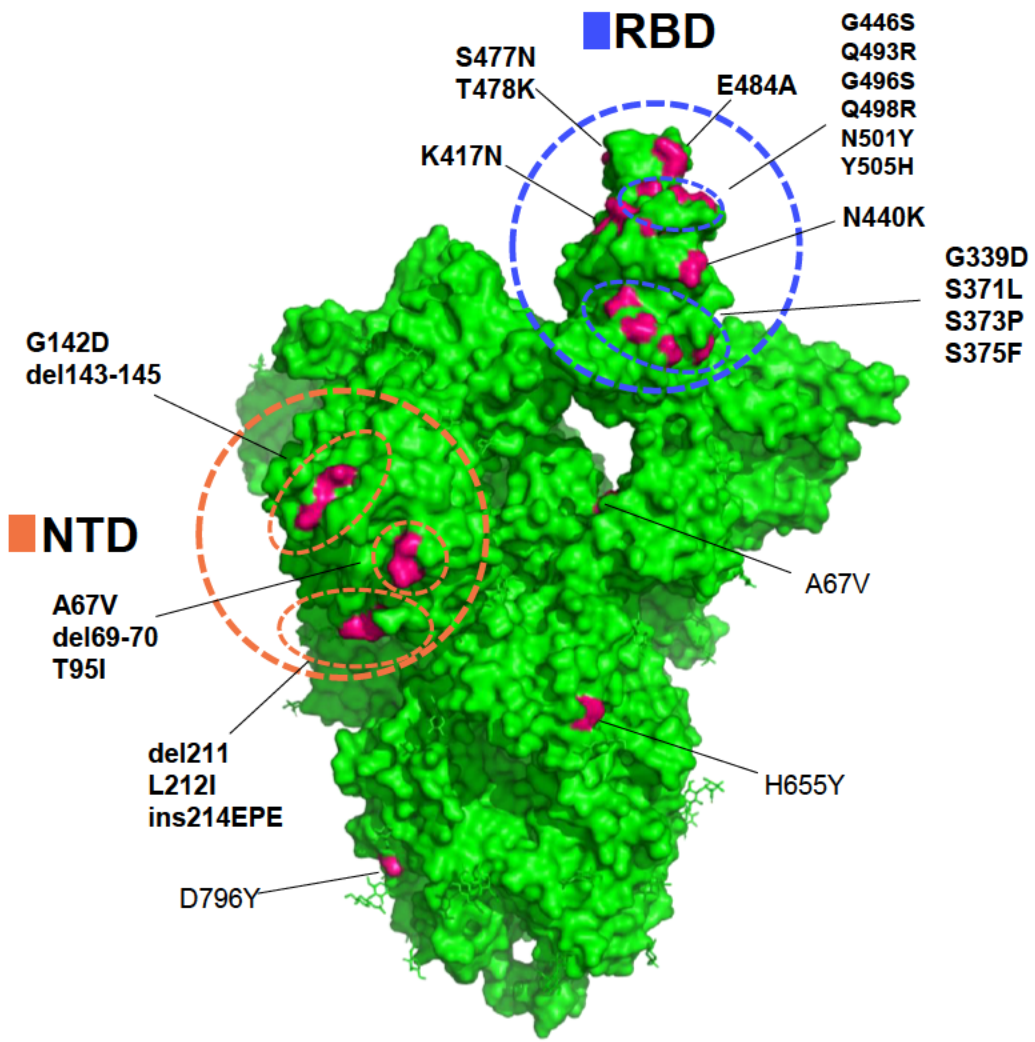
Interactions with other medicinal products or concomitant administration of COMIRNATY® with other vaccines has not been studied.

Very rare cases of myocarditis and pericarditis have been observed following vaccination with COMIRNATY® primarily in younger males, after the second dose, within 14 days following vaccination

The black equilateral triangle denotes that additional monitoring is required to capture any adverse reactions. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. Side effects can be reported to EudraVigilance [http://www.adrreports.eu/] or directly to BioNTech using email medinfo@biontech.de, telephone +49 6131 9084 0, or our website https://medicalinformation.biontech.de/

Pfizer BIONTECH

Omicron (B.1.1.529) has multiple mutations at sites which are known to be relevant for binding of neutralizing antibodies



One RBD-up conformation of SARS-CoV-2 spike with mutated AA positions highlighted in pink.
Bento DJ et al. Proc Natl Acad Sci U S A. 2021 Mar 2;118(9):e2022586118

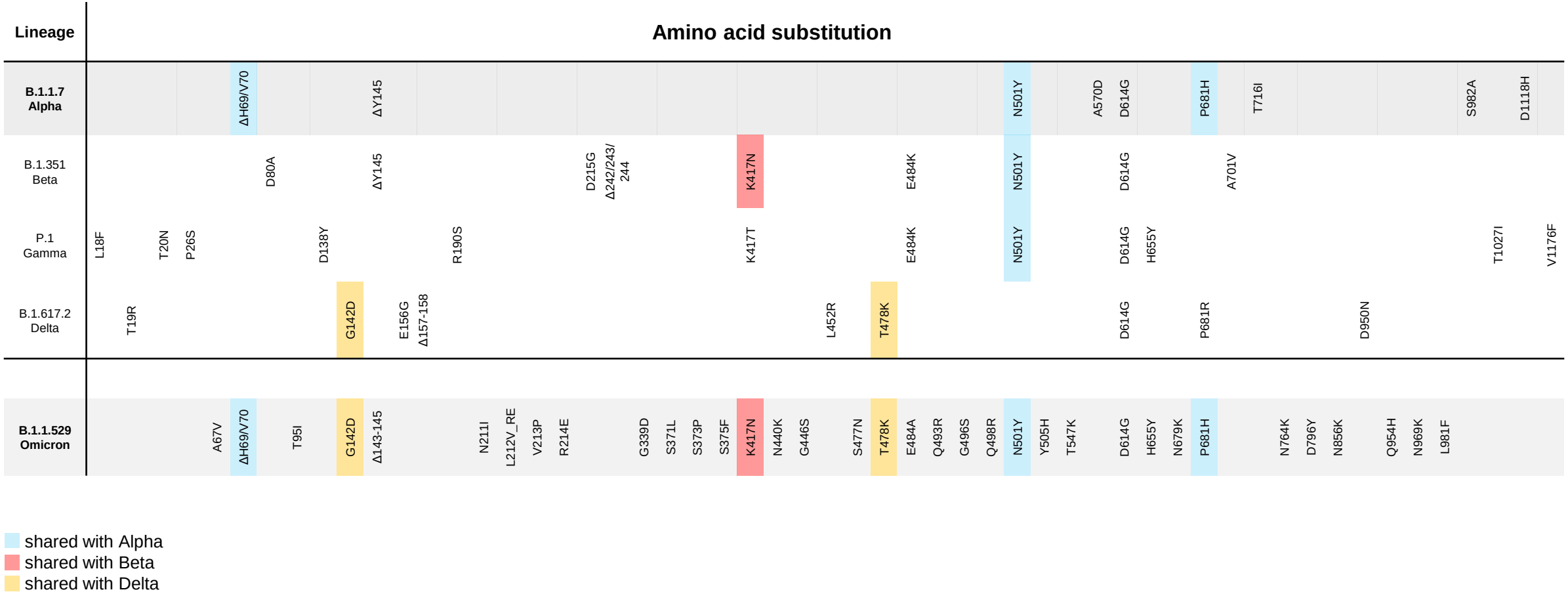
Both the receptor-binding domain (RBD) and the N-terminal domain (NTD) as immunodominant targets are affected

RBD directed mutations (15):
G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H

NTD directed mutations (8):
A67V, del69-70, T95I, G142D, del143-145, del211, L212I, ins214EPE

Pfizer BIONTECH

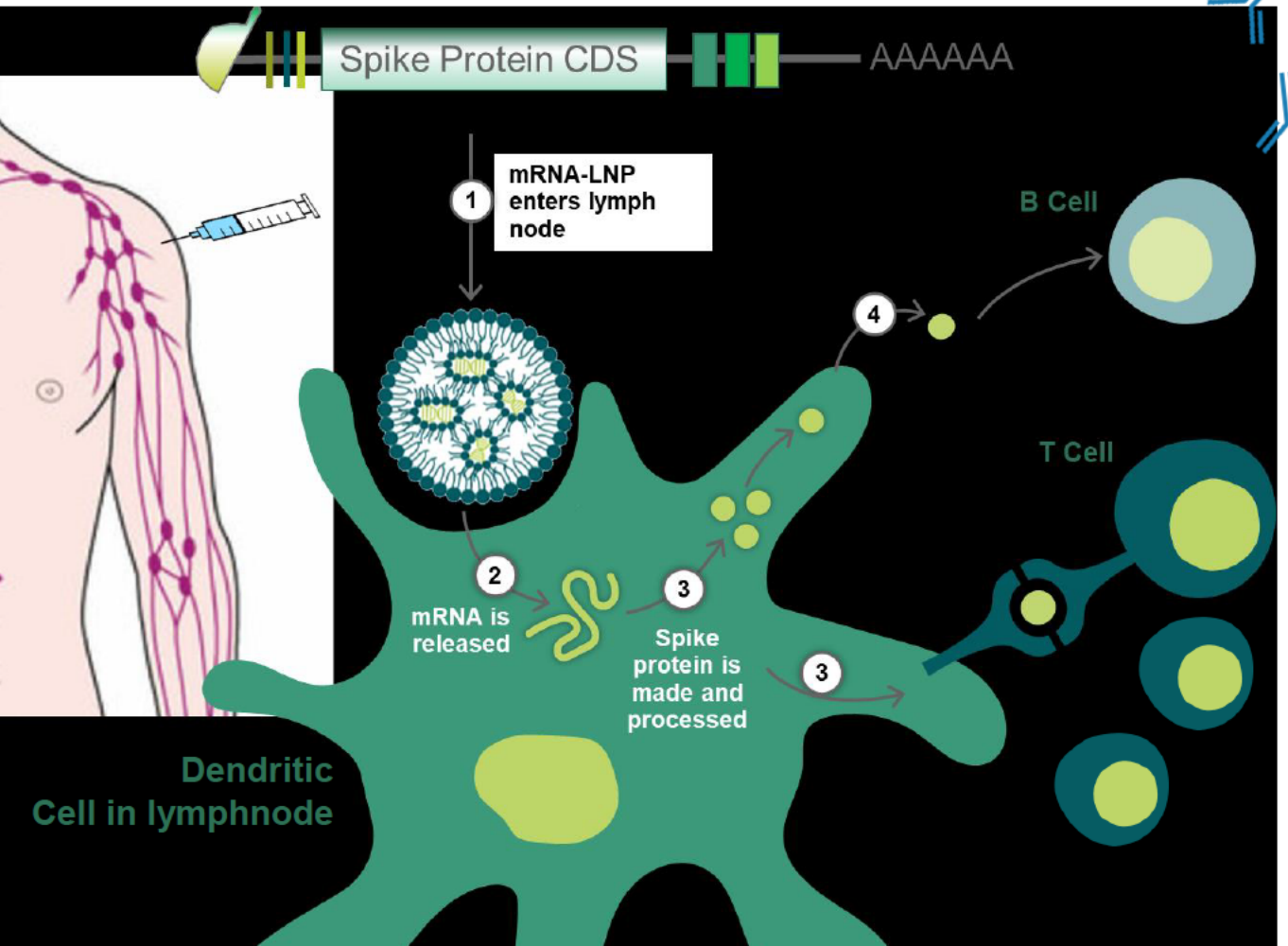
Omicron (B.1.1.529) shares multiple mutations with other SARS-CoV-2 variants



shared with Alpha
shared with Beta
shared with Delta

mRNA vaccines induce two layers of immune defense

BNT162b2 mRNA Vaccine



1st Layer of Immune Defense:

Virus Neutralizing Antibodies

Considered to

- Prevent SARS-CoV-2 infection
- Prevent Covid-19

2nd Layer of Immune Defense:

Virus Specific CD4+ & CD8+ T cells

Considered to

- Kill virus-infected cells
- Prevent severe Covid-19

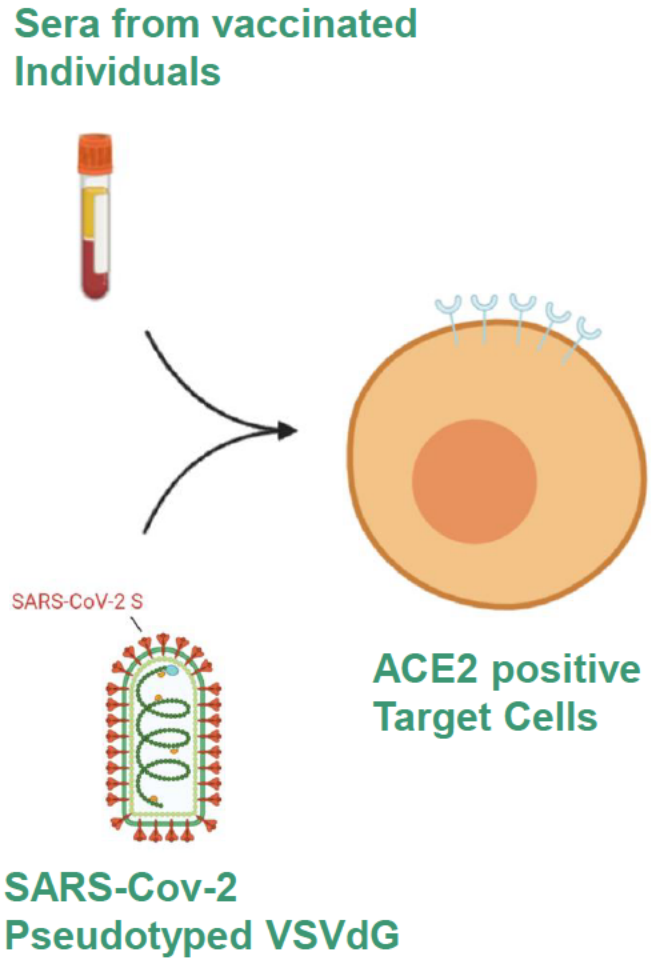
Pfizer BIONTECH

Laboratory *in vitro* pseudo-virus neutralization assay

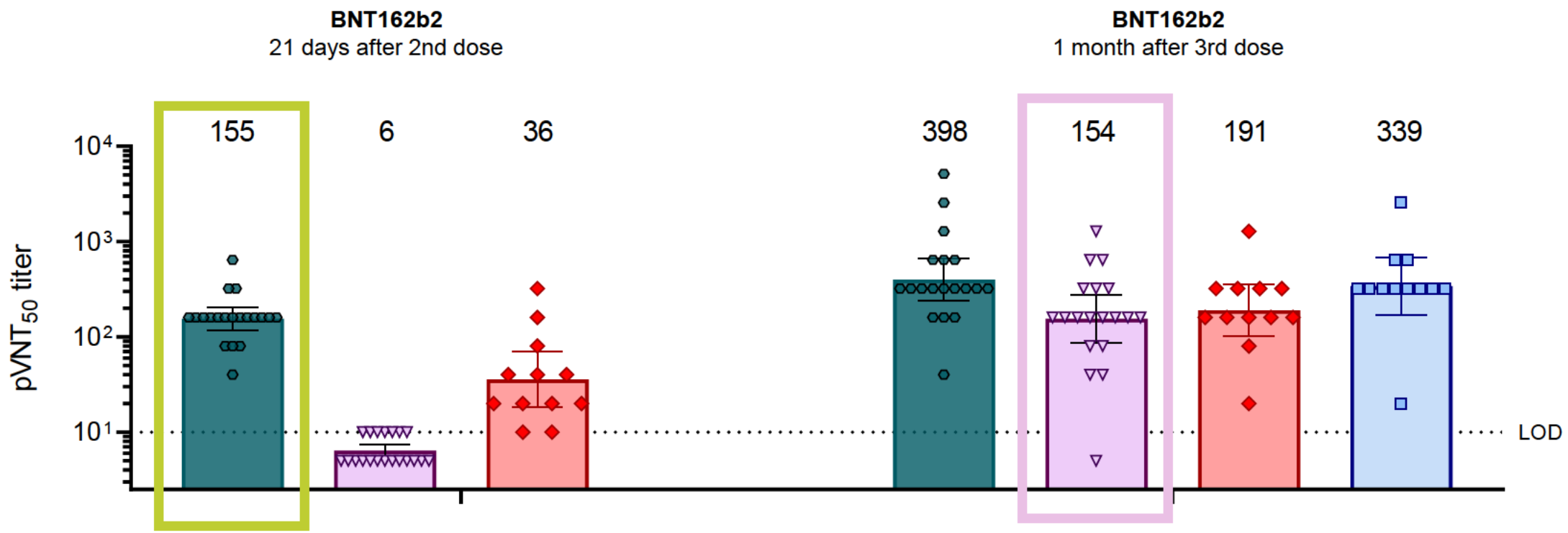
To evaluate the effectiveness of BNT162b2 against the Omicron variant, Pfizer and BioNTech tested a panel of human immune sera obtained from the blood of individuals that received **two** or **three** 30-µg doses of the current Pfizer-BioNTech COVID-19 vaccine, using a pseudovirus neutralization test (pVNT).

The sera (N=19-20) were collected from subjects **3 weeks after receiving the second dose** or **one month after receiving the third dose** of the Pfizer-BioNTech COVID-19 vaccine. Each serum was tested simultaneously for its neutralizing antibody titer against the **wild-type SARS-Cov-2 spike protein**, and the **Omicron spike** variant.

These results are **preliminary,** the companies will continue to collect more laboratory data and evaluate real-world effectiveness to assess and confirm protection against Omicron and inform the most effective path forward.



Three doses of BNT162b2 neutralize Omicron



Note: pseudovirus neutralization test (pVNT) was used with the full set of Omicron spike mutations in a pseudovirus system that recapitulates SARS-CoV-2 virus binding, cell entry and trafficking. Each serum was tested simultaneously for its 50% pseudovirus neutralizing titer (pVNT50) against the wild-type and the Omicron variant.

Pfizer BIONTECH

CD8+ T cell epitopes in BNT162b2 vaccine remain largely unaffected by omicron variant mutations

Approx. 80% of CD8+ epitopes identified by BNT / PFE are not affected by the mutations in the Omicron variant:

HLA-Allele	No of MHC-I epitopes*	No. of epitopes affected by mutations in different VOCs				
		Alpha	Beta	Gamma	Delta	Omicron
A*01:01	1	0	0	0	0	0
A*02:01	2	0	0	0	0	0
A*03:01	**2**	0	0	0	0	**1**
A*11:01	2	0	0	0	0	0
A*24:02	**5**	0	0	0	**1**	**1**
A*26:01	2	0	0	0	0	0
A*29:02	1	0	0	0	0	**1**
A*68:01	4	0	0	0	0	**1**
B*07:02	1	0	0	0	0	0
B*15:01	**3**	**1**	**2**	**1**	**1**	**2**
B*35:01	6	0	0	0	0	0
C*03:03	1	0	0	0	0	0
C*04:01	1	0	0	0	0	0
Total affected **Total unaffected**	**31**	**1 (4%)** **30 (96%)**	**2 (7%)** **26 (93%)**	**1 (4%)** **30 (96%)**	**2 (7%)** **26 (93%)**	**6 (22%)** **25 (78%)**

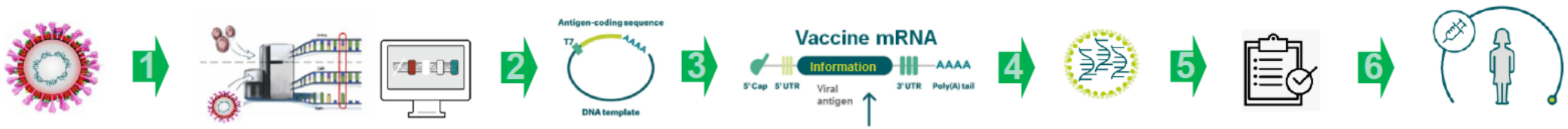
* identified as immunogenic in at least one subject. Data from 21 subjects from BNT162-01 study

Pfizer BIONTECH

Neutralization of Omicron after two doses of BNT162b2 and variant specific booster

Booster vaccine	Trial ID	Omicron neutralization by variant-specific booster compared to 3rd dose BNT162b2 [%]
BNT162b2	NCT04380701	100%
Alpha Variant	NCT05004181	466%
Beta Variant	NCT04949490	Pending
Delta Variant	NCT05004181	165%
Alpha/Delta Variant Mix	NCT05004181	155%

SARS-CoV-2 mRNA Variant Vaccine Technical Adaptation Process



SARS-CoV-2 Variant

Identification of the Virus Genetic Sequence

DNA Template

SARS-Cov-2 Vaccine mRNA

mRNA LNP

QC Released

Supply

Summary

- Preliminary laboratory studies demonstrate that three doses of the Pfizer-BioNTech COVID-19 Vaccine neutralize the Omicron variant (B.1.1.529 lineage), while two doses show significantly reduced neutralization titers
- Data indicate that a third dose of BNT162b2 increases the neutralizing antibody titers by 25-fold compared to two doses against the Omicron variant; titers after the booster dose are comparable to titers observed after two doses against the wild-type virus, which are associated with high levels of protection
- Due to presence of B and T cell memory responses in vaccinated individuals, and as 80% of epitopes in the spike protein being recognized by CD8+ T cells are not affected by the mutations in the Omicron variant, two doses may still induce protection against **severe disease**
- These results are **preliminary,** the companies will continue to collect more laboratory data and evaluate **real-world effectiveness data** to assess protection against Omicron and inform the most effective path forward.

Next Steps: Boosters and development of a variant-specific vaccine

- **Broad booster campaigns** around the world could help to better protect people and to get through the winter season
- BNT/PFE continue development of a **variant-specific vaccine** against Omicron in case it is needed with the aim to induce high levels of protection against disease as well as a prolonged protection
- First batches of a potential Omicron-based vaccine are planned to be ready for **delivery by March pending regulatory authorization**
- **Several clinical trials with variant-specific vaccines** (alpha, beta, delta and alpha/delta mix) have been previously initiated to collect safety and tolerability data

Thank you

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Study mRNA-1273-P205, mRNA-1273.214 Day 29 interim analysis topline results

Name, Affiliation

Date

No SARS-CoV-2 Variant-Based Vaccine Has Been Approved or Authorized in Any Country

No investigational variant-based vaccine described in these slides have been authorized or approved for use in any country.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Moderna. https://www.modernacovid19global.com/. Accessed February 28, 2022.

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Summary

- Moderna's bivalent platform previously demonstrated **superior neutralizing titers** against Omicron (BA.1) following a 3rd dose with a Beta-containing (.211) bivalent. Bivalent .211 also showed **improved durability** against Beta and other VOC through 6 months
- Based on these findings, Moderna has advanced a new bivalent booster based on Omicron/BA.1 (.214). Day 29 data from this study has confirmed:
  - A 4th dose of bivalent .214 resulted in **significantly higher neutralizing GMT against Omicron (BA.1)** compared to a 4th dose of prototype (GMR 1.75), evaluation of durability is ongoing
  - A 4th dose of bivalent .214 leads to **BA.1 neutralizing GMT >5-fold higher than achieved after the 3rd dose** of prototype (mRNA-1273)
  - As expected, BA.4/BA.5 resulted in 3-fold lower titers relative to BA.1, however bivalent .214 boosted **neutralizing titers against BA.4/BA.5 to similar levels achieved by prior booster (mRNA-1273, 3rd dose) against prior VOC waves,** including Delta (Fall 2021) and Omicron BA.1 (Winter 2021-2022)
- Pending regulatory review, mRNA-1273.214 is available in large quantity from August; an updated vaccine with BA.4/5 strain would not be available in similar quantities until November (assumes no clinical data required)

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Overview Phase 2/3 (P205) study for mRNA-1273.214

All participants received mRNA-1273 primary series (100 µg) and mRNA-1273 booster (50 µg)

	Second booster dose			
Trial	*Booster*	*Dose*	**Subjects (n)**	**Comments**
Phase 2/3 P205 *Only showing current arms*	**mRNA-1273**	50 µg	377	Enrolled February 21 to March 8
	mRNA-1273.214	50 µg	437	Enrolled March 8 to March 23

*Arms enrolled sequentially, safety follow-up time of **57 days** for mRNA-1273 and **43 days** for mRNA-1273.214, immunogenicity **day 29** data*

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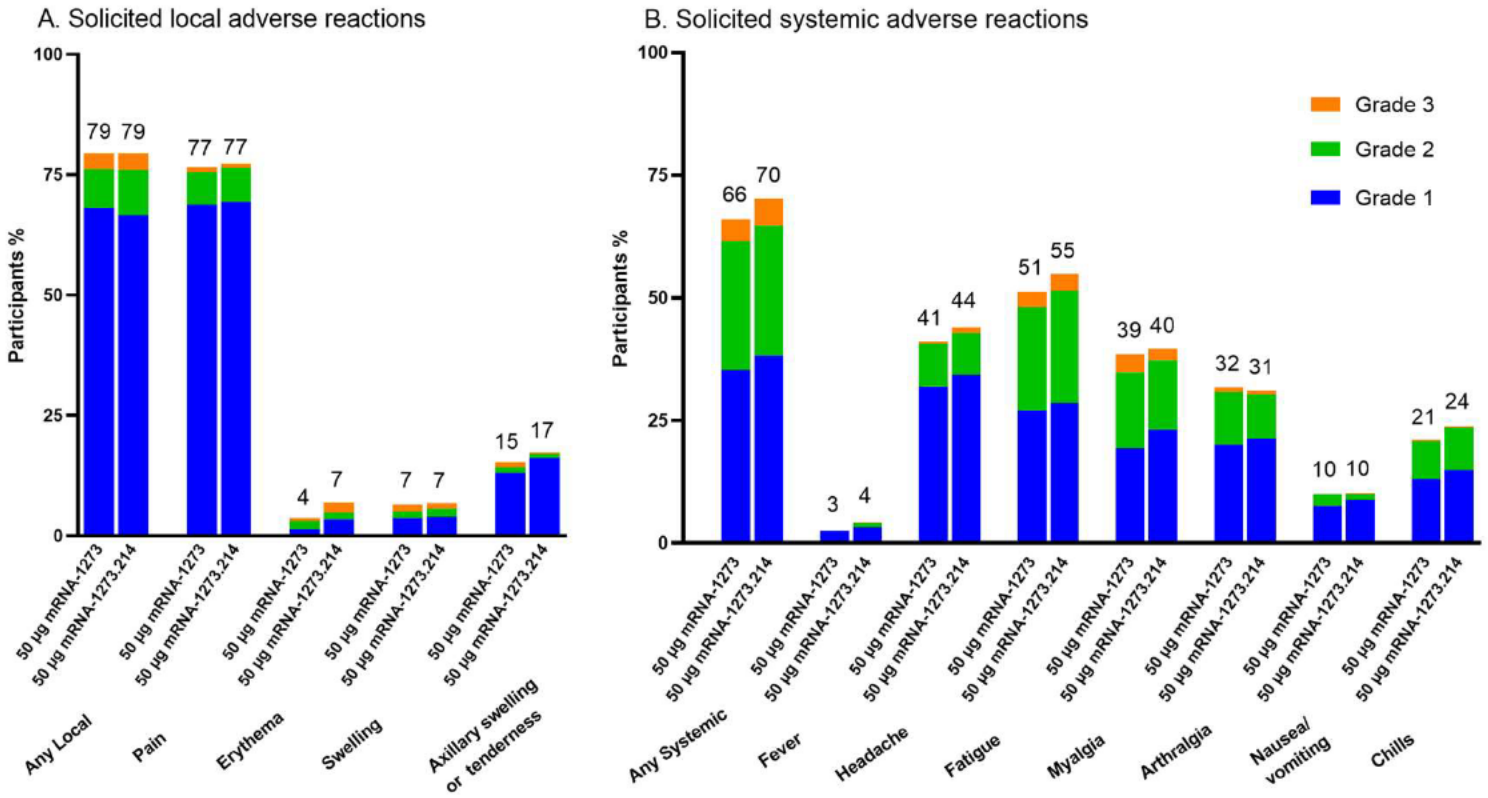
The reactogenicity profile of the 50-µg mRNA-1273.214 booster candidate was similar to the authorized 50-µg mRNA-1273 booster as a second booster dose

Adverse reactions within 7 days of the booster dose



- The frequency and types of unsolicited adverse events were also comparable.

Up to 28 days post-booster:

- No fatal events.
- Two serious adverse events in two mRNA-1273.214 participants (prostate cancer, traumatic fracture)
- One serious adverse event in one mRNA-1273 participant (spinal osteoarthritis)

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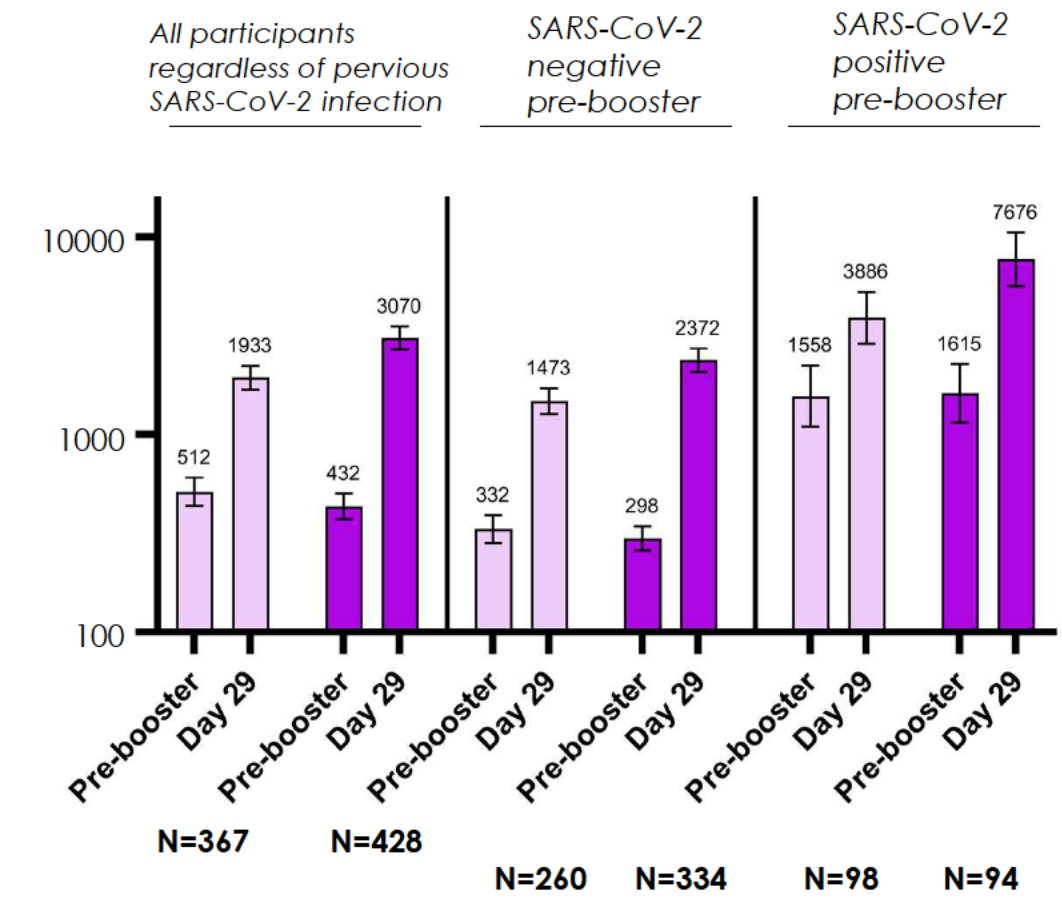
Omicron observed neutralizing antibody titers



Omicron neutralizing titers **were significantly higher following the bivalent (.214) booster** compared to prototype for all participants

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Bivalent booster (.214) resulted in superior neutralizing antibody titers against **Omicron**

All participants *SARS-CoV-2 negative and positive pre-booster*

	mRNA-1273.214 50 µg (N=428)	**mRNA-1273** 50 µg (N=367)
Pre-booster GMT, 95% CI	432.05 (372.47, 501.17)	511.98 (433.39, 604.84)
Estimated GMTs (95% CI) at Day 29[a]	3232.52 (2951.83, 3539.89)	1815.14 (1650.05, 1996.74)
GMFR (95% CI) at Day 29, 95% CI	7.11 (6.48, 7.79)	3.78 (3.42, 4.17)
GMR (97.5% CI)[a]	**1.78** (1.56, 2.04)	
Seroresponse rate (95% CI) at Day 29[b]	380/380, 100 (99.0, 100)	340/342, 99.4 (97.9, 99.9)
Difference in seroresponse rates (97.5% CI)[c]	**1.2** (-1.3, 3.7)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, prior SARS-CoV-2 infection, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 97.5% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

Bivalent booster (.214) resulted in **superior neutralizing GMT against Omicron** compared to mRNA-1273 for all participants

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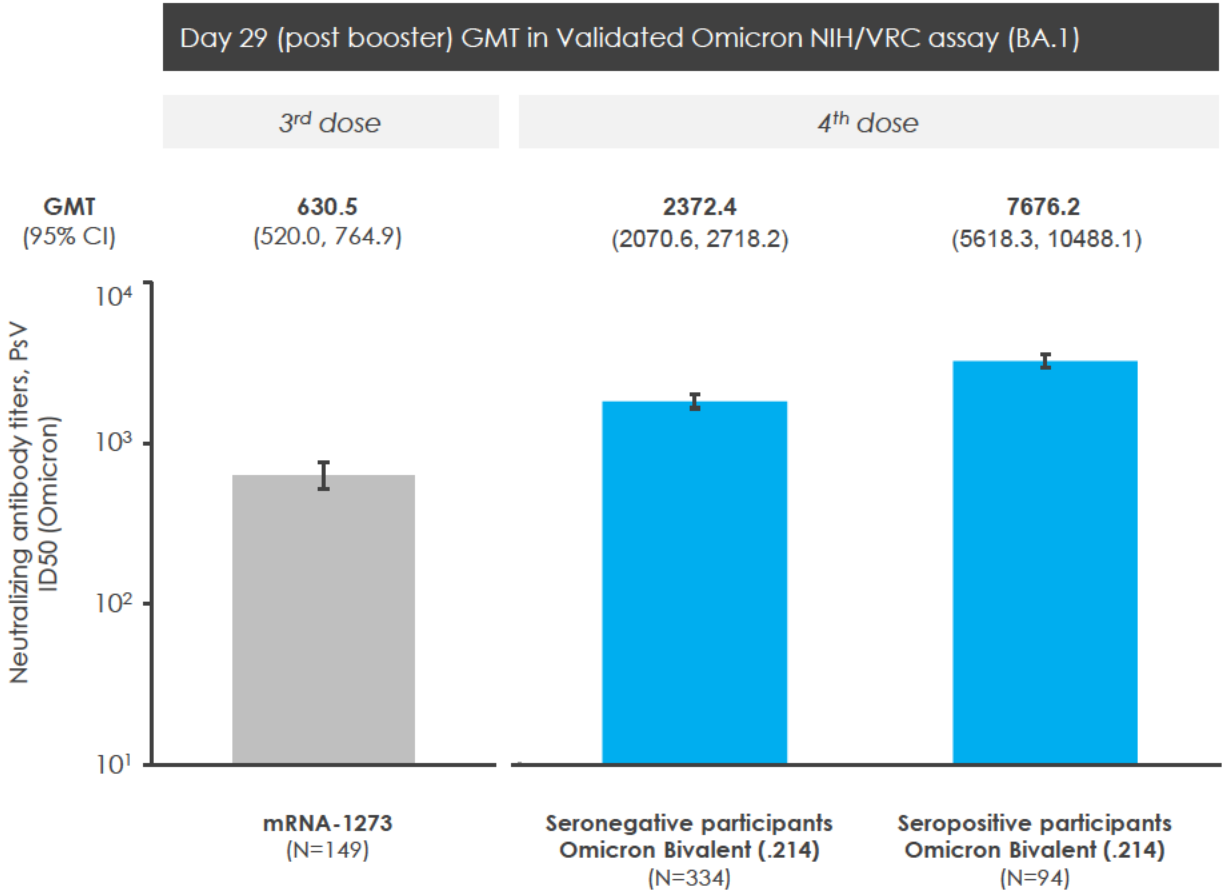
Bivalent .214 increased BA.1 neutralizing titers to levels 4- to 12-fold higher than dose 3 prototype booster



After .214 booster, **Omicron neutralizing GMT (BA.1) are 4- to 12-fold higher** than neutralizing titers after third dose mRNA-1273 3rd dose

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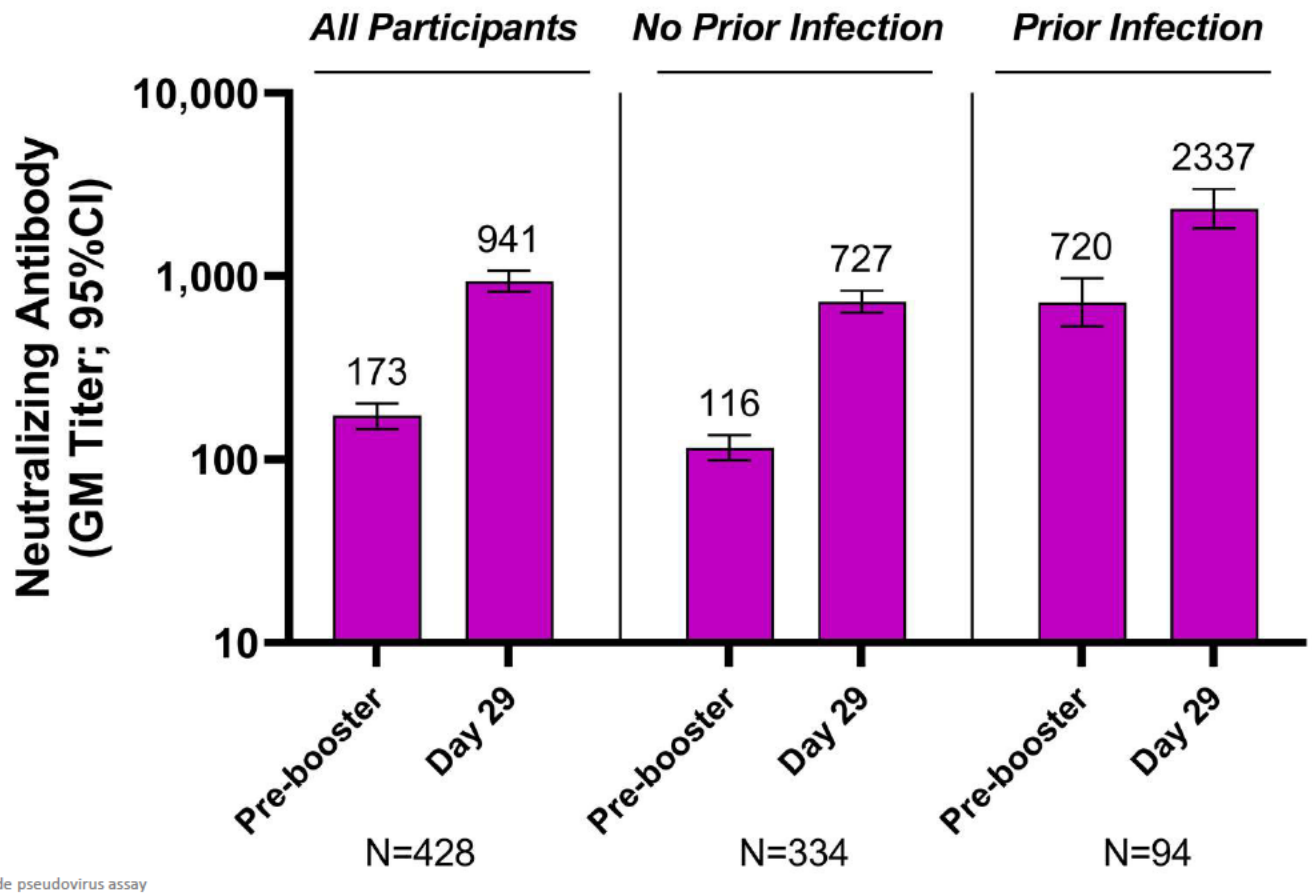
Bivalent booster (.214) elicited a potent neutralizing antibody response against the **Omicron BA.4/5 subvariants**



Research-grade pseudovirus assay

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mRNA-1273.214 boosts neutralizing titers against **BA.4/5**

GMT in BA.4/5 assay conducted at Duke/VRC (research grade, validation underway)

	All participants (N=428)	No prior infection (N=334)	Prior infection (N=94)
Pre-booster GMT, 95% CI	172.7 (147.5, 202.3)	115.6 (98.5, 135.6)	719.5 (531.6, 973.9)
Observed GMTs at Day 29, (95% CI)	**940.6** (826.3 , 1070.6)	**727.4** (632.9, 836.1)	**2337.4** (1825.5, 2992.9)
GMFR (95% CI) at Day 29, 95% CI	5.4 (5.0, 5.9)	6.3 (5.7, 6.9)	3.3 (2.8, 3.8)

- High neutralizing titers demonstrated against BA.4/5
- Highest GMFR seen for baseline seronegative recipients (6.3-fold rise)
- Highest GMT achieved in baseline seropositive recipients

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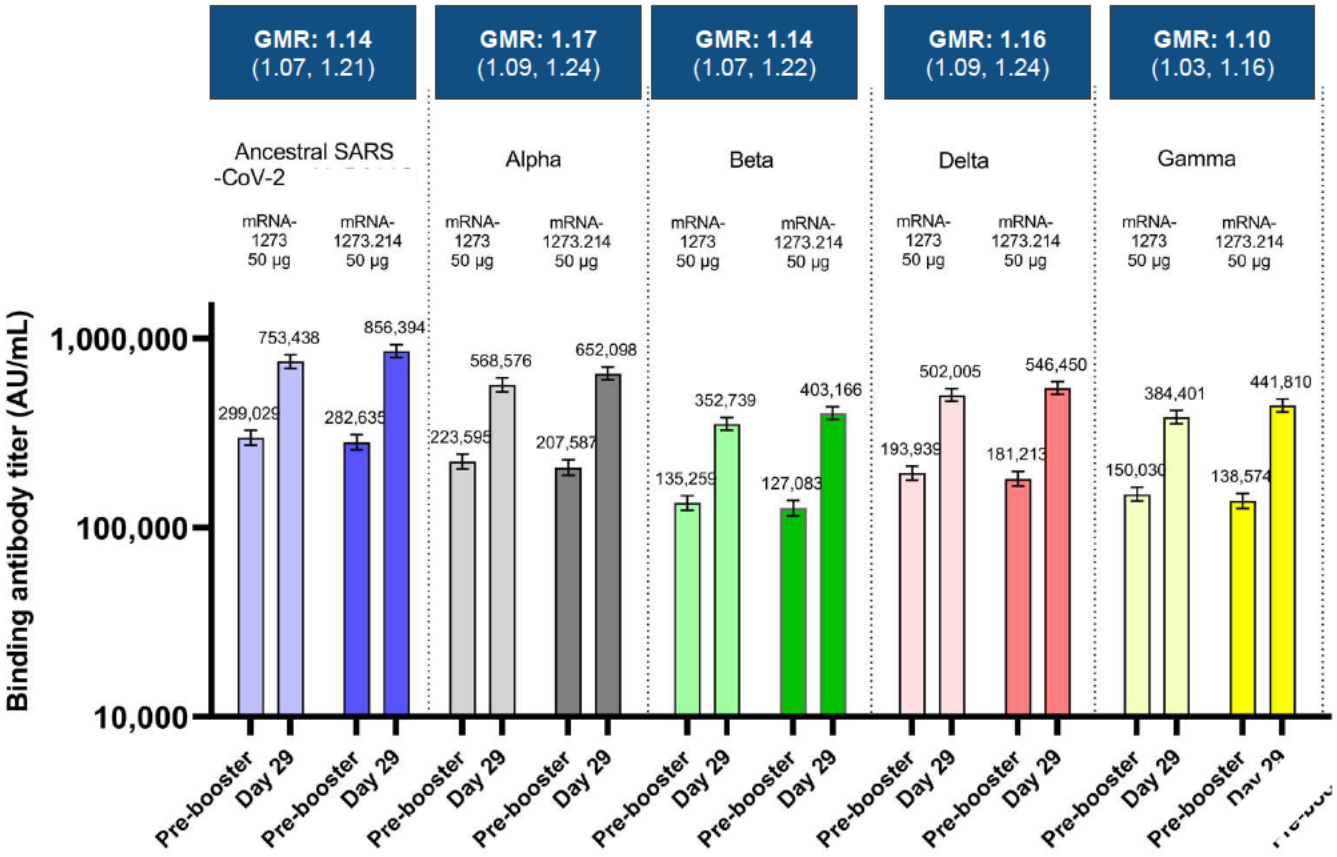
Binding antibody titers are higher for bivalent (.214) against **other variants tested**



mRNA-1273 50 µg: n between 334-365, mRNA-1273.214 50 µg: n between 384-423

Meso Scale Discovery (MSD) assay

moderna

Bivalent booster (.214) elicited higher neutralizing antibody titers against **ancestral** SARS-CoV-2 (D614G)

	No prior infection participants		*All participants*	
	mRNA-1273.214 50 µg (N=334)	**mRNA-1273** 50 µg (N=260)	**mRNA-1273.214** 50 µg (N=428)	**mRNA-1273** 50 µg (N=367)
Pre-booster GMT, 95% CI	1266.74 (1120.19, 1432.47)	1521.00 (1352.77, 1710.15)	1603.35 (1420.26, 1810.05)	1944.78 (1725.35, 2192.12)
Estimated GMTs (95% CI) at Day 29[a]	6422.32 (5990.12, 6885.71)	5286.63 (4887.07, 5718.86)	6555.69 (6122.34, 7019.72)	5301.37 (4931.77, 5698.66)
GMFR (95% CI) at Day 29, 95% CI	4.72 (4.36, 5.11)	3.71 (3.42, 4.03)	4.13 (3.84 4.44)	3.11 (2.88 3.36)
GMR (97.5% CI)[a]	**1.22** (1.08, 1.37)		**1.24** (1.12, 1.37)	
Seroresponse rate (95% CI) at Day 29[b]	334/334, 100 (98.9, 100)	260/260, 100 (98.6 100)	383/383, 100 (99.0 100)	347/347, 100 (98.9 100)
Difference in seroresponse rates (97.5% CI)[c]	**0**		**0**	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups for SARS-CoV-2 negative pre-booster participants. For all participants, model also includes prior SARS-CoV-2 infection.

[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.

[c] 97.5% CI is calculated using a stratified Miettinen-Nurminen method and adjusting by age group for SARS-CoV-2 negative pre-booster participants. For all participants, both age group and prior SARS-CoV-2 infection are adjusted. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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P205 Study Limitations

- Study was not randomized to compare different booster candidates or dose levels head-to-head
  - Booster candidates were evaluated in an open-label study design, with non-contemporaneous enrolment of vaccine groups
- Study was not designed to evaluate vaccine effectiveness or multiple intervals between booster doses

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Conclusions

- mRNA-1273.214 4th dose booster was well-tolerated, with similar safety & reactogenicity profile to prototype
- **All primary and key secondary immunogenicity objectives were met:**
  - mRNA-1273.214 (50 µg) elicited a **superior neutralizing antibody response against Omicron** and ancestral (D614G), compared to the prototype mRNA-1273 (50 µg)
  - **High absolute neutralizing titers against Omicron BA.1** following .214 bivalent, GMT of ~2400 and ~7700 for seronegative and seropositive respectively
  - **Superior binding antibody titers against prior VOC** (Alpha, Beta, Delta, Gamma, Omicron) for .214 compared to 4th dose of prototype
- Following .214 booster, **BA.4/BA.5-specific GMT are higher than levels demonstrated by prior booster against prior VOC waves**, including Omicron BA.1 and Delta
  - GMFR of 5.4-fold (95% CI: 5.0-5.9) following booster; all subjects had detectable neutralizing antibodies
- Based on 6-month durability previously demonstrated with bivalent .211 (Beta), Moderna **expects to see an increased durability for bivalent .**214 (Omicron) when compared to monovalent prototype booster
- Submission to regulators to be completed in next 2 weeks. Pending review and approval, deliveries of mRNA-1273.214 booster can begin in late July/early August

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Back-up

Primary and key secondary immunogenicity objectives

Primary

- To demonstrate non-inferiority of the Omicron antibody response of mRNA-1273.214 (50 µg) when administered as a second booster dose compared to mRNA-1273 (50 µg) when administered as a second booster dose based on the geometric mean titer ratio (GMR) and seroresponse (SRR) difference

- To demonstrate superiority of the Omicron antibody response of mRNA-1273.214 (50 µg) when administered as a second booster dose compared to mRNA-1273 (50 µg) when administered as a second booster dose based on the geometric mean titer ratio (GMR)

- To demonstrate non-inferiority of the ancestral SARS-CoV-2 antibody response of mRNA-1273.214 (50 µg) when administered as a second booster dose compared to mRNA-1273 (50 µg) when administered as a second booster dose based on the geometric mean titer ratio (GMR)

Key Secondary

- To demonstrate non-inferiority of the ancestral SARS-CoV-2 antibody response of mRNA-1273.214 (50 µg) when administered as a second booster dose compared to mRNA-1273 (50 µg) when administered as a second booster dose based on (SRR) difference

Immunogenicity objectives tested 28 days after the booster dose (Day 29) and 90 days (Day 91) after the booster dose (Day 91) with an alpha of 0.025 (2-sided) respectively at each one of the two time points.

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Chu, et al., Nat Med https://doi.org/10.1038/s41591-022-01739-w

Demographics and baseline characteristics were consistent between groups

Age at Screening (yr) Mean (range)	57.3 (20, 88)	57.5 (20, 96)
Age subgroup ≥18 and <65 years ≥65 years	263 (60.2) 174 (39.8)	227 (60.2) 150 (39.8)
Gender Male Female	179 (41.0) 258 (59.0)	186 (49.3) 191 (50.7)
Duration between second dose of mRNA-1273 in the primary series and the first booster of mRNA-1273 (months) Median Q1, Q3	8.0 (7.4, 9.0)	8.0 (7.4, 8.5)
Duration between first booster dose of mRNA-1273 and the second booster (months) Median Q1, Q3	4.5 (3.9, 4.9)	4.4 3.9, 4.9
SARS-CoV-2 infection Pre-booster Negative Positive* Missing	340 (77.8) 96 (22.0) 1 (0.2)	267 (70.8) 101 (26.8) 9 (2.4)

**SARS-CoV-2 testing was performed with polymerase chain reaction (PCR) and SARS-CoV-2 nucleocapsid antibody test. A positive test (either PCR or antibody test) was needed for the SARS-CoV-2 infection positive group.*

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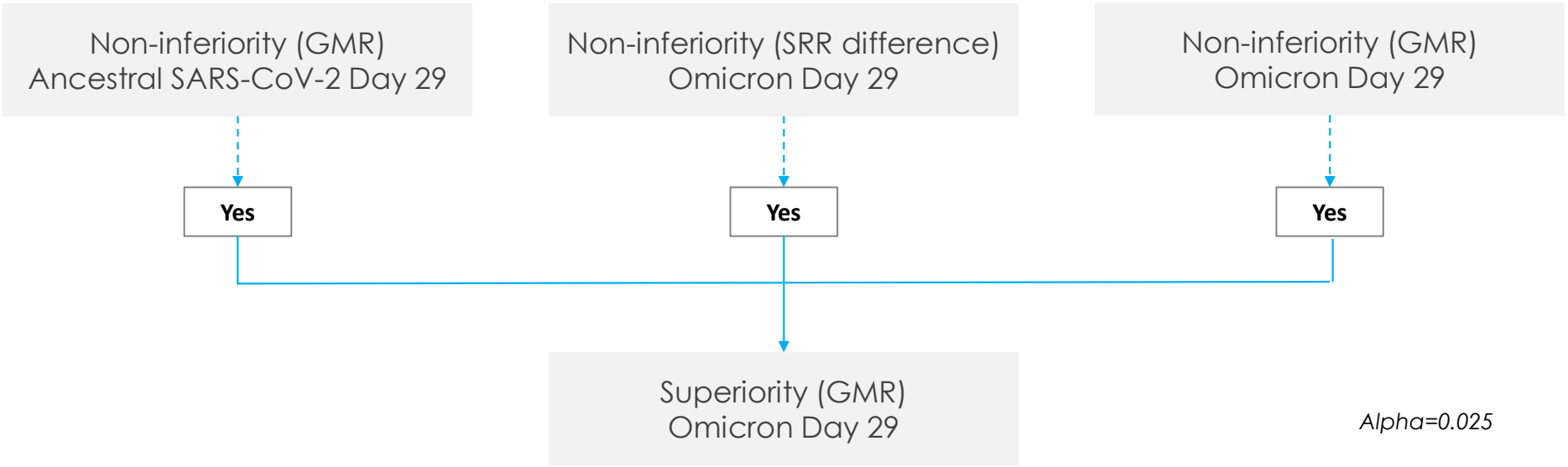
Primary immunogenecity objectives

The Day 29 testing sequence for the immunogenecity endpoints is the following:



Alpha=0.025

GMR: geometric mean titer ratio; SRR: seroresponse

Bivalent booster (.214) resulted in superior neutralizing GMT against **Omicron**

Only participants with no previous SARS-CoV2 infection

	mRNA-1273.214 50 µg (N=334)	**mRNA-1273** 50 µg (N=260)
Pre-booster GMT, 95% CI	298.13 (258.75, 343.49)	332.02 (282.05, 390.85)
Estimated GMTs (95% CI) at Day 29[a]	2479.89 (2264.47, 2715.80)	1421.24 (1282.98, 1574.41)
GMFR (95% CI) at Day 29, 95% CI	7.96 (7.18, 8.82)	4.44 (3.97, 4.96)
GMR (97.5% CI)[a]	**1.75** (1.49, 2.04)	
Seroresponse rate (95% CI) at Day 29[b]	333/333, 100 (98.9, 100)	256/258, 99.2 (97.2, 99.9)
Difference in seroresponse rates (97.5% CI)[c]	**1.5** (-1.1, 4.0)	

Primary endpoint for testing non-inferiority and superiority was seronegative participants

- Bivalent booster (.214) resulted in superior neutralizing GMT against Omicron compared to mRNA-1273 for all participants (includes both **seronegative participants** and **seropositive participants)**

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 97 5% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Omicron neutralizing antibody responses were consistently higher with mRNA-1273.214, compared to mRNA-1273, in participants with prior SARS-CoV-2 infection

Participants with prior infection

	mRNA-1273.214 50 µg (N=94)	**mRNA-1273** 50 µg (N=98)
Pre-booster GMT, 95% CI	1614.6 (1149.7, 2267.7)	1558.4 (1088.9, 2230.1)
Estimated GMTs (95% CI) at Day 29[a]	7669.2 (6470.7, 9089.6)	4041.5 (3375.1, 4839.5)
GMFR (95% CI) at Day 29, 95% CI	4.8 (4.0, 5.7)	2.5 (2.1, 3.0)
GMR (95% CI)[a]	1.90 (1.50, 2.40)	
Seroresponse rate (95% CI) at Day 29[b]	47/47, 100 (92.5, 100)	76/76, 100 (95.3, 100)
Difference in seroresponse rates (95% CI)[c]	0	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[C] 95% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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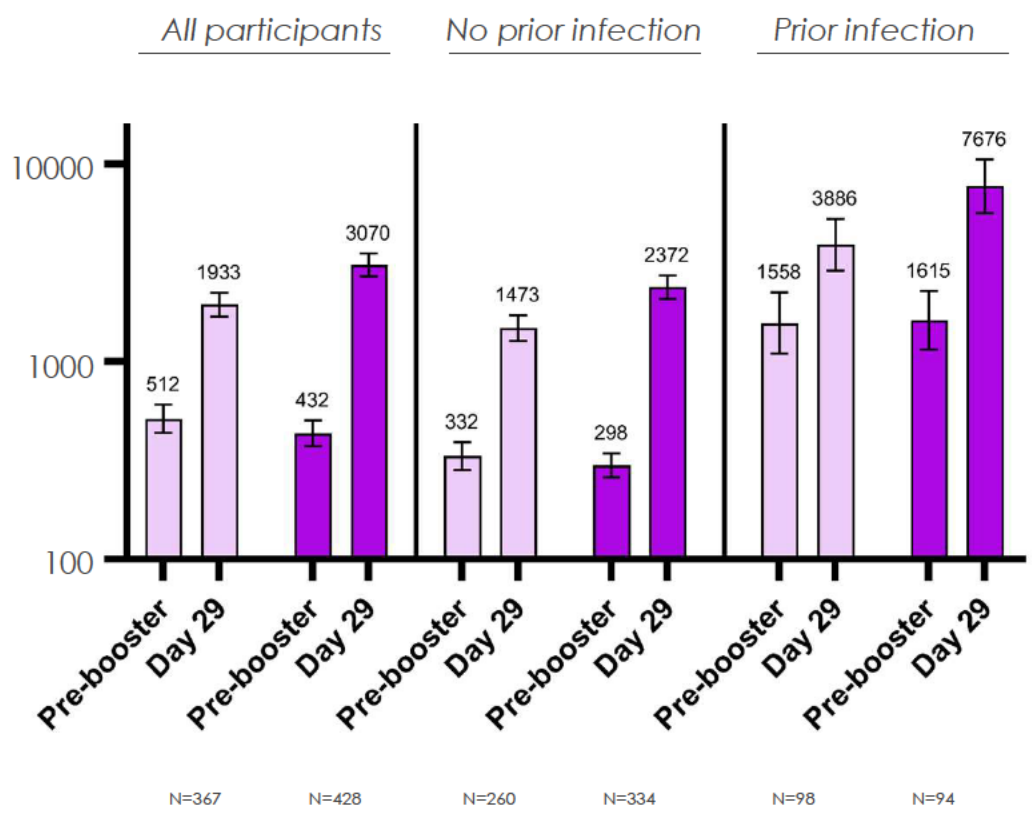
Omicron neutralizing titers (PsVNT50)

Omicron (BA.1) neutralizing antibody titers (PsVNT50)



Omicron neutralizing titers **were significantly higher following bivalent (.214) booster** compared to prototype for all participants and both seronegative and baseline seropositive participants

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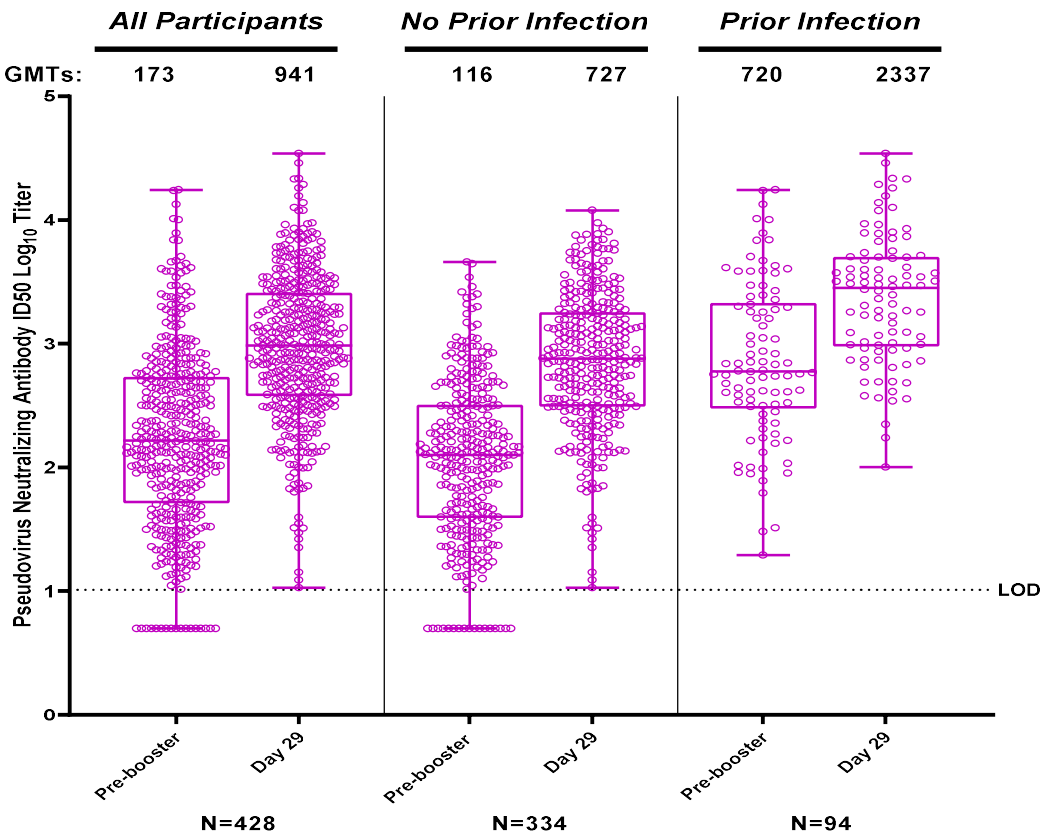
Bivalent booster (.214) elicited a potent neutralizing antibody response against the **Omicron BA.4/5 subvariants**



Research-grade pseudovirus assay. Lower limit of detection (LoD) =10. Values below LoD were imputed as half of the LoD.

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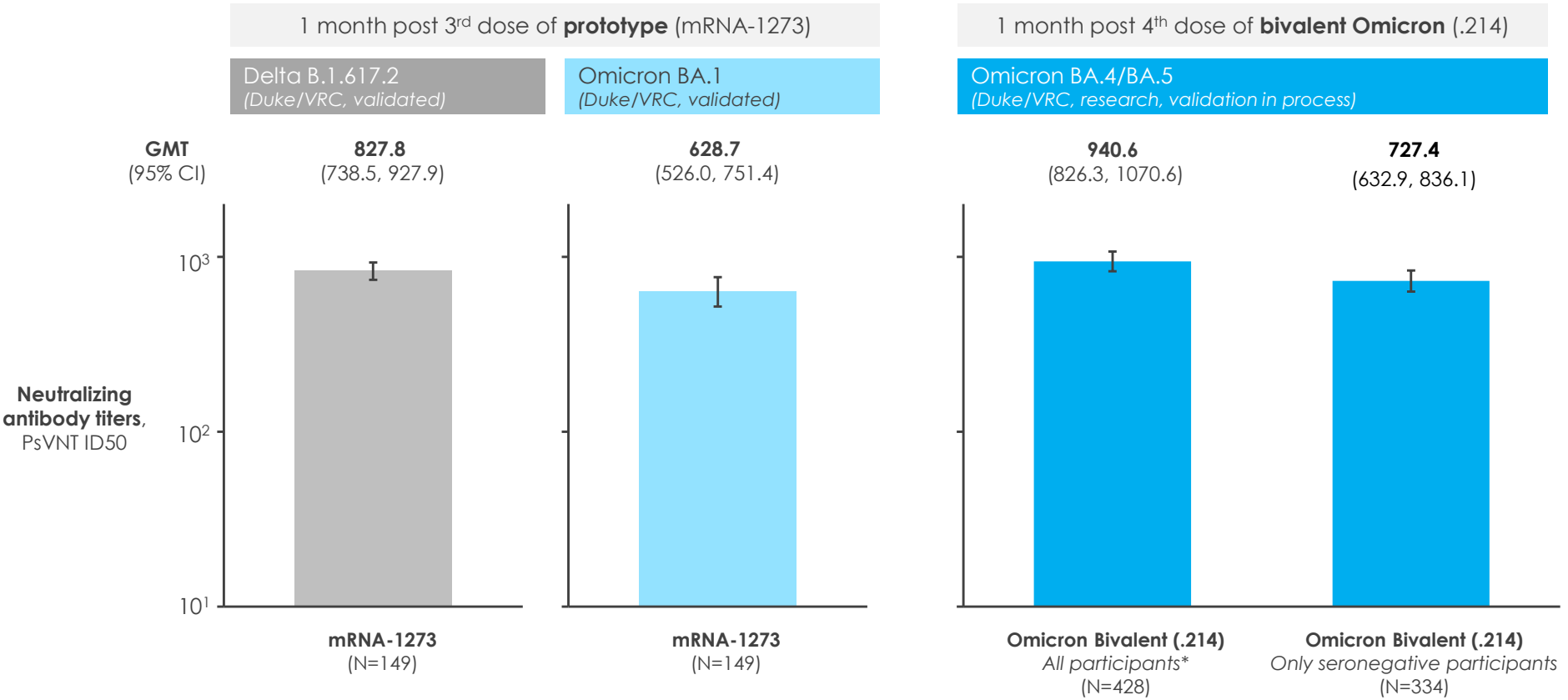
Bivalent .214 booster increased BA.4/BA.5-specific neutralizing titers to levels demonstrated against previous VOC



*Note: 22% of .214 recipients were seropositive at baseline among these participants (N=94) 1 month post bivalent .214 booster BA.4/BA.5 GMT was 2337.4 (1825.5 2992.9)

Chu et al *Nature Medicine (2022)*, https://doi.org/10.1038/s41591-022-01739-w
Chu et al *preprint* https://assets.researchsquare.com/files/rs-1555201/v1_covered.pdf?c=1650045900 (Fig.3 Suppl. Table 4)

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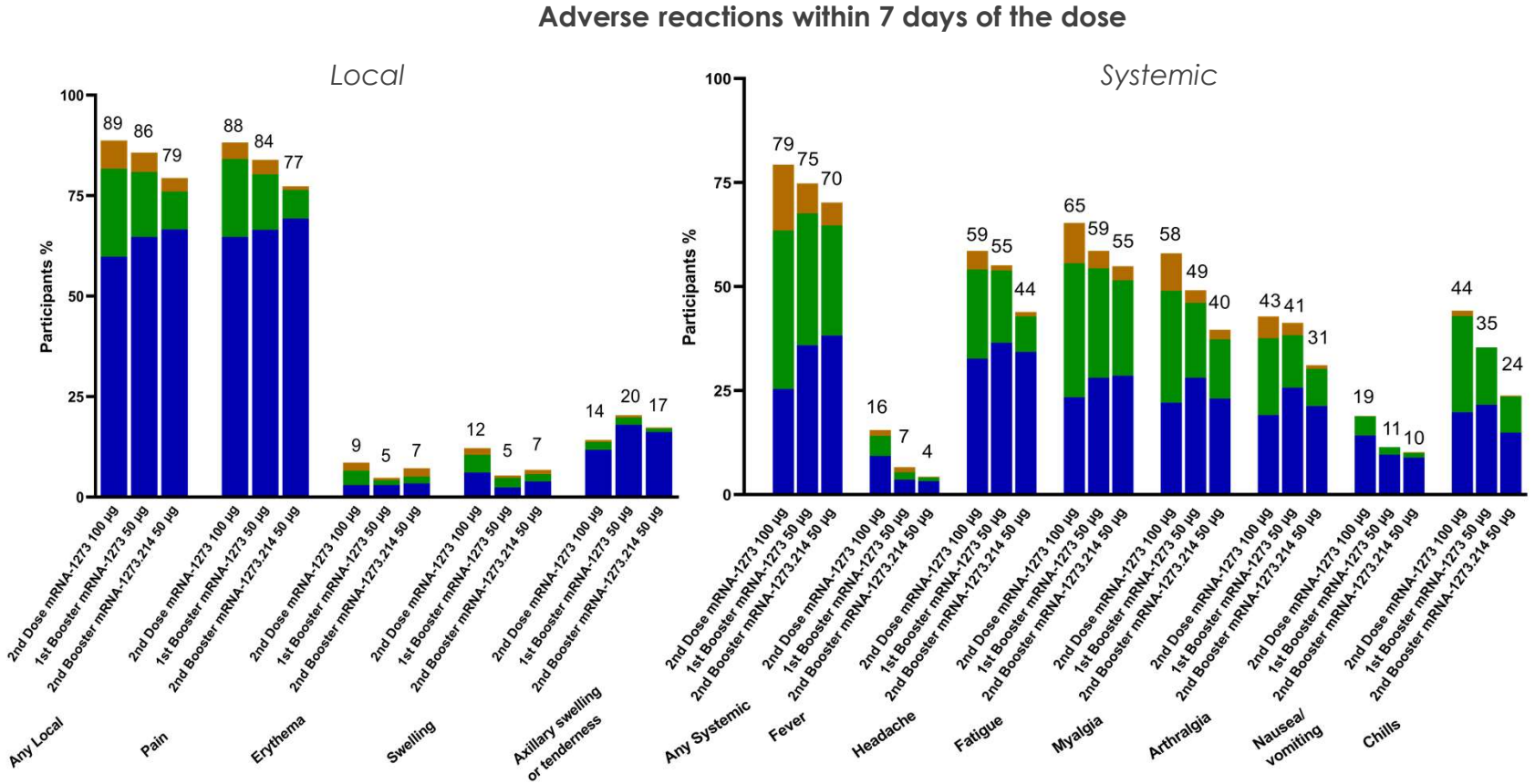
Solicited adverse reactions were consistent with prior doses



Baden et al., NEJM, 2021

Choi et al., Nat Med, 2022

Source trial: P301(primary 100 µg dose 2) P201 (50 µg booster 1) P205 (50 µg booster 2)

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Duke/VRC BA.4/BA.5 research assay is consistent with published literature

Baseline group (Moderna P2/3, .214)	**Sample (N)**	**BA.1 GMT**	**BA.4/5 GMT**	**Fold decrease** *(BA.4/5 vs. BA.1)*
Seronegative	337	2372	727	3.26-fold
Seropositive	94	7676	2374	3.23-fold

Combined 3.2-fold

Publication	**Description**	**N** (sample)	**Fold decrease** (BA.4/5 vs. BA.1)
Hachmann et al 2022 (Dan Barouch, Harvard)	3 doses vaccine Vaccine + infection	27 27	3.3-fold 2.9-fold
Tuekprakhon et al 2022 (Gavin Screaton, Oxford)	3 doses (mRNA) 3 doses (ChAdOx1)	20 41	3.2-fold 2.1-fold
Willett et al 2022 (Thomas Peacock, Imperial)	3 doses vaccine (older cohort)	6	1.2-fold
Wang et al 2022 (David Ho, Columbia)	3 doses vaccine	16	3.7-fold
Qu et al 2022 (Ohio State)	3 doses vaccine	15	1.5-fold
Quandt et al 2022 (BioNTech)	3 doses vaccine Vaccine + infection	19 10	2.2-fold 5.2-fold

Median 2.9-fold

**Calculated from data. N.b body of manuscript refers to fold drop relative to BA.2 assay*

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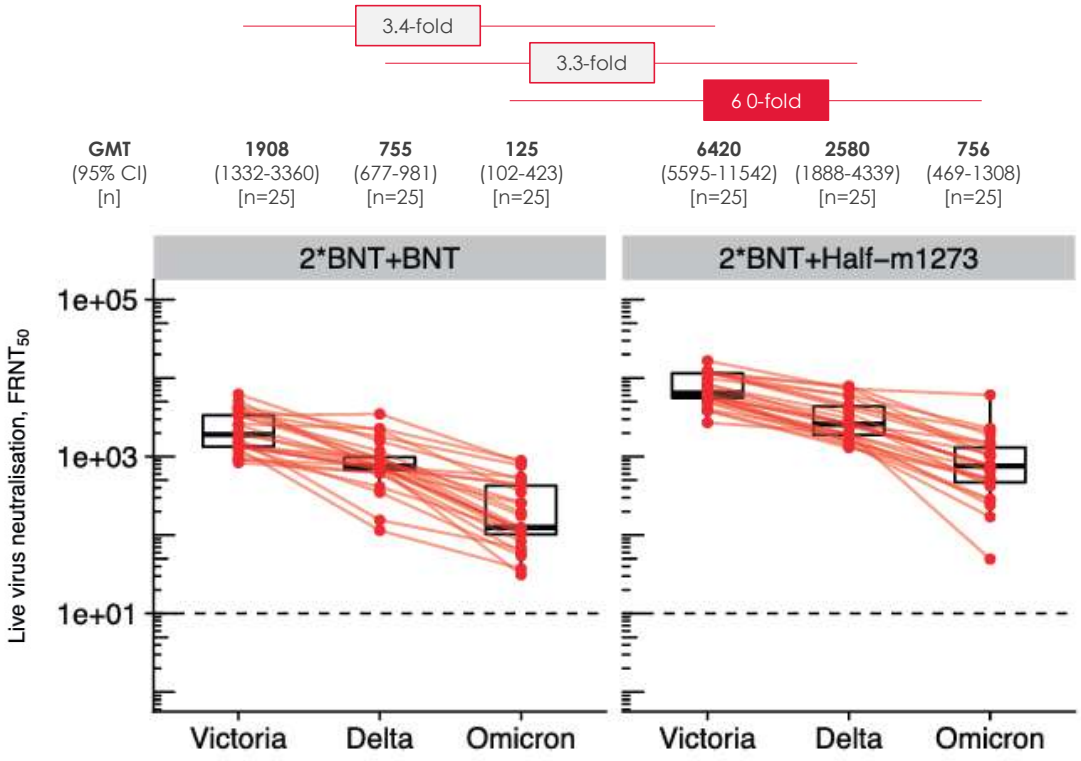
Published data show third dose mRNA-1273 booster resulted in neutralizing titers against Omicron (BA.1)

Liu et al.
Journal of Infection
2022

COV-BOOST study (UK)

Participants who received 2 doses of BNT were randomized to receive a 3rd dose of BNT or booster dose (50 mcg) of mRNA-1273



https://www.journalofinfection.com/article/S0163-4453(22)00200-6/fulltext

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Neutralizing antibody geometric mean ratio: 50 µg mRNA-1273.211 compared to 50 µg mRNA-1273

Variant	Time	mRNA-1273.211 GMT* (95% CI)	mRNA-1273 GMT* (95% CI)	GMT Ratio (95% CI)
Ancestral SARS-Cov-2 with D614G	Day 29	2278.0 (2074.0, 2502.1)	1782.7 (1561.3, 2035.6)	**1.28 (1.08, 1.51)**
	Day 181	1040.0 (926.4, 1167.3)	617.2 (525.1, 725.5)	**1.68 (1.38, 2.06)**
Beta	Day 29	1095.3 (981.1, 1222.7)	825.6 (706.6, 964.7)	**1.33 (1.09, 1.61)**
	Day 181	343.5 (303.7, 388.5)	125.2 (105.4, 148.8)	**2.74 (2.22, 3.40)**
Omicron	Day 29	1379.3 (1209.9, 1572.4)	636.7 (529.1, 766.3)	**2.17 (1.73, 2.72)**
	Day 181	308.0 (265.8, 356.9)	145.6 (118.1, 179.5)	**2.32 (1.80, 2.98)**
Delta	Day 29	1483.0 (1335.9, 1646.3)	838.8 (724.4, 971.2)	**1.77 (1.48, 2.12)**
	Day 181	492.9 (438.3, 554.2)	400.8 (340.4, 471.8)	**1.23 (1.01, 1.50)**

***GMT = estimated geometric least square means with a Mixed Model for Repeated Measures adjusting for pre-booster titer levels, nominal alpha of 0.05**

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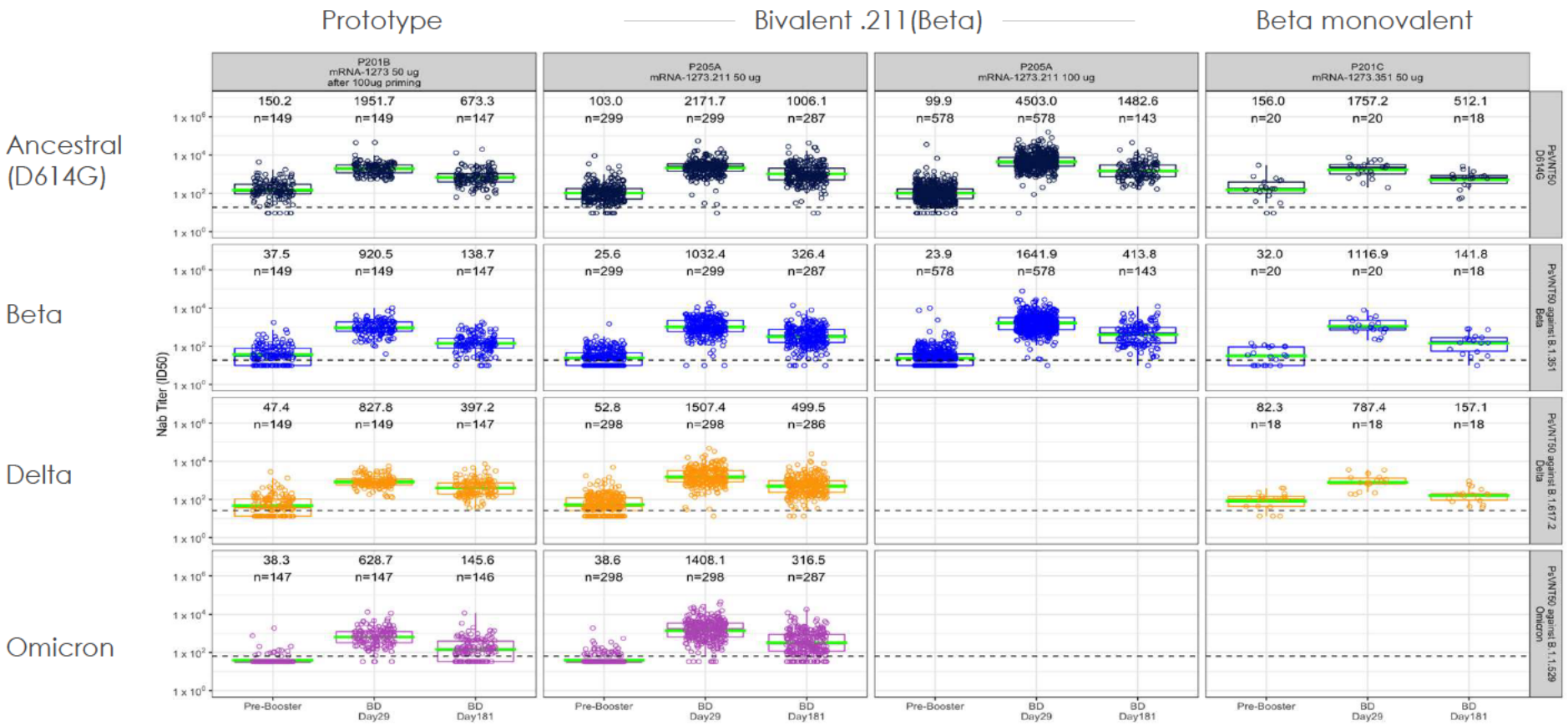
Data with .211 (Beta) demonstrated advantages of bivalent approach against wider range of variants



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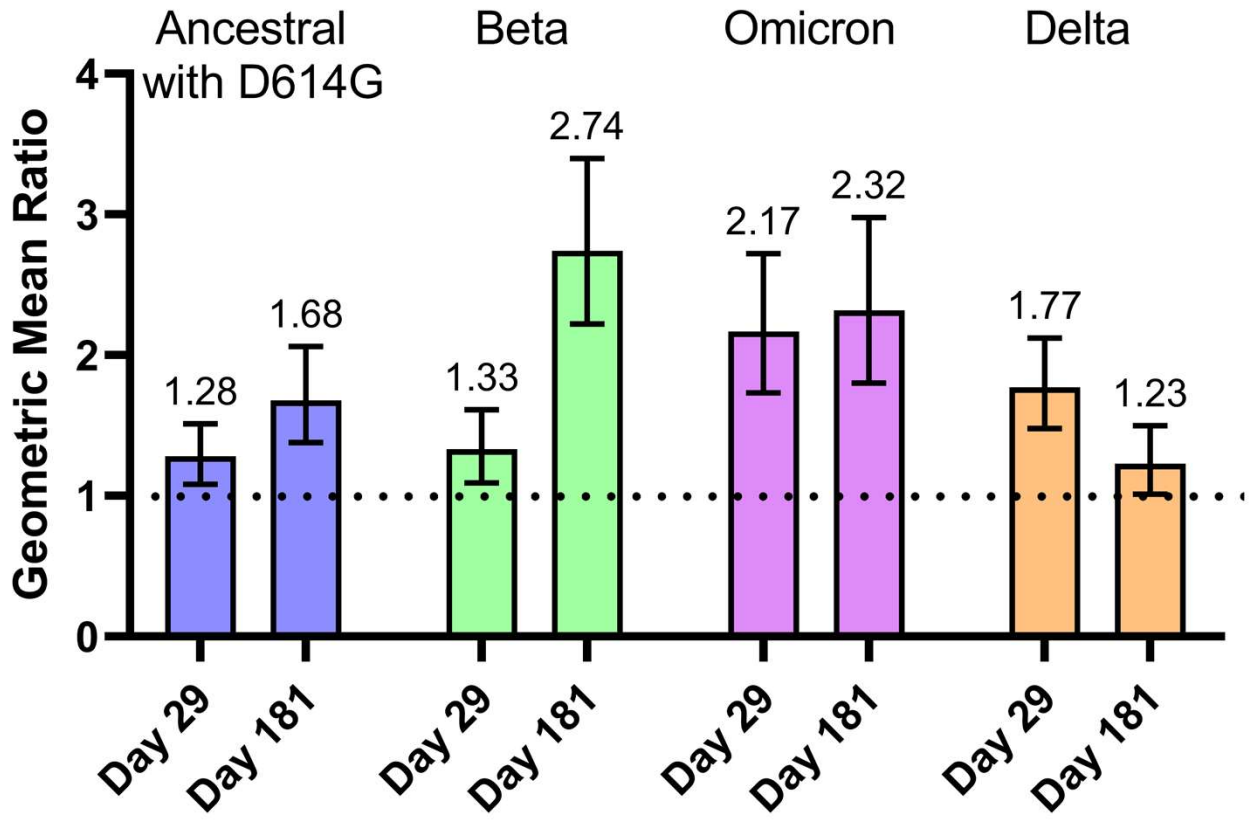
Neutralizing antibody geometric mean ratio: 50 µg mRNA-1273.211 compared to 50 µg mRNA-1273



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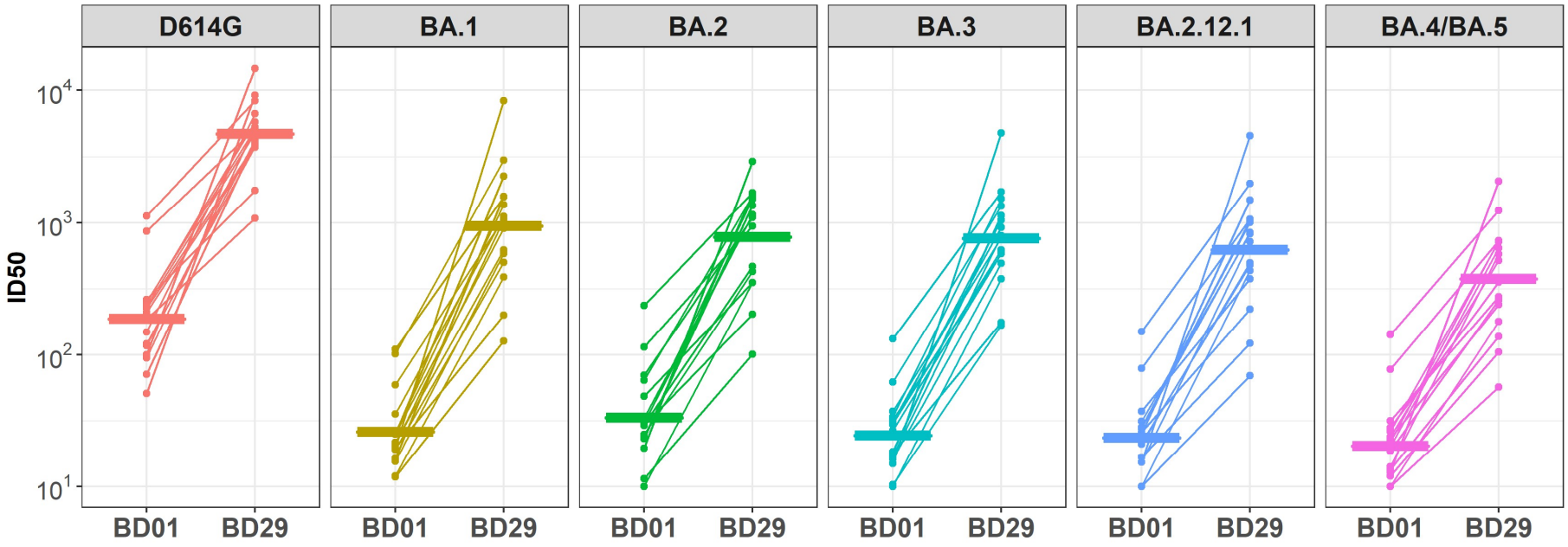
Neutralization of Omicron Subvariants by Sera from mRNA-1273 Vaccine Recipients in Study DMID 21-0012

mRNA-1273 50-µg given as a first booster dose, n=16



	D614G		BA.1		BA.2		BA.3		BA.2.12.1		BA.4/BA.5	
	BD01	BD29	BD01	BD29	BD01	BD29	BD01	BD29	BD01	BD29	BD01	BD29
GMT	188	4679	26	945	33	780	25	764	24	626	20	378
Fold decrease from D614G		--		5.0		6.0		6.1		7.5		12.4

Pseudovirus research-grade assays
Duke Laboratory

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Boosting with Bivalent Vaccines

Scientific Strategy

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Executive Summary

- COVID-19 continues to evolve **with more variants emerging while booster coverage rates are significantly low**
- **Neutralizing antibody (nAb)** responses to **ancestral strain** and **variants are increased after boosting** with bivalent vaccines
- **Titers wane more slowly with bivalent boosting**, with duration of antibody response noted up to 6 months compared to monovalent boosting
- **Bivalent vaccines provide cross neutralization against multiple variants of concern, including Omicron subvariants BA.1, BA.4/5, BA.2.75, BQ.1.1**
  - Even lower levels of specific nAbs and specific memory B-cells may provide increased protection; early nAb responses might overlook later benefits of Omicron-adapted vaccines
- **Ensuring appropriate vaccination rates and following up on real world evidence (RWE) will be critical to determining vaccination performance against emerging variants**

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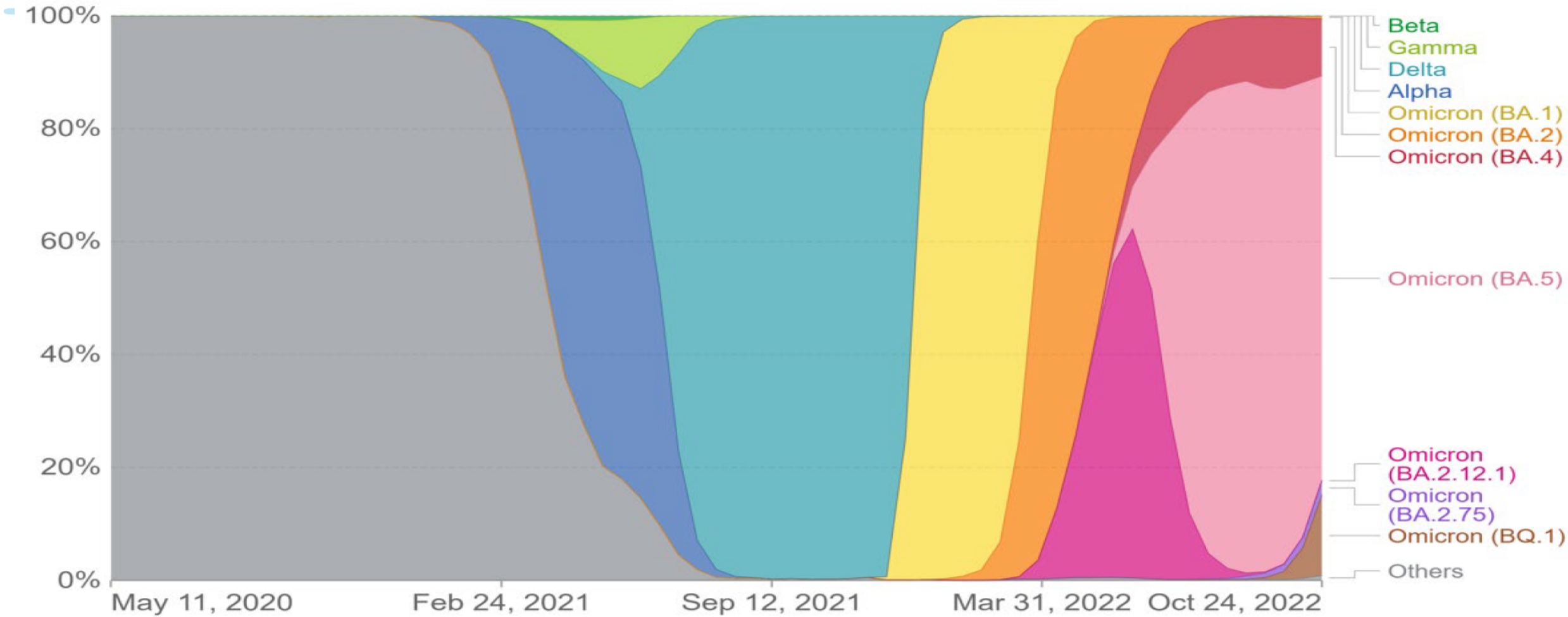
SARS-CoV-2 Continues to be a Global Problem as New Variants Repeatedly Emerge



Source: GISAID, via CoVariants.org – Last updated 31 October 2022 OurWorldInData.org/coronavirus • CC BY

Note: Recently-discovered or actively-monitored variants may be overrepresented, as suspected cases of these variants are likely to be sequenced preferentially or faster than other cases.

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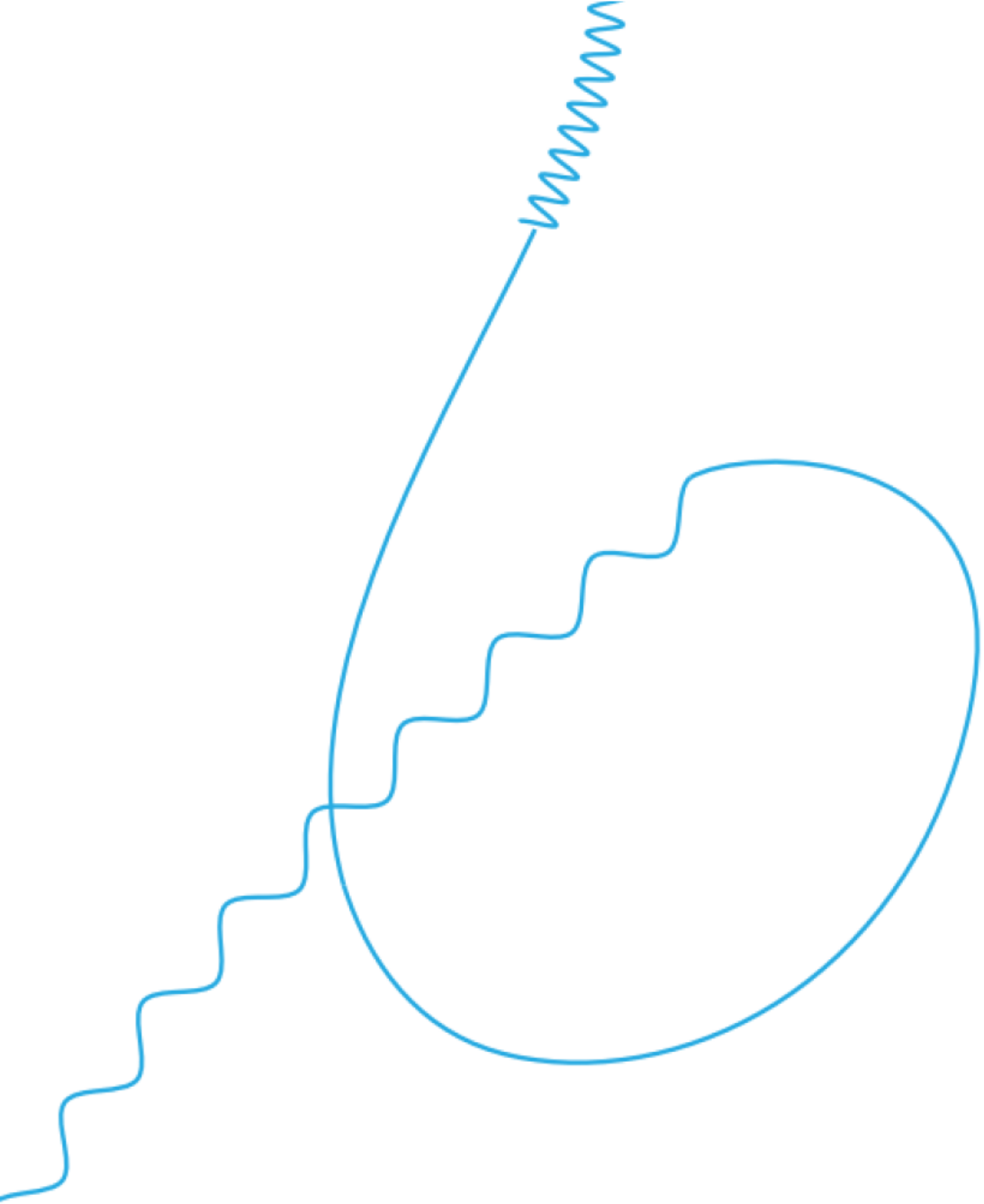

Bivalent vaccines: What have we learned?

Do bivalent vaccines induce:

- **Higher immune responses than monovalent vaccines?**
- **Longer duration of antibody titers?**
- **Broader cross-neutralizing antibody titers?**

Are bivalent vaccines effective?

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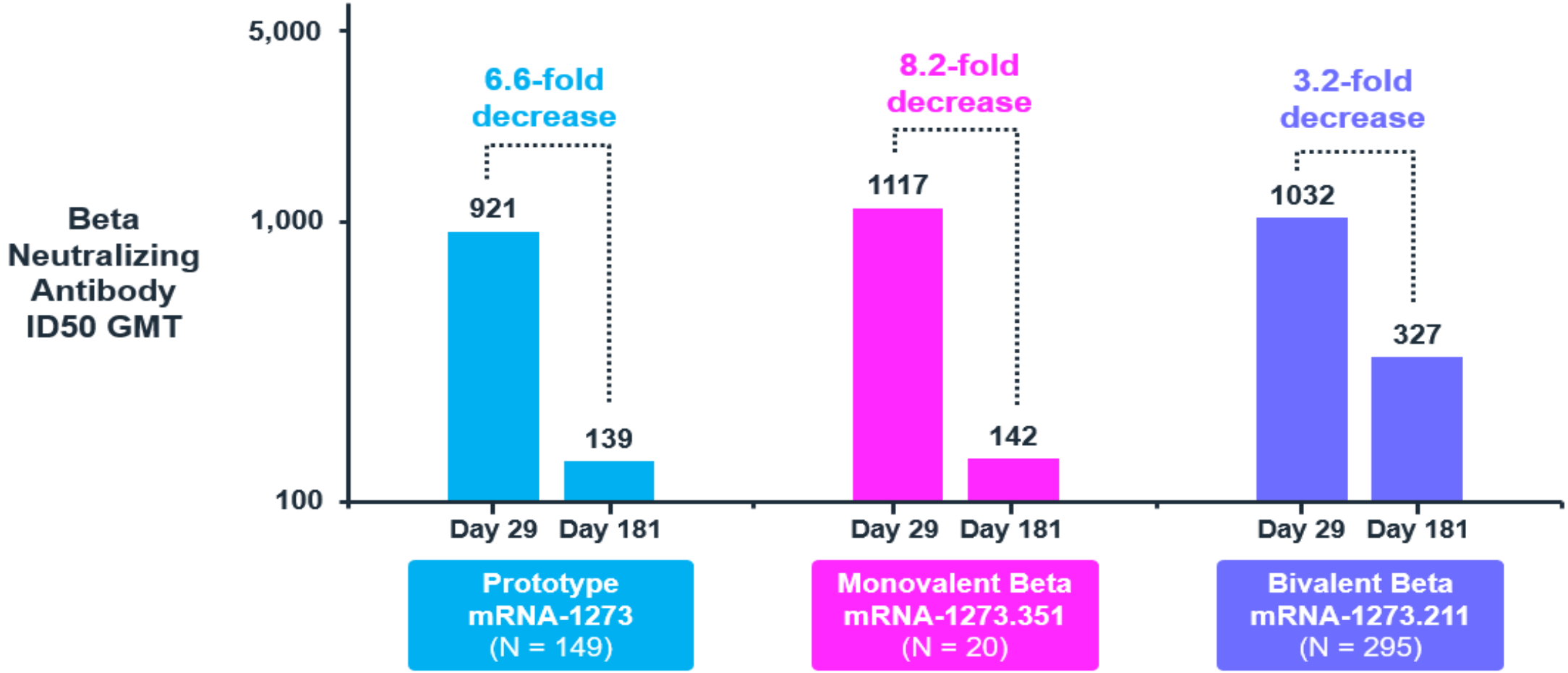
Precursor Beta-containing Bivalent Vaccine mRNA-1273.211 Demonstrated That Titers Waned More Slowly Through 6 months Compared to Monovalent Boosting



Chalkias S, et al. *medRxiv*. Published (peer review pending) June 25, 2022. https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf. Accessed June 27, 2022.
Choi A, et al. *Nat Med*. September 15, 2021. https://doi.org/10.1038/s41591-021-01527-y.

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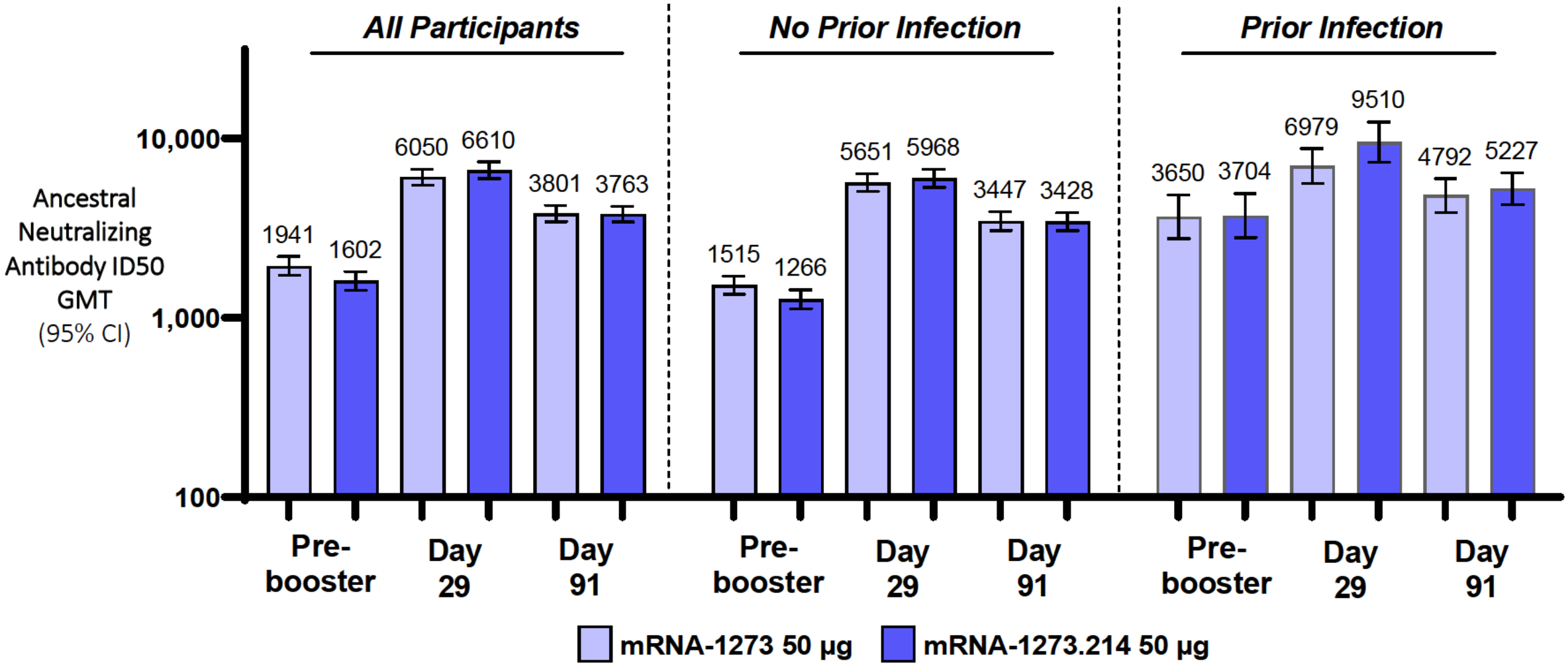
Ancestral SARS-CoV-2 D614G Neutralizing Titers After 4th Dose with BA.1 Bivalent mRNA-1273.214 Were Non-inferior Compared to mRNA-1273

Study 205, Per-Protocol Immunogenicity Set



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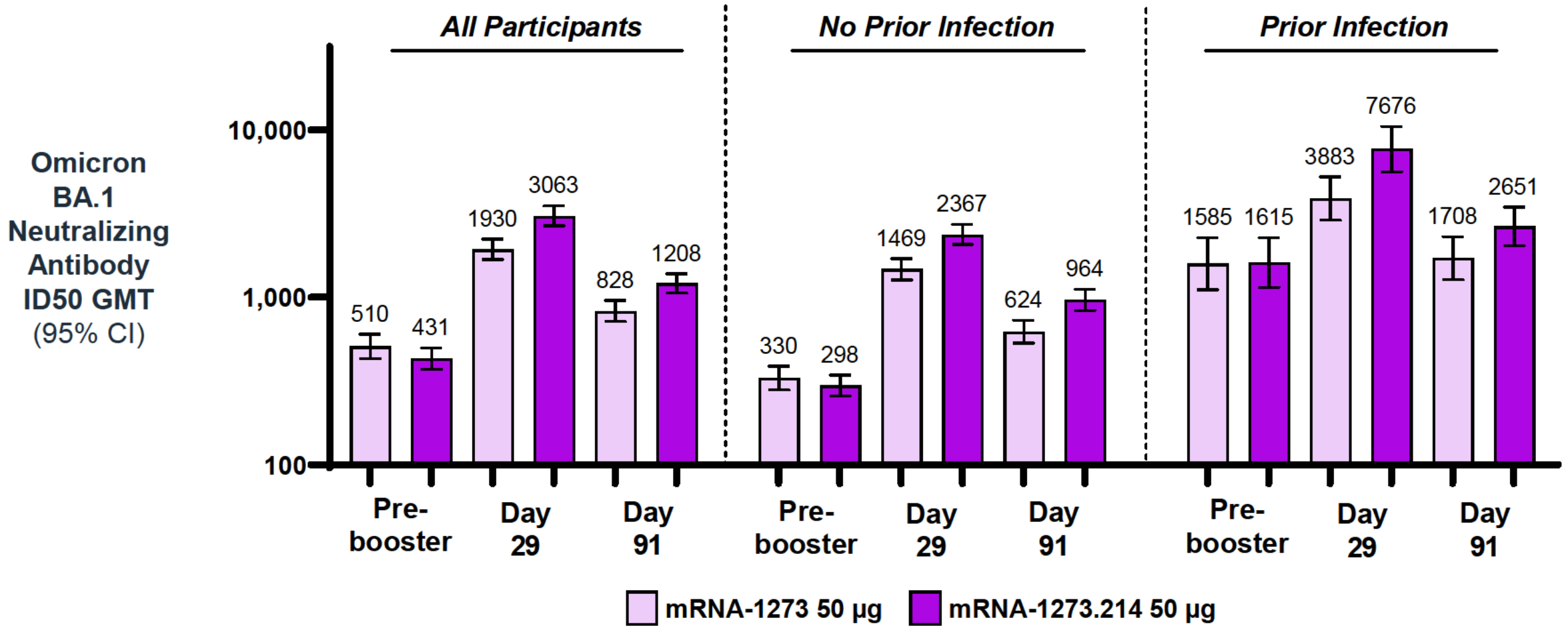
mRNA-1273.214 Demonstrated Superior nAB Titers Against BA.1 (Omicron) Compared to Monovalent mRNA-1273, Irrespective of Prior Infection



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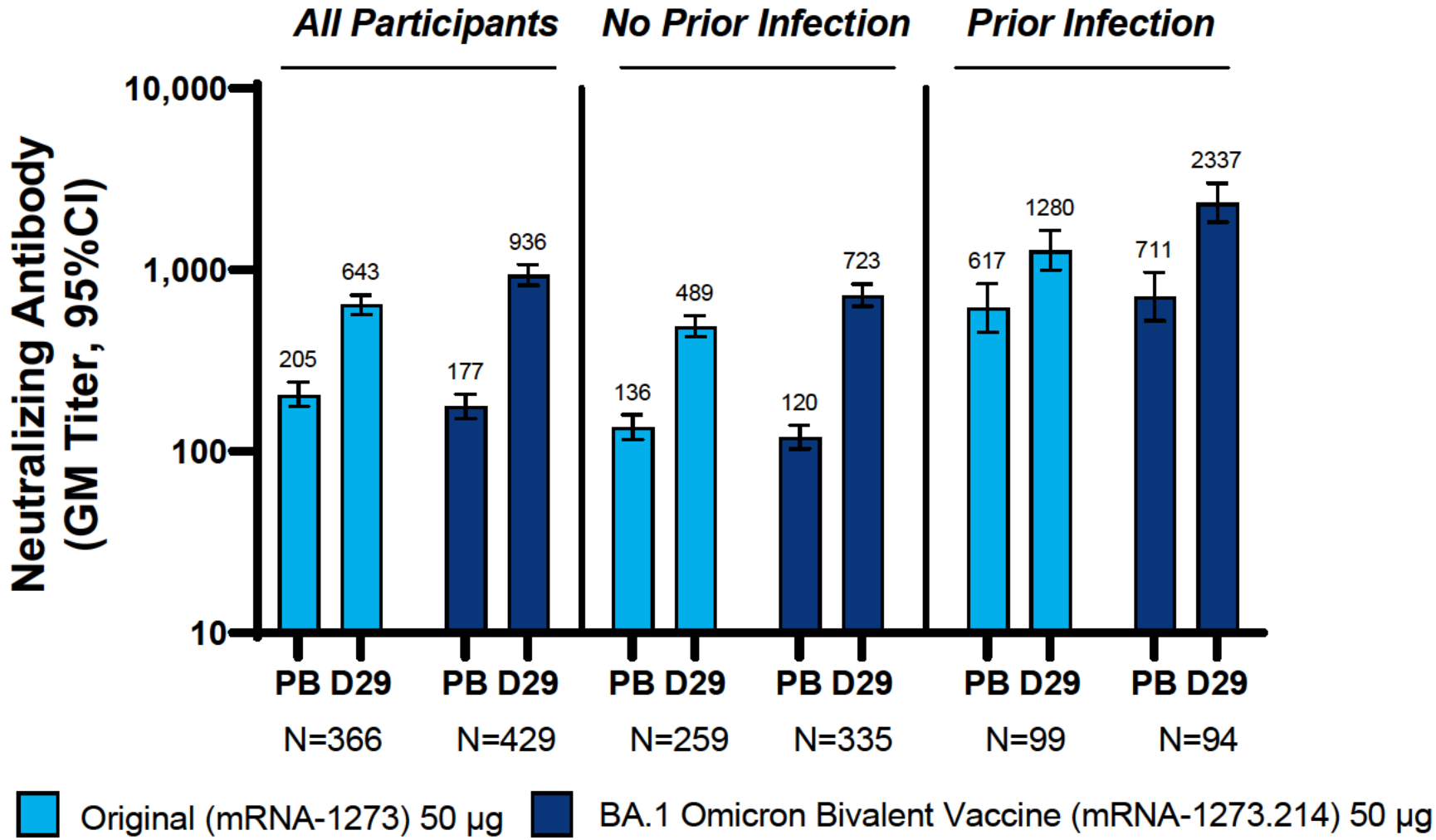
4th Dose with Omicron BA.1 Bivalent Booster mRNA-1273.214 Resulted in Higher Neutralizing Antibody Titers against Omicron BA.4 & BA.5 than mRNA-1273 at Day 29



Pre-booster (**PB**), Day 29 post-boost (**D29**)

Pre-booster SARS-CoV-2 infection status not known for n=8 participants in the mRNA-1273 group.

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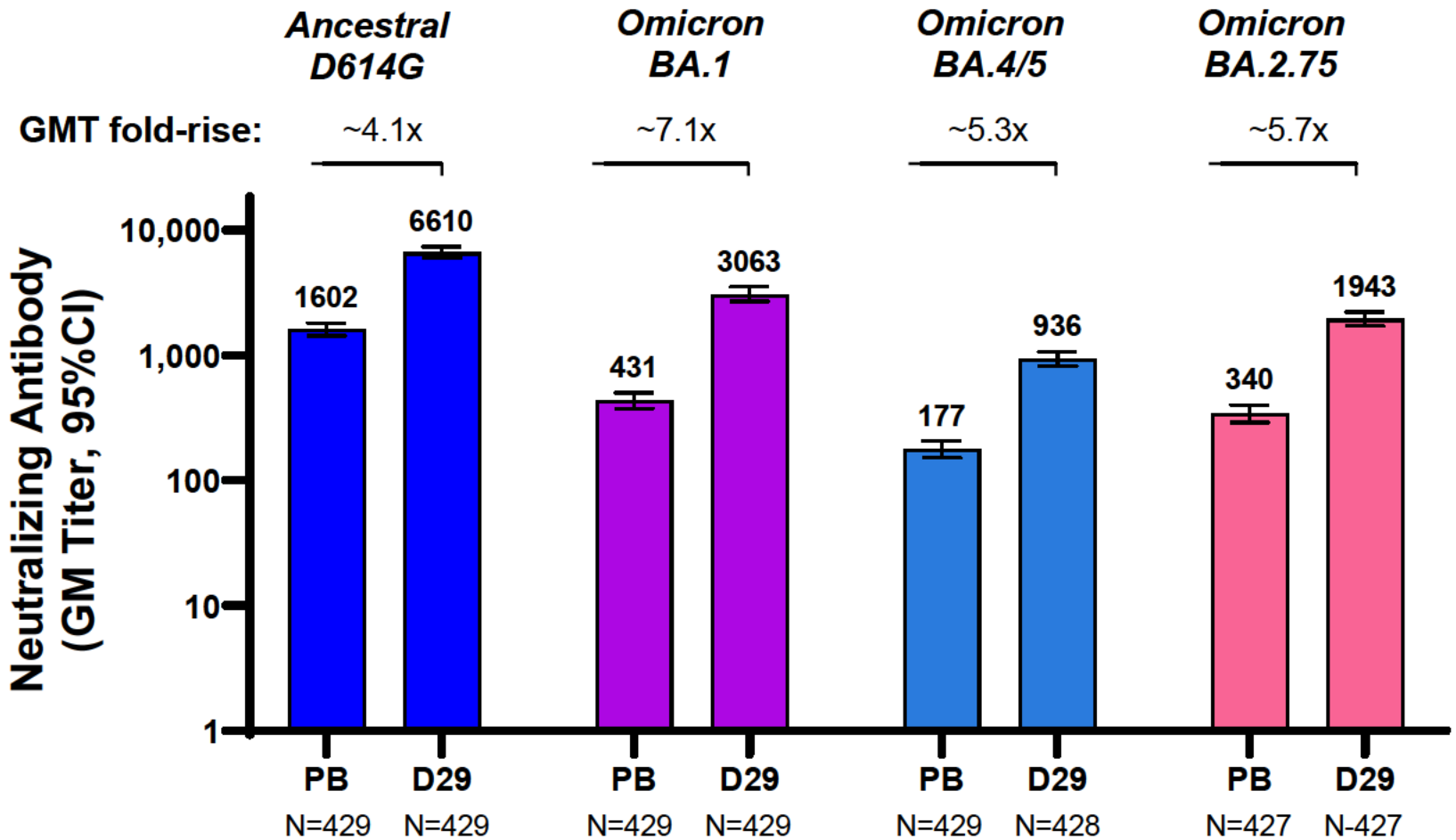
Omicron BA.1 Bivalent Vaccine mRNA-1273.214 Exhibited Cross-Neutralization Across Multiple Omicron Variants

Study 205, Per-Protocol Immunogenicity Set



~4.1 – 7.1 fold increase in titers following receipt of BA.1 Omicron Bivalent Booster (mRNA-1273.214)

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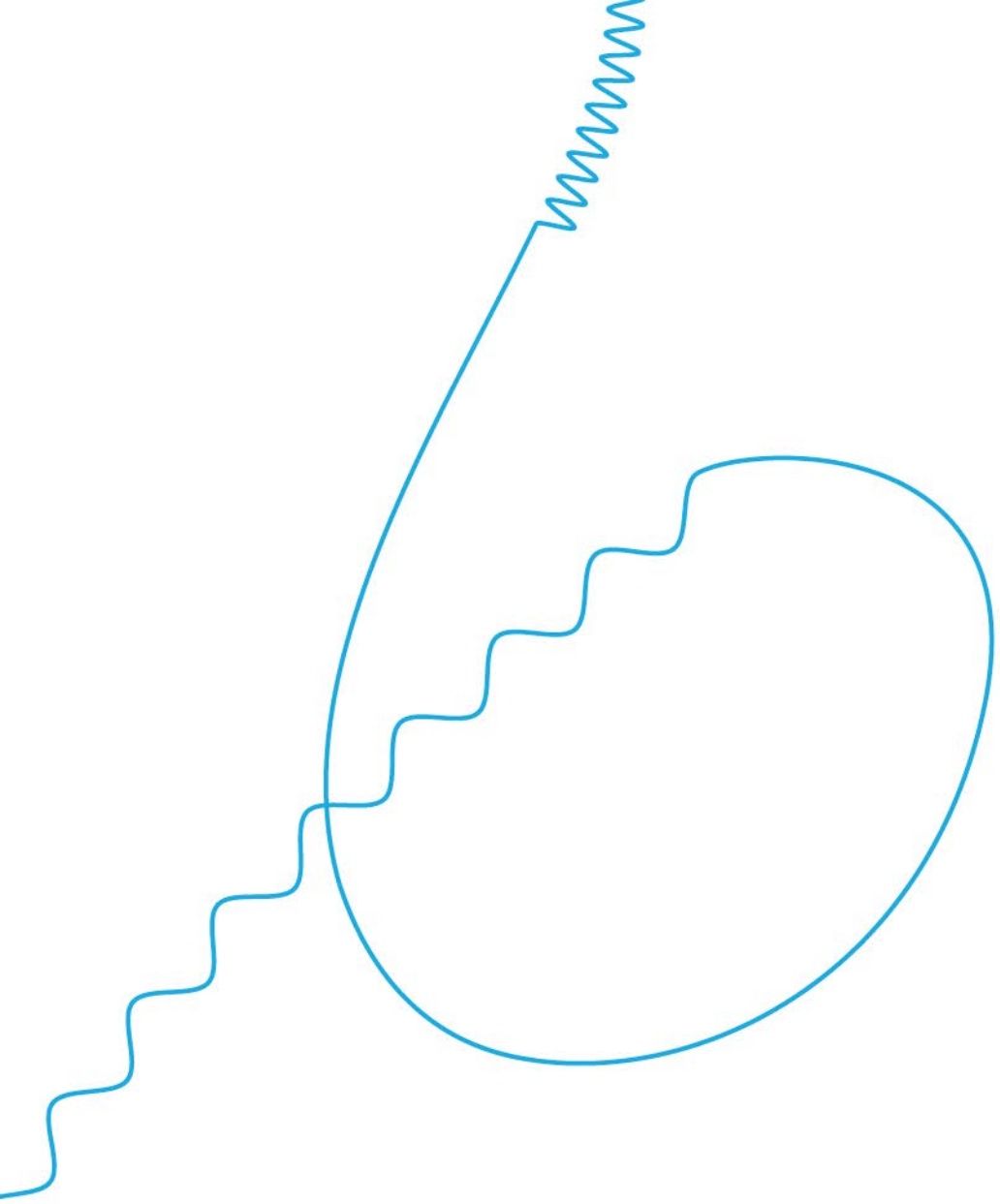

Study mRNA-1273-P205, Day 29 mRNA-1273.222 interim results

November 2022

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Key Points

- The incidence of local and systemic adverse reactions of the bivalent Omicron BA.4/BA.5-containing mRNA-1273.222 was similar to or lower than that of prior mRNA-1273 doses.
- A 50 µg booster dose of the bivalent Omicron BA.4/BA.5 mRNA-1273.222 met all pre-specified immunogenicity objectives at Day 29 post-booster, including superior neutralizing antibody response against Omicron BA.4/BA.5 and non-inferior response against the ancestral SARS-Cov-2 D614G when compared to mRNA-1273.
- The Omicron BA.4/BA.5 geometric mean titer ratios of mRNA-1273.222 versus mRNA-1273 were 5.11 (4.10, 6.36) and 6.29 (5.27, 7.51) for participants with and without SARS-CoV-2 infection pre-booster, respectively.
- Neutralizing antibody responses against BA.4/BA.5 were consistent between participants ages 65 and older and under 65.
- mRNA-1273.222 exhibited cross-neutralization against Omicron BQ.1.1

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Key Points

- Both the Omicron BA.4/BA.5 bivalent mRNA-1273.222 and the Omicron BA.1 bivalent mRNA-1273.214, met all pre-specified immunogenicity objectives in the respective studies (205H and 205G).

- Both vaccines elicited superior neutralizing antibody responses against the variant contained in the vaccine (BA.4/BA.5 and BA.1, respectively), compared to mRNA-1273.

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Phase 2/3 Safety and Immunogenicity Clinical Study of Omicron BA.4/BA.5 Bivalent Booster

Omicron BA.4/BA.5 - containing vaccine mRNA-1273.222 50 µg

25 µg
Original SARS-CoV-2

+

25 µg
Omicron Variant (BA.4/BA.5)

Bivalent Vaccine	Enrollment	Dose	N	Median Follow-up
BA.4/BA.5 Omicron (mRNA-1273.222)	August 10-23, 2022	4th (2nd booster)	511	37 days
mRNA-1273	Feb 18-Mar 8, 2022	4th (2nd booster)	376	127 days

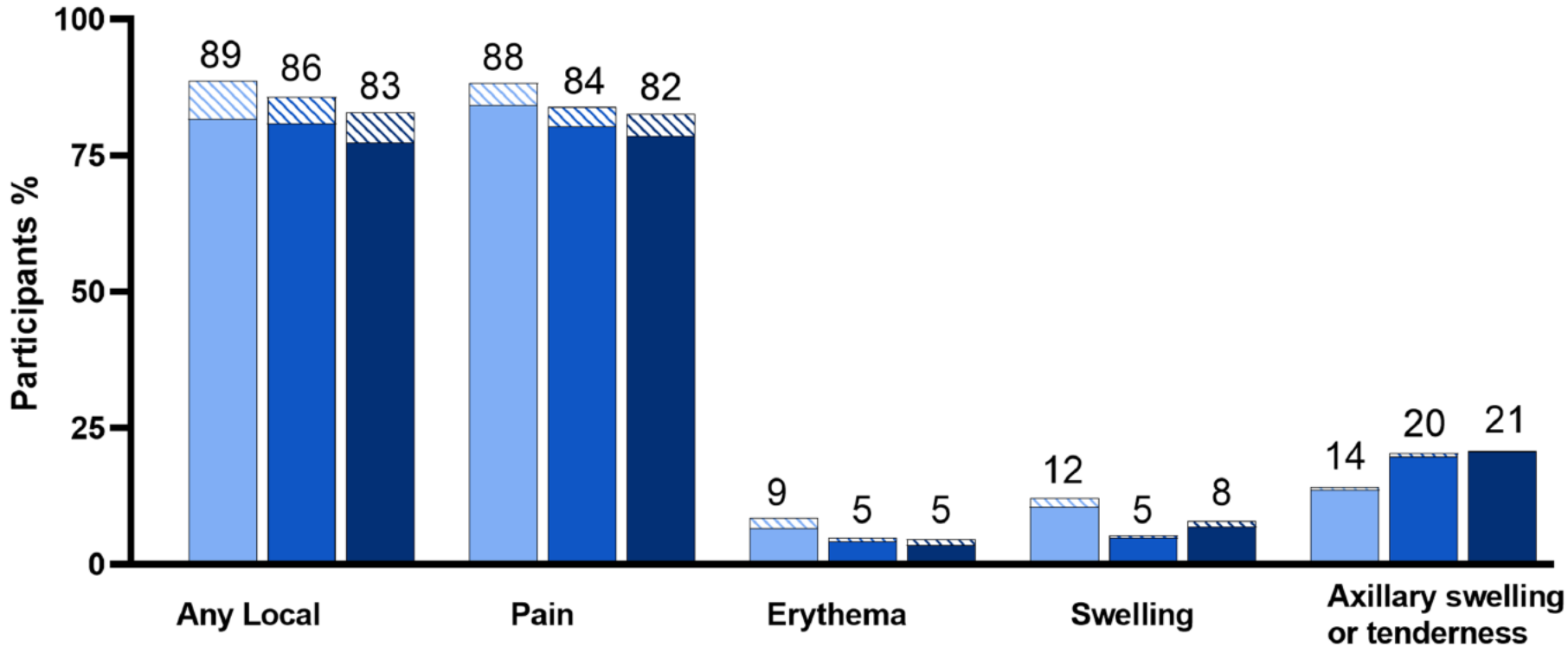
- Participants previously received a primary series (100 µg) and a 3rd dose (50 µg booster) of mRNA-1273

Demographics and Baseline Characteristics

Characteristic	4th Dose	
	Original (mRNA-1273) N = 376	BA.4/BA.5 Omicron Bivalent (mRNA-1273.222) N =511
Mean Age – Years	**57.6**	**50.8**
Median Age – Years (range)	**60.5** (20, 96)	**50.0** (19, 89)
≥ 65 years	**39.9%**	**20.5%**
Non-White Race	**13.3%**	**16.0%**
Hispanic / Latino Ethnicity	**9.8%**	**11.4%**
Interval between 2nd and 3rd Dose (months) – median (range)	**8.0** (5.6, 14.4)	**8.2 (2.2, 17.5)**
Interval between 3rd and 4th Dose (months) – median (range)	**4.4** (3.0, 10.2)	**9.5 (3.4, 12.2)**
Prior SARS-CoV-2 Infection	**26.9%**	**56.0%**

Local Reactogenicity of BA.4/BA.5 Bivalent as 4th Dose Similar to or Lower than 2nd Dose of Primary Series and 3rd Dose of mRNA-1273

Study 205, Safety Set



Solicited local adverse reactions within 7 days after injection. No mRNA-1273.222 Grade 4 events reported. 2nd dose mRNA-1273 (Baden et al, *NEJM* 384:403, 2021); 3rd dose mRNA-1273 (Chu et al, *Nat Med* 28:1041, 2022);

2nd Dose Original (mRNA-1273)
N = 14,677

3rd Dose (1st booster) Original (mRNA-1273)
N = 167

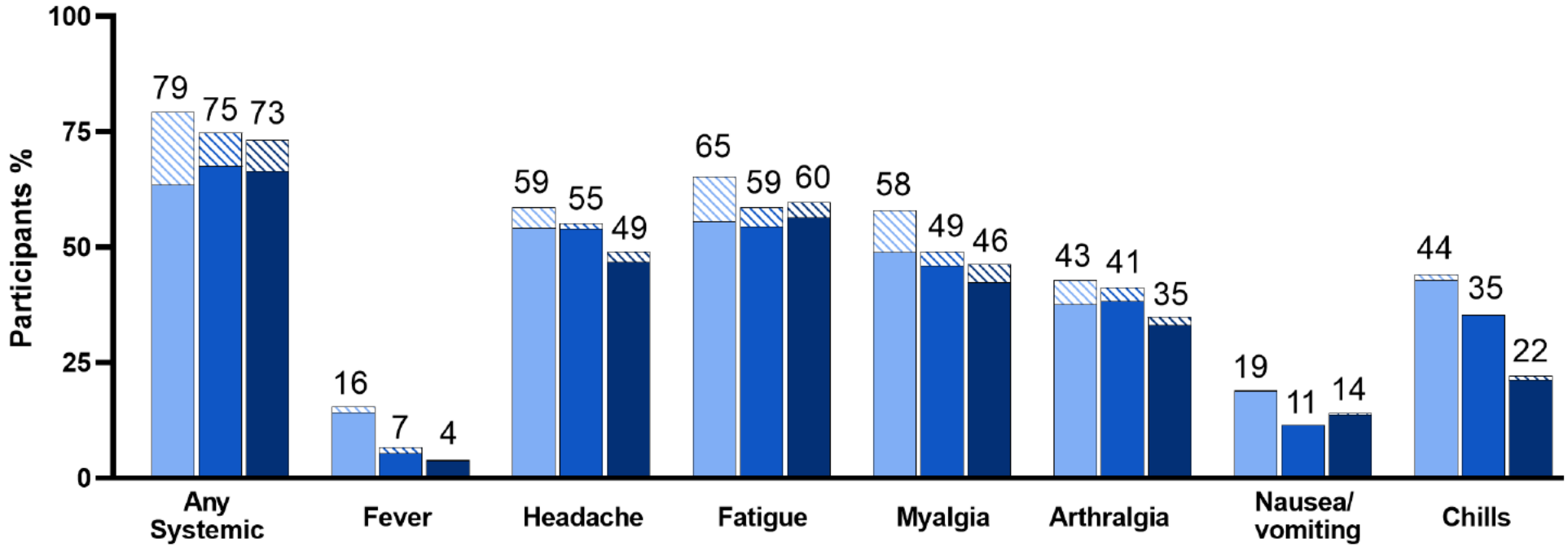
4th Dose (2nd booster) using BA.4/5 Omicron (mRNA-1273.222)
N =511

Grade 1-2

Grade 3

Systemic Reactogenicity of BA.4/BA.5 Bivalent as 4th Dose Similar to or Lower than 2nd Dose of Primary Series and 3rd Dose of mRNA-1273

Study 205, Safety Set



2nd Dose Original (mRNA-1273) N = 14,677

3rd Dose (1st booster) Original (mRNA-1273) N = 167

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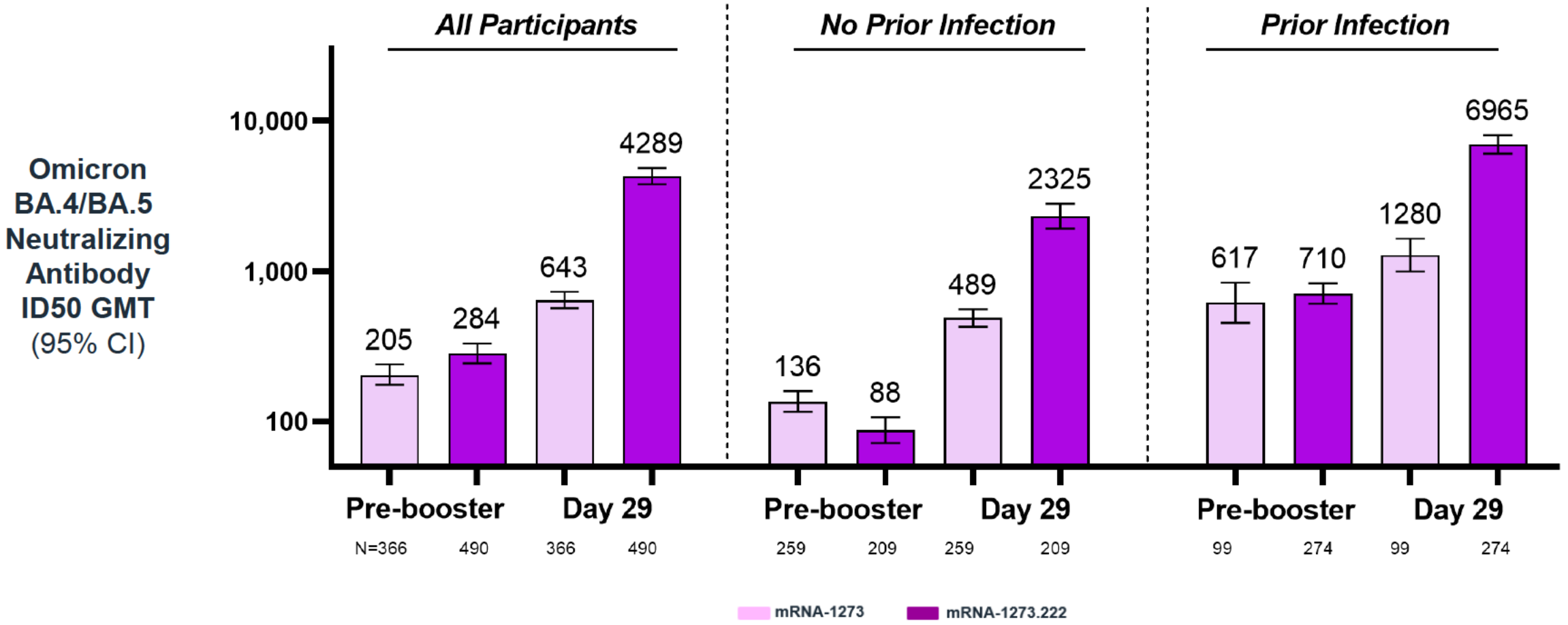
Grade 1-2

Grade 3

Solicited local adverse reactions within 7 days after injection. No mRNA-1273.222 Grade 4 events reported. 2nd dose mRNA-1273 (Baden et al, *NEJM* 384:403, 2021); 3rd dose mRNA-1273 (Chu et al, *Nat Med* 28:1041, 2022);

Omicron BA.4/BA.5 Neutralizing Antibody Titers After 4th Dose Higher with BA.4/BA.5 Bivalent than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set



Bivalent Booster (.222) Resulted in Superior Neutralizing Antibody Titers Against Omicron BA.4/BA.5

Participants <u>without</u> prior infection

	mRNA-1273 50 µg (N=259)	mRNA-1273.222 50 µg (N=209)
Pre-booster GMT, 95% CI	136.1 (116.3, 159.3)	87.9 (72.2, 107.1)
Observed GMTs (95% CI) at Day 29	488.5 (427.4, 558.4)	2324.6 (1921.2, 2812.7)
Estimated GMTs (95% CI) at Day 29[a]	436.7 (389.1, 490.0)	2747.3 (2399.2, 3145.9)
GMFR (95% CI) at Day 29, 95% CI	3.6 (3.3, 4.0)	26.4 (22.0, 31.9)
GMR (95% CI)[a]	**6.29 (5.27, 7.51)**	
SRR (95% CI) at Day 29[b] , Pre-dose 1	222/257 86.4% (81.6%, 90.3%)	205/209 98.1% (95.2%, 99.5%)
Difference in SRR (95% CI)[c] , Pre-dose 1	12.1% (6.9%, 17.3%)	
SRR (95% CI) at Day 29[b] , Pre-Booster	98/259 37.8% (31.9%, 44.0%)	190/209 90.9% (86.2%, 94.4%)
Difference in SRR (95% CI)[c] , Pre-Booster	53.9% (46.7%, 61.2%)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 95% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

Bivalent Booster (.222) Resulted in Superior Neutralizing Antibody Titers Against Omicron BA.4/BA.5

Participants <u>with</u> prior infection

	mRNA-1273 50 µg (N=99)	mRNA-1273.222 50 µg (N=274)
Pre-booster GMT, 95% CI	616.8 (453.1, 839.8)	710.2 (606.9, 831.1)
Observed GMTs (95% CI) at Day 29	1280.2 (996.7, 1644.3)	6964.5 (6043.7, 8025.4)
Estimated GMTs (95% CI) at Day 29[a]	1490.2 (1217.3, 1824.4)	7607.7 (6607.4, 8759.5)
GMFR (95% CI) at Day 29, 95% CI	2.1 (1.8, 2.4)	9.8 (8.4, 11.4)
GMR (95% CI)[a]	**5.11 (4.10, 6.36)**	
SRR (95% CI) at Day 29[b] , Pre-dose 1	74/76 97.4% (90.8%, 99.7%)	162/162 100% (97.8%, 100%)
Difference in SRR (95% CI)[c] , Pre-dose 1	5.5% (0.5%, 10.5%)	
SRR (95% CI) at Day 29[c] , Pre-Booster	17/99, 17.2% (10.3%, 26.1%)	203/274, 74.1% (68.5%, 79.2%)
Difference in SRR (95% CI)[d] , Pre-Booster	55.3% (46.2%, 64.4%)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[d] 95% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Bivalent booster (.222) Resulted in Superior Neutralizing Antibody Titers Against Omicron BA.4/BA.5

All participants

	mRNA-1273 50 µg (N=366)	mRNA-1273.222 50 µg (N=490)
Pre-booster GMT, 95% CI	205.3 (175.8, 239.8)	284.2 (243.9, 331.3)
Observed GMTs (95% CI) at Day 29	642.5 (567.1, 727.9)	4289.4 (3789.0, 4855.9)
Estimated GMTs (95% CI) at Day 29[a]	725.7 (653.2, 806.4)	4198.3 (3819.2, 4615.2)
GMFR (95% CI) at Day 29, 95% CI	3.1 (2.9, 3.4)	15.1 (13.3, 17.1)
GMR (95% CI)[a]	**5.79 (5.05, 6.63)**	
SRR (95% CI) at Day 29[b] , Pre-dose 1	304/341 89.1% (85.4%, 92.2%)	370/375 98.7% (96.9%, 99.6%)
Difference in SRR (95% CI)[c] , Pre-dose 1	8.7% (5.1%, 12.3%)	
SRR (95% CI) at Day 29[b] , Pre-Booster	121/366 33.1% (28.3%, 38.1%)	398/490 81.2% (77.5%, 84.6%)
Difference in SRR (95% CI)[c] , Pre-Booster	54.5% (48.8%, 60.1%)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, age groups, and SARS-CoV-2 status.
[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.
[c] 95% CI was calculated using a stratified Miettinen-Nurminen method and adjusting by age group and SARS-CoV-2 status. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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Bivalent Booster (.222) Elicited Higher Neutralizing Antibody Titers Against Ancestral SARS-CoV-2 D614G

	No prior infection participants		*All participants*	
	mRNA-1273 50 µg (N=259)	**mRNA-1273.222** 50 µg (N=209)	**mRNA-1273** 50 µg (N=366)	**mRNA-1273.222** 50 µg (N=490)
Pre-booster GMT, 95% CI	1515.4 (1347.5, 1704.2)	796.9 (678.7, 935.8)	1941.0 (1721.5, 2188.4)	1619.7 (1439.3, 1822.8)
Observed GMTs (95% CI) at Day 29	5651.4 (5055.7, 6317.3)	7322.4 (6386.2, 8395.7)	6050.2 (5466.3, 6696.4)	9318.9 (8541.0, 10167.7)
Estimated GMTs (95% CI) at Day 29[a]	4882.2 (4457.7, 5347.1)	9555.8 (8593.6, 10625.7)	5609.4 (5165.8, 6091.2)	10658.0 (9909.2, 11463.3)
GMFR (95% CI) at Day 29, 95% CI	3.7 (3.4, 4.1)	9.2 (7.9, 10.6)	3.1 (2.9, 3.4)	5.8 (5.2, 6.3)
GMR (95% CI)[a]	**1.96 (1.70, 2.25)**		**1.90 (1.71, 2.11)**	
SRR (95% CI) at Day 29[b] , Pre-dose 1	259/259 100% (98.6%, 100%)	209/209 100% (98.3%, 100%)	346/346 100% (98.9%, 100%)	387/387 100% (99.1%, 100%)
Diff. in SRR (95% CI)[c] , Pre-dose 1	0		0	
SRR (95% CI) at Day 29[b] , Pre-Booster	111/259 42.9% (36.7%, 49.1%)	168/209 80.4% (74.3%, 85.5%)	132/366 36.1% (31.1%, 41.2%)	300/490 61.2% (56.8%, 65.6%)
Diff. in SRR (95% CI)[c] , Pre-Booster	37.3% (29.0%, 45.6%)		33.1% (26.9%, 39.3%)	

[a] Based on ANCOVA modeling; the model includes adjustment for treatment group, pre-booster antibody titers, and age groups for SARS-CoV-2 negative pre-booster participants. For all participants, model also includes prior SARS-CoV-2 infection.

[b] Seroresponse at a participant level is defined as a change from below the LLOQ to equal or above 4 x lower limiting of quantification (LLOQ) if the participant's baseline is below the LLOQ, or at least a 4-fold rise if the baseline is equal to or above the LLOQ.

[c] 95% CI is calculated using a stratified Miettinen-Nurminen method and adjusting by age group for SARS-CoV-2 negative pre-booster participants. For all participants, both age group and prior SARS-CoV-2 infection are adjusted. The SRR difference is a calculated common risk difference using inverse-variance stratum weights and the middle point of Miettinen-Nurminen confidence limits of each one of the stratum risk differences

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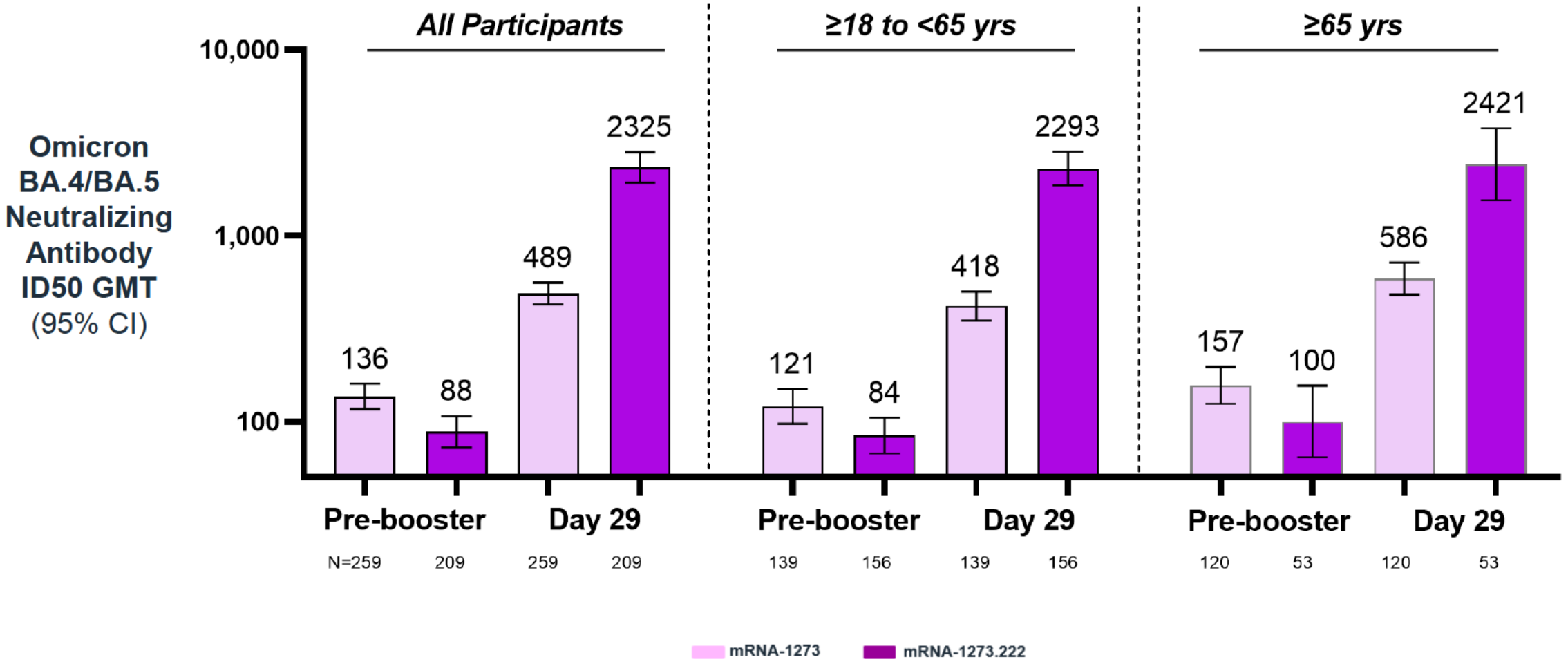
Omicron BA.4/BA.5 Neutralizing Antibody Titers Consistently Higher in Adults ≥ 65 After 4th Dose with BA.4/BA.5 Bivalent than mRNA-1273

Study 205, Per-Protocol Immunogenicity Set with No Prior Infection



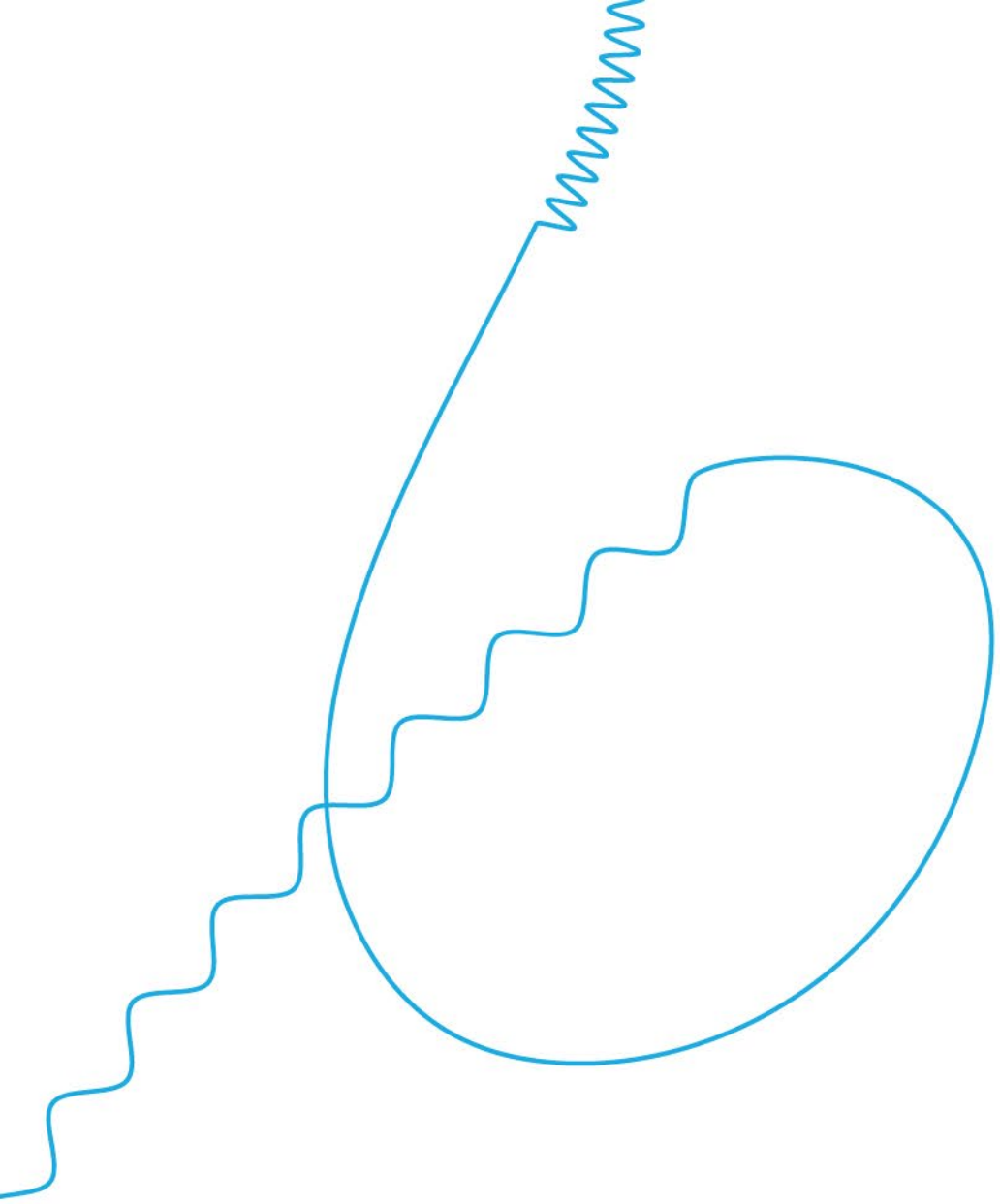
Omicron BA.4/BA.5 Bivalent Vaccine Exhibited Cross-Neutralization against BQ.1.1 at Day 29

N=40 participants with no prior infection

	mRNA-1273.222 50 µg (N=40) BA.4/BA.5	mRNA-1273.222 50 µg (N=40) BQ.1.1
Pre-booster GMT, 95% CI	122.8 (74.3, 203.1)	31.7 (19.6, 51.3)
Observed GMTs (95% CI) at Day 29	3355.4 (2109.9, 5336.2)	621.9 (422.2, 916.2)
GMFR (95% CI) at Day 29, 95% CI	27.2 (15.9, 47.0)	19.6 (11.7, 32.8)
fold change from BA.4/BA.5 GMT at Day 29	5.4-fold	

Research-grade assay

19.6-fold increase in BQ.1.1 titers following receipt of Omicron Bivalent Booster (mRNA-1273.222)



Back-up

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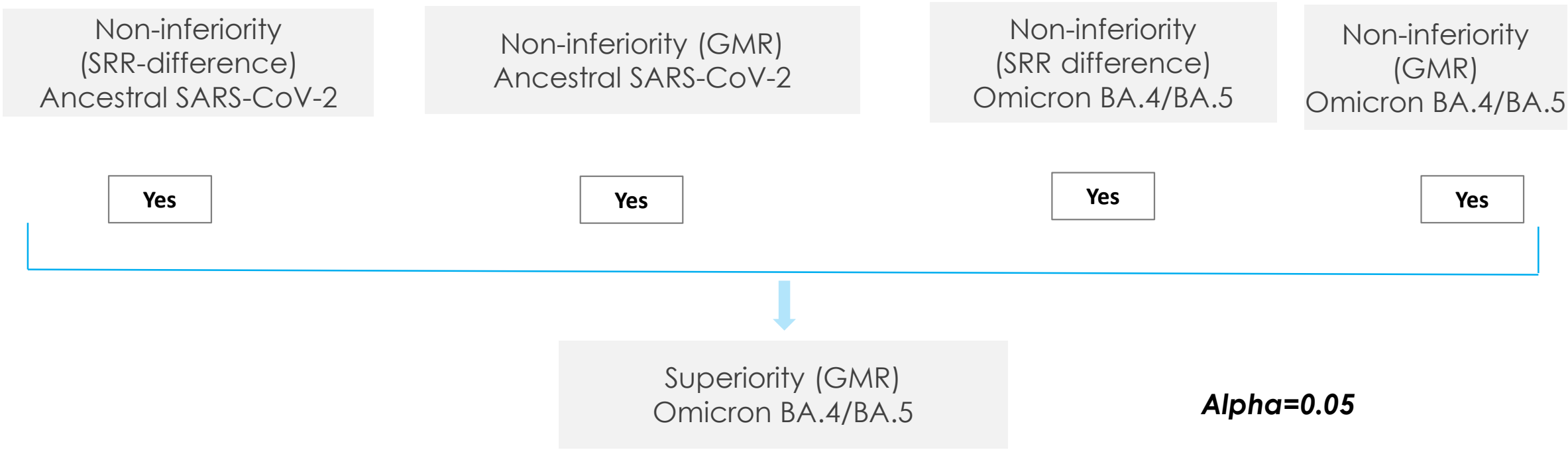
Primary immunogenicity objectives

The Day 29 testing sequence for the immunogenicity endpoints is the following:



GMR: geometric mean titer ratio; SRR: seroresponse

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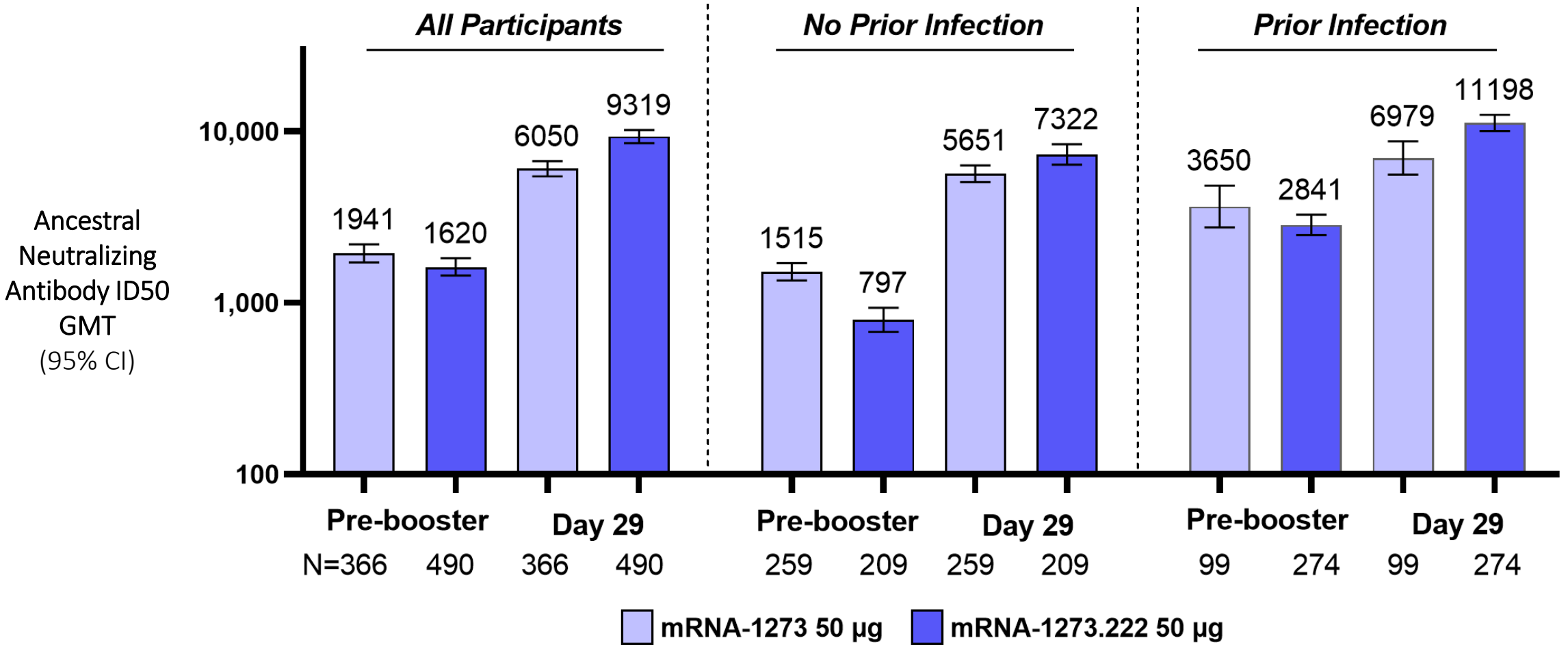
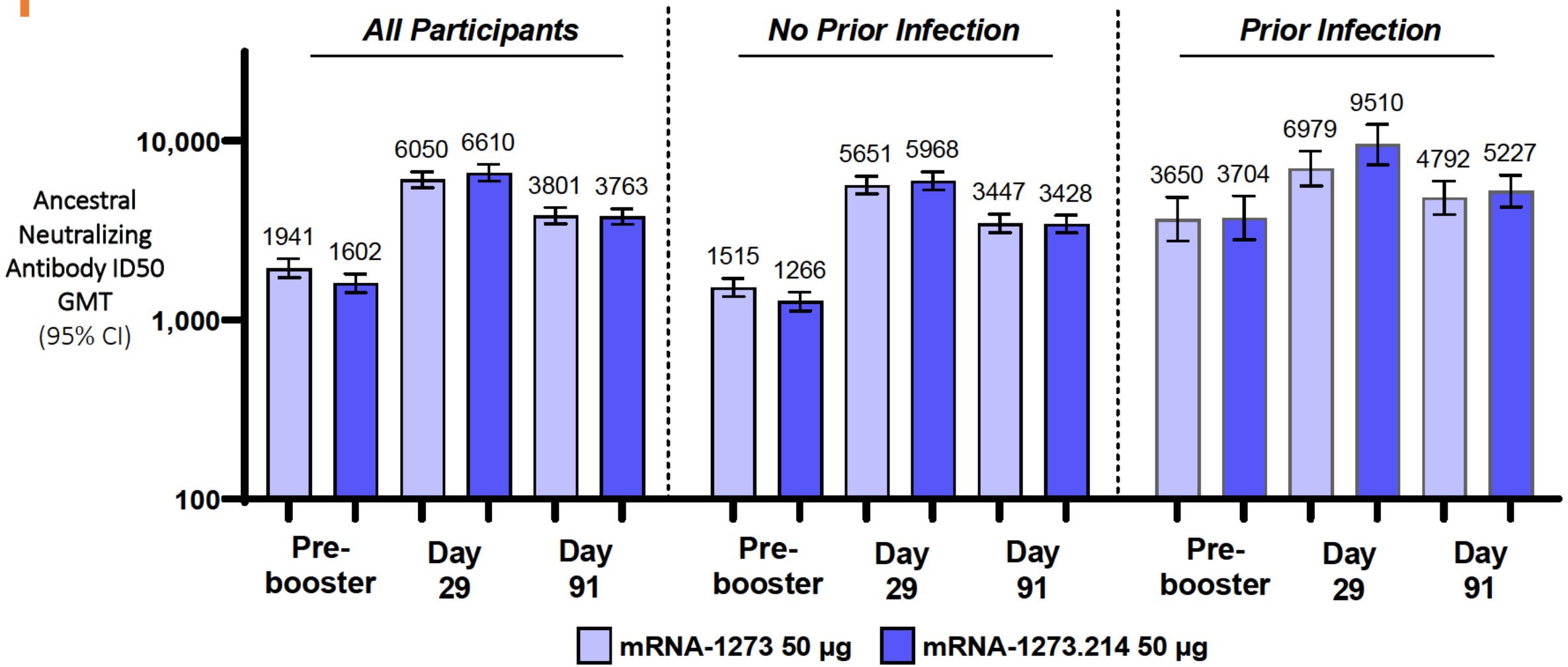
Ancestral SARS-CoV-2 D614G Neutralizing Titers After 4th Dose with BA.4/BA.5 Bivalent mRNA-1273.222 were non-inferior compared to mRNA-1273

Study 205, Per-Protocol Immunogenicity Set

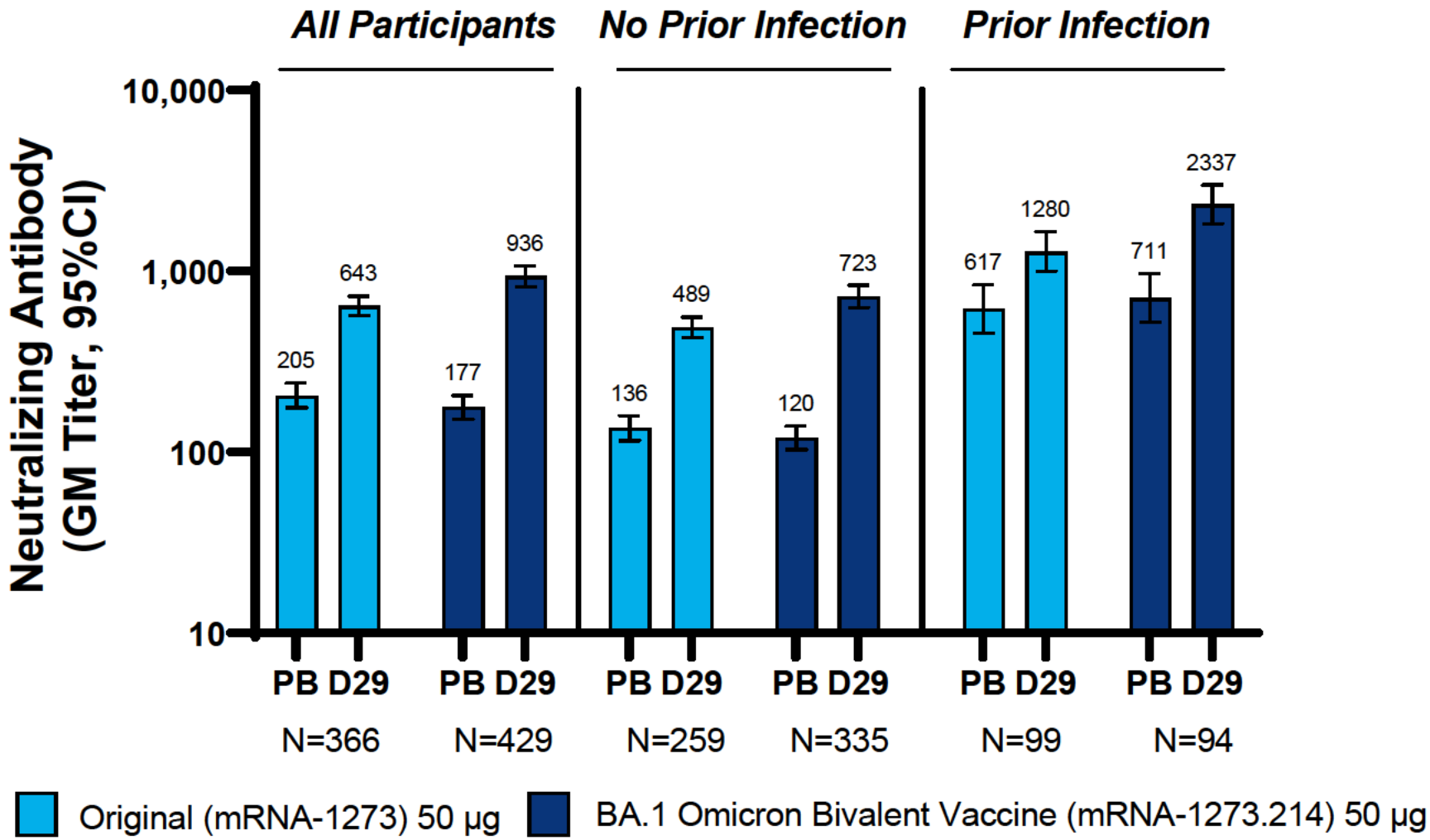


Ancestral SARS-CoV-2 D614G Neutralizing Titers After 4th Dose with BA.1 Bivalent mRNA-1273.214 were non-inferior compared to mRNA-1273

Study 205, Per-Protocol Immunogenicity Set



4th Dose with Omicron BA.1 Bivalent Booster mRNA-1273.214 Resulted in Higher Neutralizing Antibody Titers against Omicron BA.4 & BA.5 than mRNA-1273 at Day 29



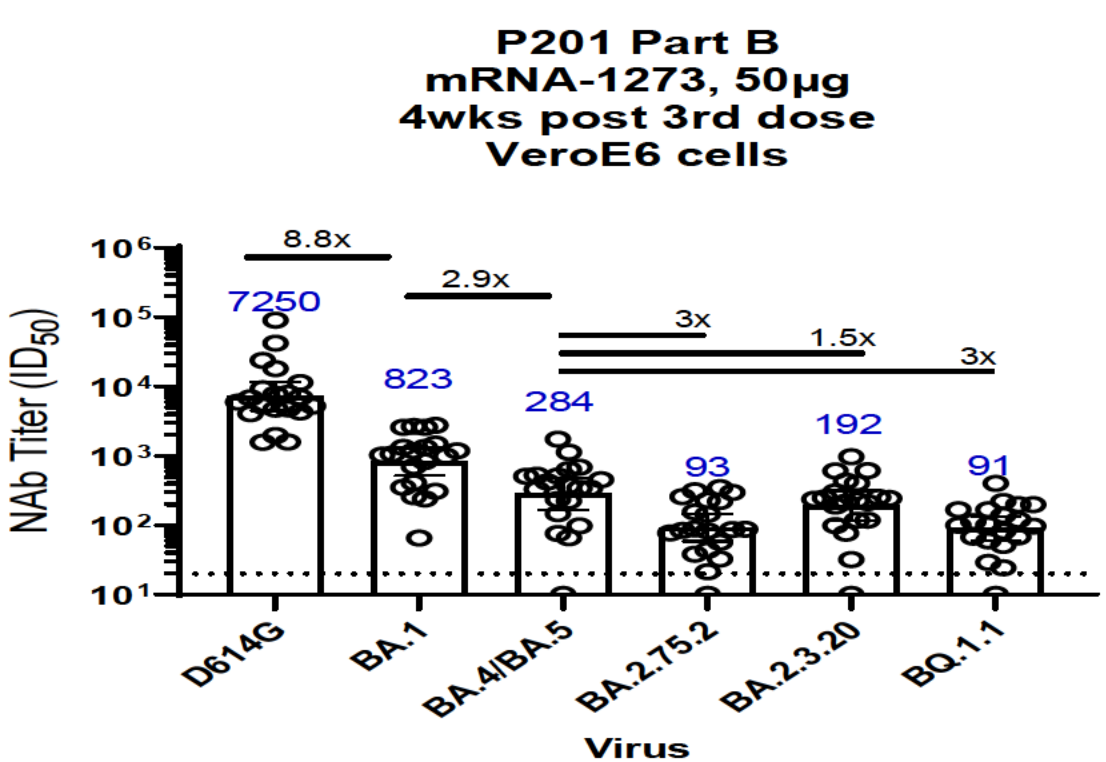
Pre-booster (**PB**), Day 29 post-boost (**D29**)

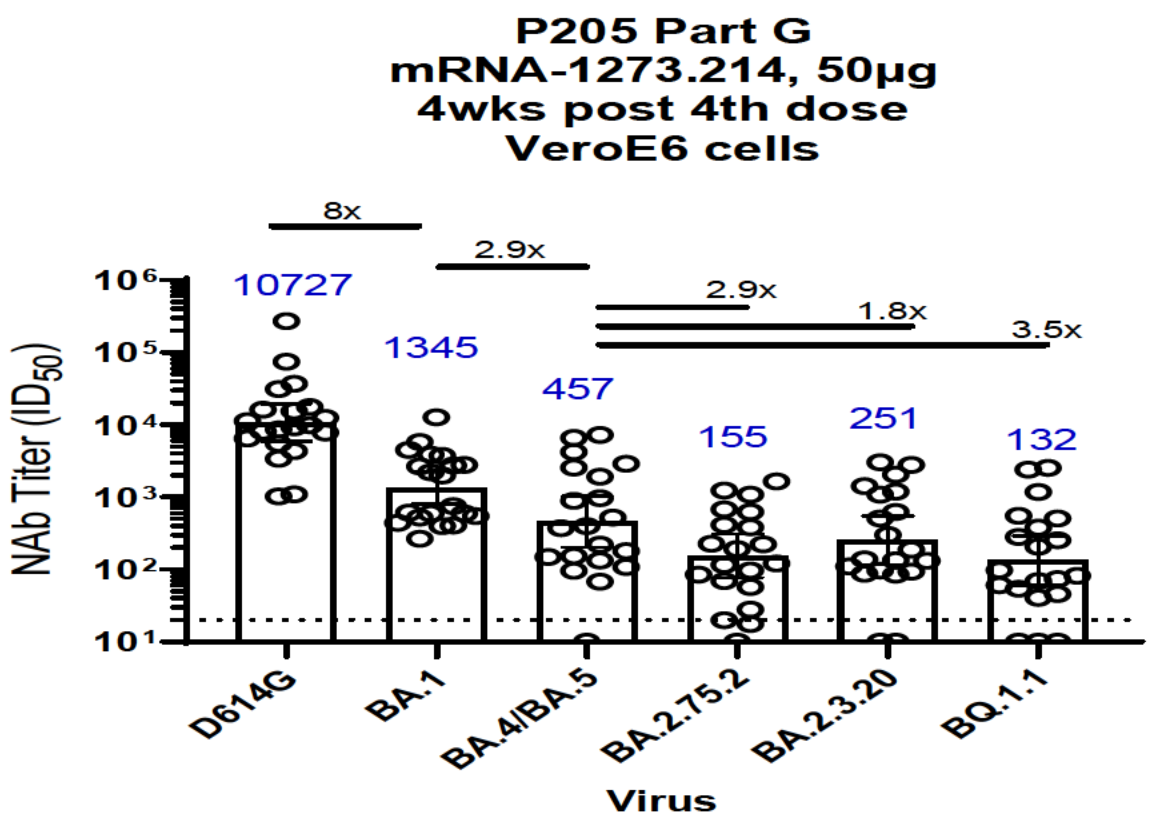
Pre-booster SARS-CoV-2 infection status not known for n=8 participants in the mRNA-1273 group.

Do Bivalent Vaccines Protect Against Other Emerging Variants, e.g., BQ1.1?

Preliminary Data Indicate That mRNA 1273.214 Generates nAB Titers Against Emerging Omicron Subvariants at Day 29

Trial	Cohort	1st & 2nd dose	3rd dose	4th dose	Timepoint	Sample Size
P201	Part B	mRNA-1273 100 µg	mRNA-1273 50 µg	N/A	PD3-D29	N=20
P205	Part G	mRNA-1273 100 µg	mRNA-1273 50 µg	mRNA-1273.214 50 µg	PD4-D29	N=20





Research assay

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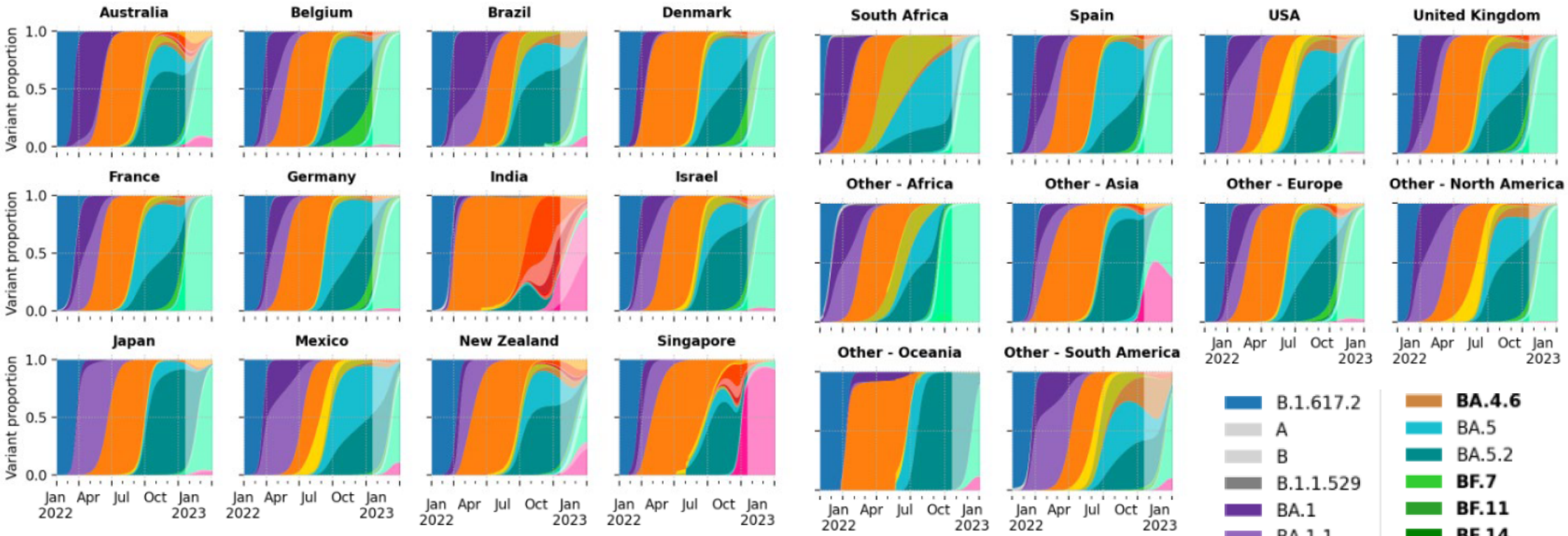
Variant Evolution Prediction



https://github.com/gerstung-lab/SARS-CoV-2-International/blob/e27d84192805c86baba5e543446ac05bbb4eb1e1/plots/variant-share-latest.png

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Additional Back up slides

Antibody response following bivalent booster may require more time to show differences

1. Maturation of existing antibodies, particularly to the original variant generate cross reactive low affinity antibodies

2. Activation of Naïve B Cells starts with first exposure to the new variant (Omicron) and requires time to generate high affinity maturation antibodies

3. Even low levels of specific neutralizing antibodies may provide increased protection as shown in previous efficacy trial with mRNA-1273

4. T cell epitopes remain largely unchanged in the variants allowing for continued strong protection against severe disease, hospitalizations and death

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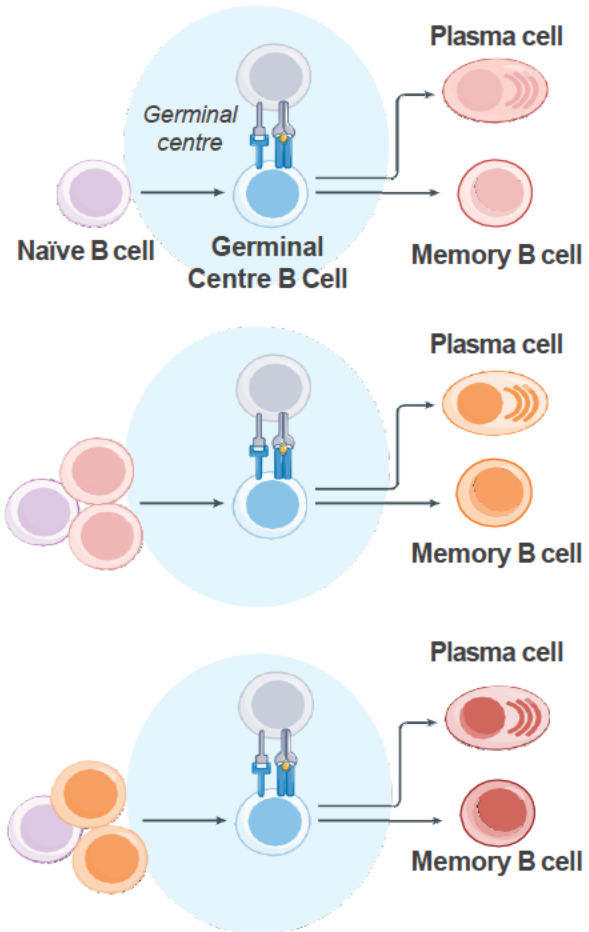
1 Maturation of existing antibodies, particularly to the original variant generate cross reactive low affinity antibodies

Subsequent exposure to the virus and/or booster doses, triggers increased memory B-cell production and affinity maturation

- Higher antibody affinity leading to greater neutralization
- Greater breadth of response due to increased cross reactivity



Primary Series (Dose 1)	
Response magnitude	++
Neutralizing activity	++
Neutralizing breadth	+

Primary Series (Dose 2)	
Response magnitude	+++
Neutralizing activity	+++
Neutralizing breadth	++

Bivalent Booster (Dose 3)	
Response magnitude	+++
Neutralizing activity	+++
Neutralizing breadth	+++

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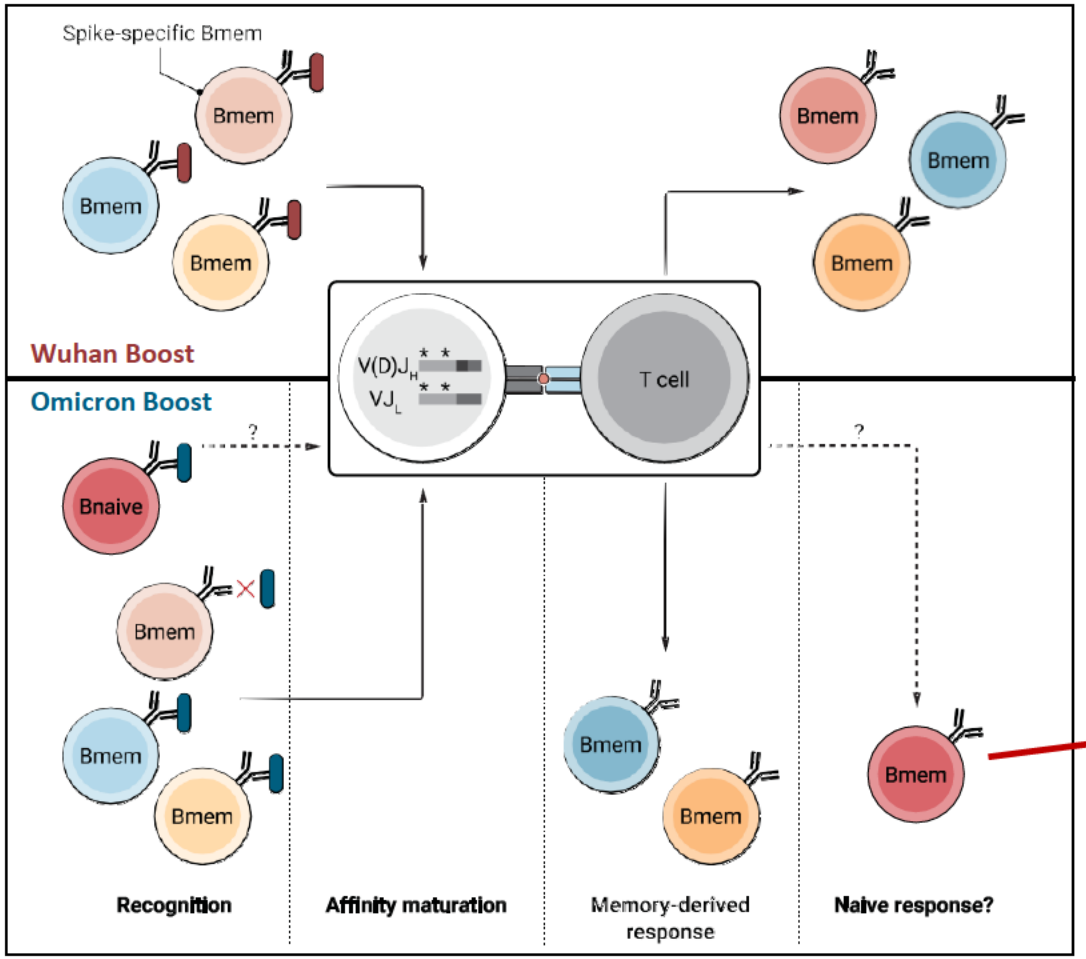
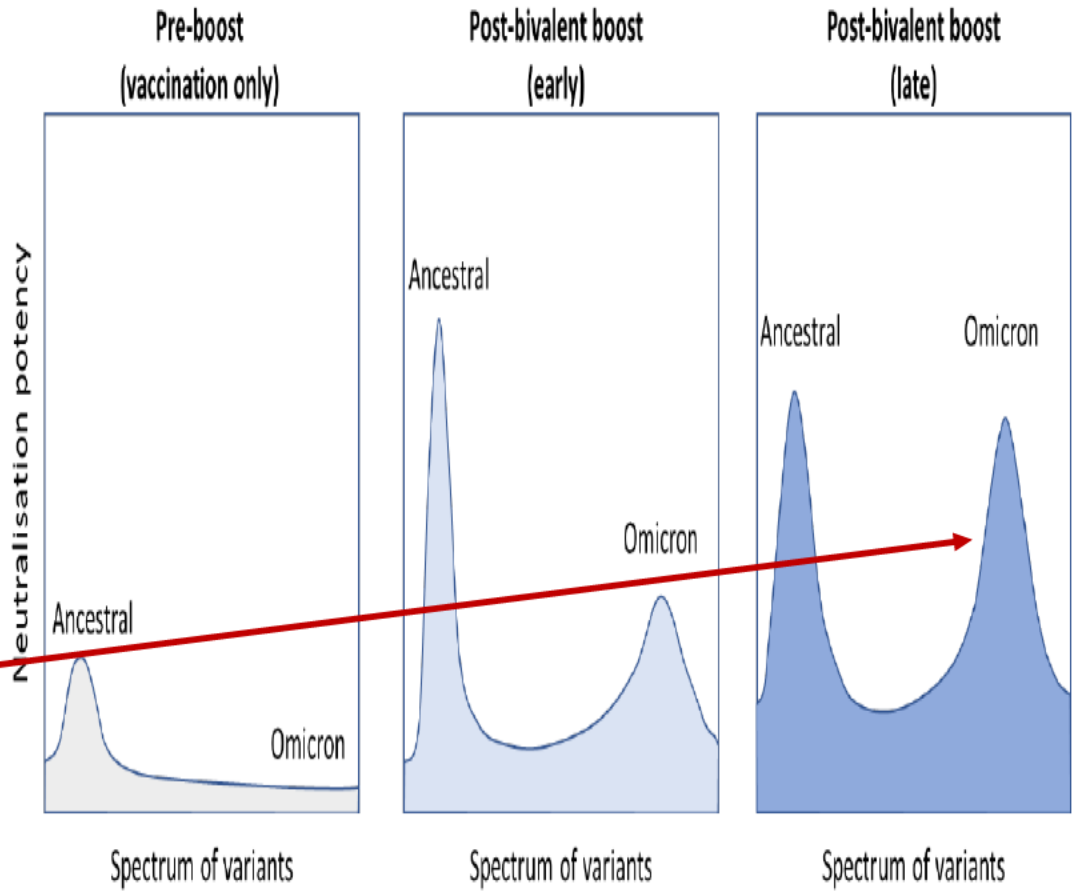
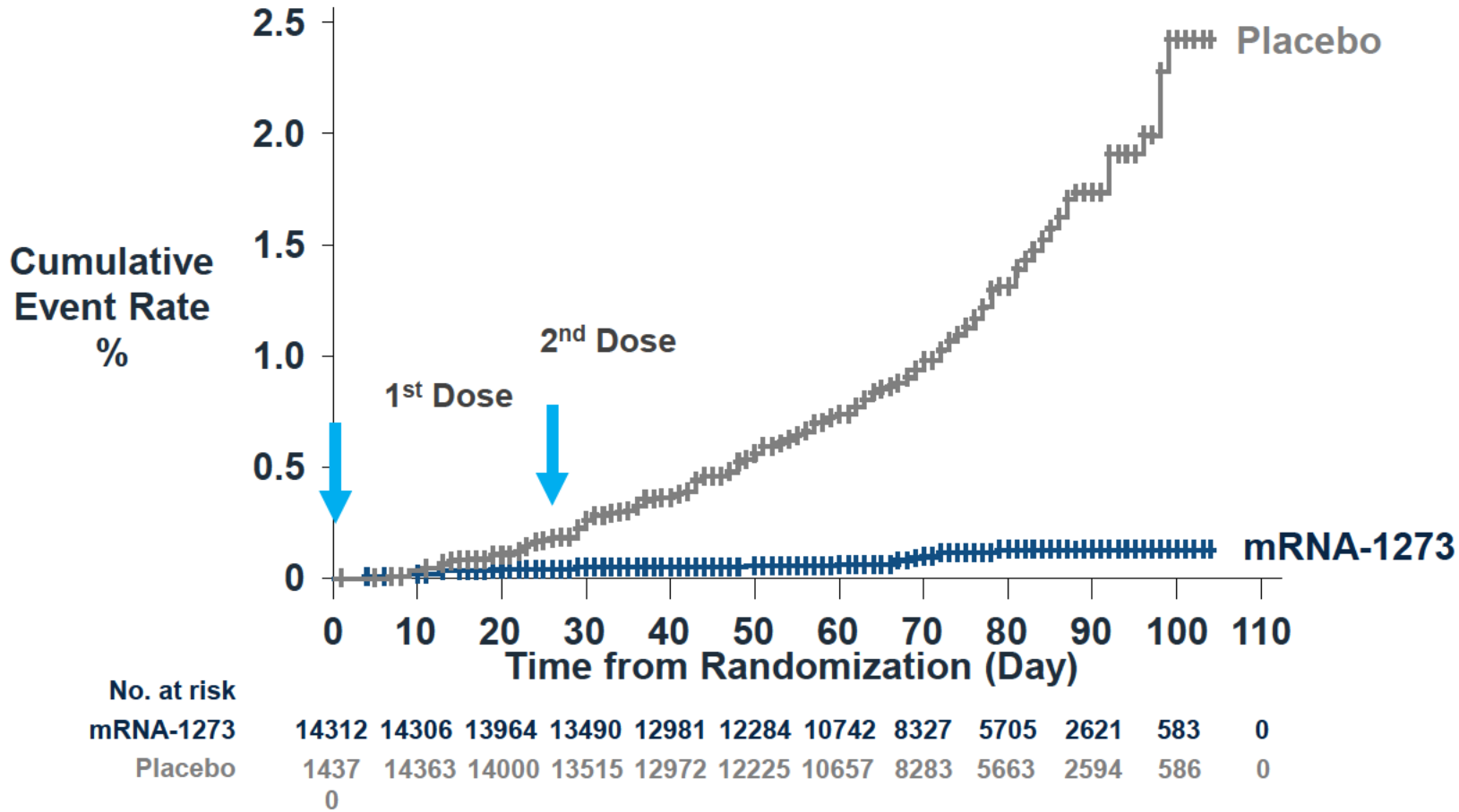
2 Activation of Naïve B Cells starts with first exposure to the new variant (Omicron) and requires time to generate high affinity maturation antibodies

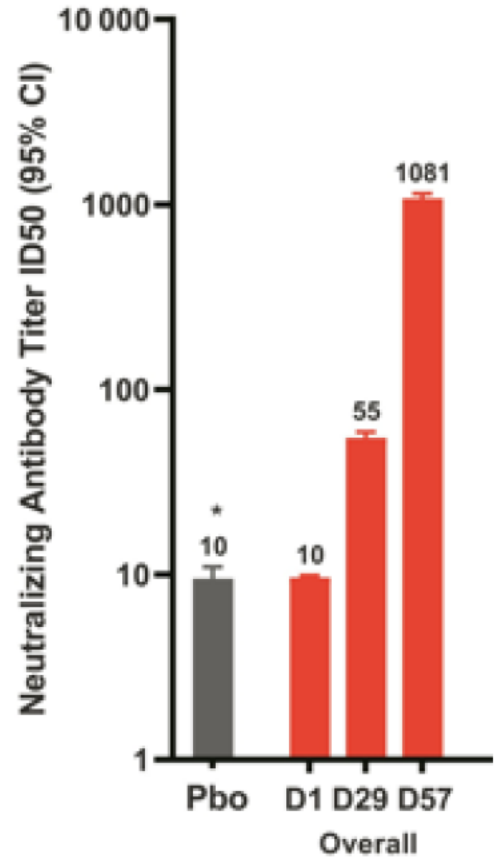




3 Even low levels of specific neutralizing antibodies may provide increased protection as shown in previous efficacy trial with mRNA-1273

Kaplan Meier estimates of time to first occurrence of COVID-19 starting after randomization in the Cove trial





Baden nejm 2021; El Sahly J Inf Dis 2022

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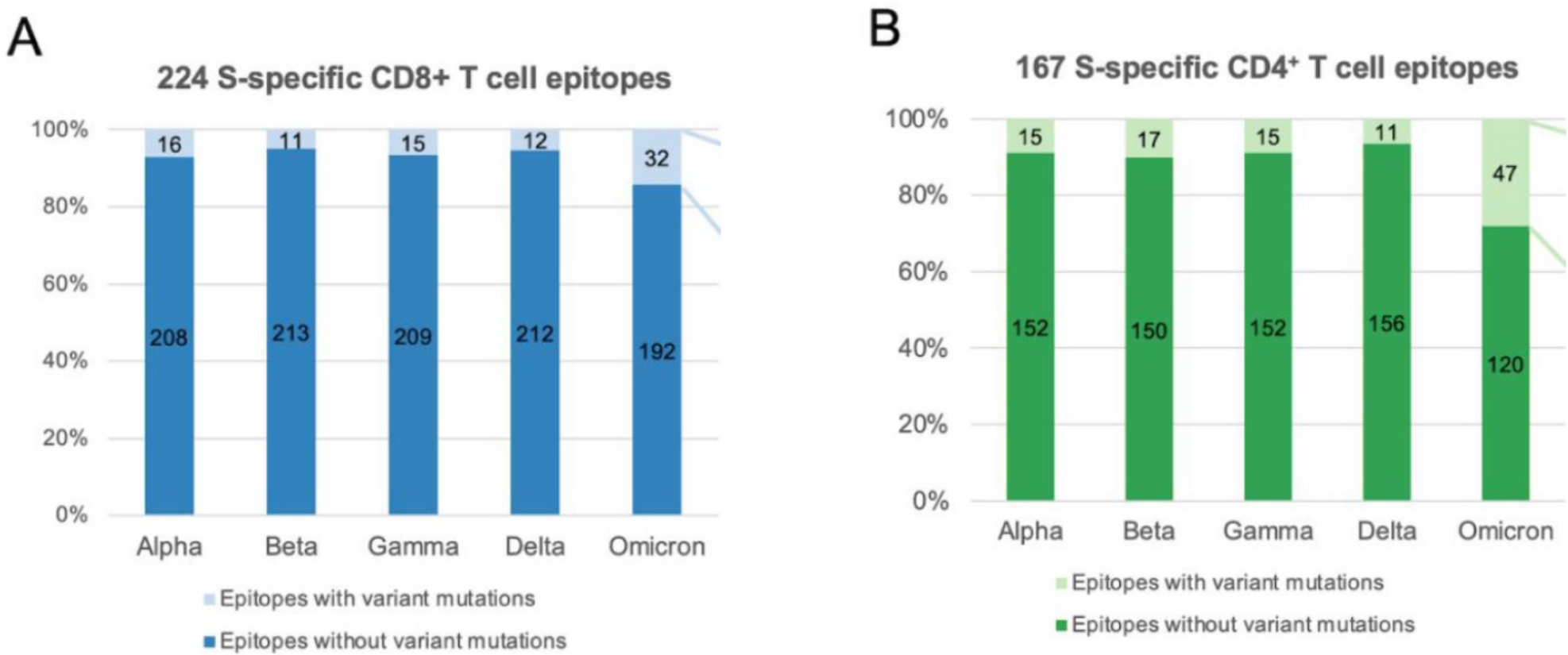
4 T cell epitopes remain largely unchanged in the variants allowing for continued strong protection against severe disease, hospitalization and death



Percentage of S-specific SARS-CoV-2 T cell epitopes with and without mutations present in the five VOCs: (A) $CD8_+$ T cell epitopes. (B) $CD4_+$ T cell epitopes

Ahmed et al., 14 Dec: SARS-CoV-2 T cell responses are expected to remain robust against Omicron | bioRxiv

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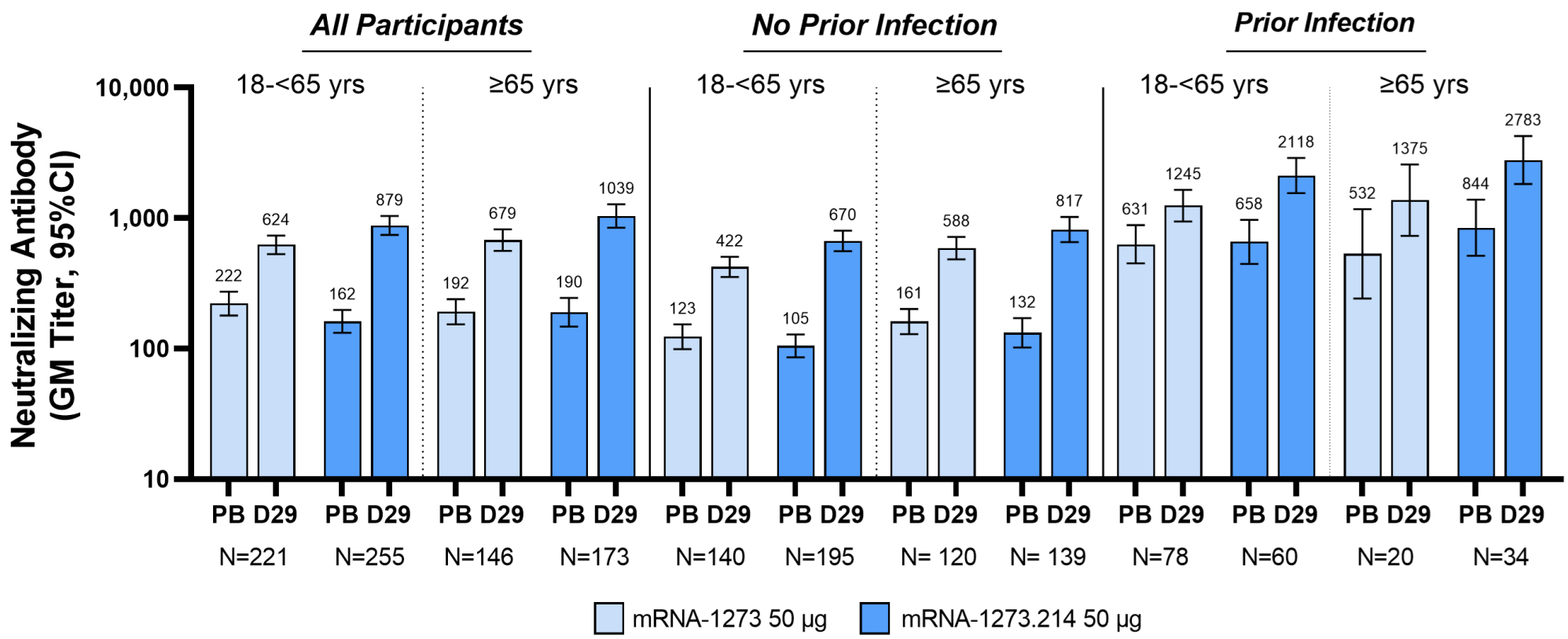
Bivalent booster (mRNA-1273.214) Resulted in Higher nAb Titers Against BA.4, BA.5 Across Age Groups, Including Age ≥65



Pre-booster (**PB**), Day 29 post-boost (**D29**)

Cha kias S, et al. A Bivalent Omicron-Containing Booster Vaccine against Covid-19, NEJM, Sept 16th 2022, DOI: 10.1056/NEJMoa2208343

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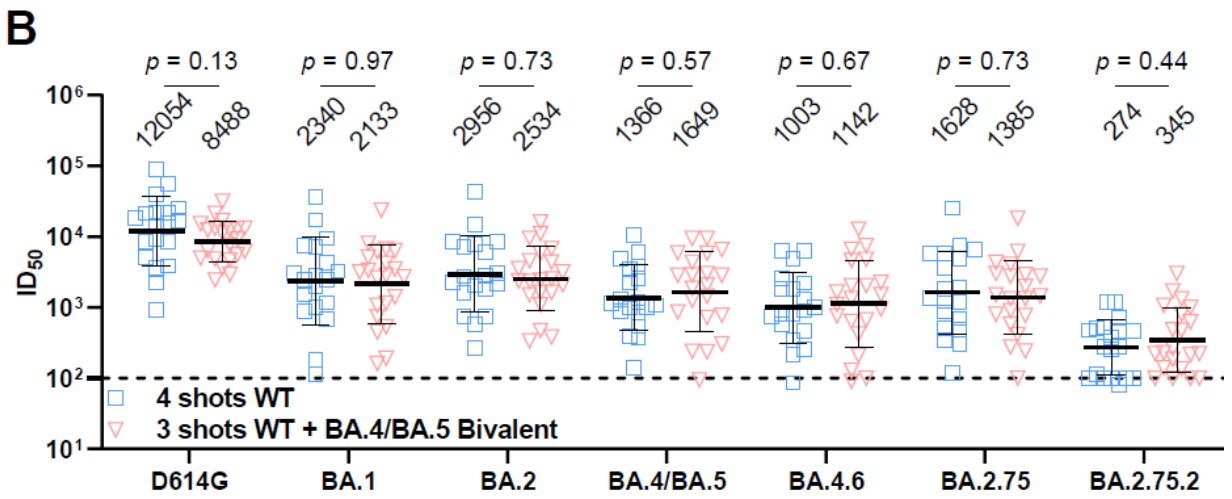
Why did Wang et al Not Find Greater Separation of Titers Early After Boosting With Wild-type (WT) Versus an Omicron-specific Booster?



Comparison of antibody responses induced by a fourth dose of the original WT mRNA vaccine versus a fourth dose of a BA.4/BA.5 bivalent mRNA vaccine (both Pfizer and Moderna were included .)

- The **study was very small**: Bivalent booster recipients n=21, monovalent doses n=19
- **Vaccination schemes were mixed**, with many receiving heterologous boosting
- There was **no adjustment for baseline titers, age or time since vaccination** which differed between the cohorts
  - 36 years vs 55 years of age for bivalent vs.WT cohorts
  - 24 (20,36) days WT, 26.4 (23,30) days bivalent
- There was **no prespecified statistical plan**
- **The variant specific response at this early time point may have been lost in the signal from cross neutralizating ABs resulting from previous vaccination**

- Wang et al bioRxiv Oct 24,2022 https://doi.org/10.1101/2022.10.22.513349;

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