VACCINE DEVELOPMENT

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Disclosure

Research Support from: Pfizer; funds to my institution for contracted vaccine trial work

I **do not** intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Learning Objectives

At the conclusion of the presentation, participants should be able to:

1) Describe the development and testing process for vaccines in the United States

2) Describe common adverse events following COVID vaccination

3) Explain the post-licensure vaccine safety mechanisms in place in the United States

Epidemiology 101

Descriptive Studies:

- Case report – One individual
- Case series – Multiple individuals

Interesting, but don't really prove anything

May be useful for generating hypotheses

Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination

Mayme Marshall, MD,[a] Ian D. Ferguson, MD,[b] Paul Lewis MD, MPH,[a] Preeti Jaggi, MD,[c] Christina Gagliardo, MD,[d,e] James Stewart Collins, MD,[f] Robin Shaughnessy, MD,[a] Rachel Caron, BA,[a] Cristina Fuss, MD,[g] Kathleen Jo E. Corbin, MD, MHS,[b] Leonard Emuren, MBBS, PhD,[b] Erin Faherty, MD,[b] E. Kevin Hall, MD,[b] Cecilia Di Pentima, MD, MPH,[d,e] Matthew E. Oster, MD, MPH,[c] Elijah Paintsil, MD,[b] Saira Siddiqui, MD,[d] Donna M. Timchak, MD,[d,h] Judith A. Guzman-Cottrill, DO[a]

Trials of coronavirus disease 2019 (COVID-19) vaccination included limited numbers of children, so they may not have detected rare but important adverse events in this population. We report 7 cases of acute myocarditis or myopericarditis in healthy male adolescents who presented with chest pain all within 4 days after the second dose of Pfizer-BioNTech COVID-19 vaccination. Five patients had fever around the time of presentation. Acute COVID-19 was ruled out in all 7 cases on the basis of negative severe acute respiratory syndrome coronavirus 2 real-time reverse transcription polymerase chain reaction test results of specimens obtained by using nasopharyngeal swabs. None of the patients met criteria for multisystem inflammatory syndrome in children. Six of the 7 patients had negative severe acute respiratory syndrome coronavirus 2 nucleocapsid antibody assay results, suggesting no previous infection. All patients had an elevated troponin. Cardiac MRI revealed late gadolinium enhancement characteristic of myocarditis. All 7 patients resolved their symptoms rapidly. Three patients were treated with nonsteroidal antiinflammatory drugs only, and 4 received intravenous immunoglobulin and corticosteroids. In this report, we provide a summary of each adolescent's clinical course and evaluation. No causal relationship between vaccine administration and myocarditis has been established. Continued monitoring and reporting to the US Food and Drug Administration Vaccine Adverse Event Reporting System is strongly recommended.

On December 11, 2020, the US Food and Drug Administration issued an emergency use authorization (EUA) for the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) mRNA vaccine for prevention of COVID-19 for individuals aged ≥16 years.[1] On May 10, 2021, the US Food and Drug

years. This vaccine was demonstrated to have a 94% to 95% efficacy in preventing COVID-19 infection in participants aged 16 to 55 years and 100% efficacy in the group of those aged 12 to 15 years.[1,2] Systemic reactogenicity occurred more commonly in younger

abstract

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Drs Marshall and Guzman-Cottrill drafted the initial manuscript, designed the data collection instruments, collected data, participated in literature review, and reviewed and revised the manuscript; Drs Jaggi and Lewis drafted case details for the initial manuscript, designed the data collection instruments, collected data, and reviewed and revised the manuscript; Drs Collins, Ferguson Gagliardo, and Shaughnessy drafted case details for the initial manuscript, collected data, and reviewed and revised the manuscript; Drs Corbin, Di Pentima, Emuren, Faherty, Fuss, Hall, Oster, Paintsil, Siddiqui, and Timchak reviewed clinical data and critically reviewed and revised the manuscript for important intellectual subject matter content; Ms Caron participated in drafting the initial manuscript, the data collection, and the literature review; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Findings Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls (p=0·003), low haemoglobin in four children, and a low serum IgA in four children.

Epidemiology 101

Observational:

Case-control – Start with an outcome of interest and compare exposures between those with the outcome and those without

Cohort – Follow a group of individuals over time and compare outcomes between those with a given exposure and those without

Epidemiology 101

Experimental:

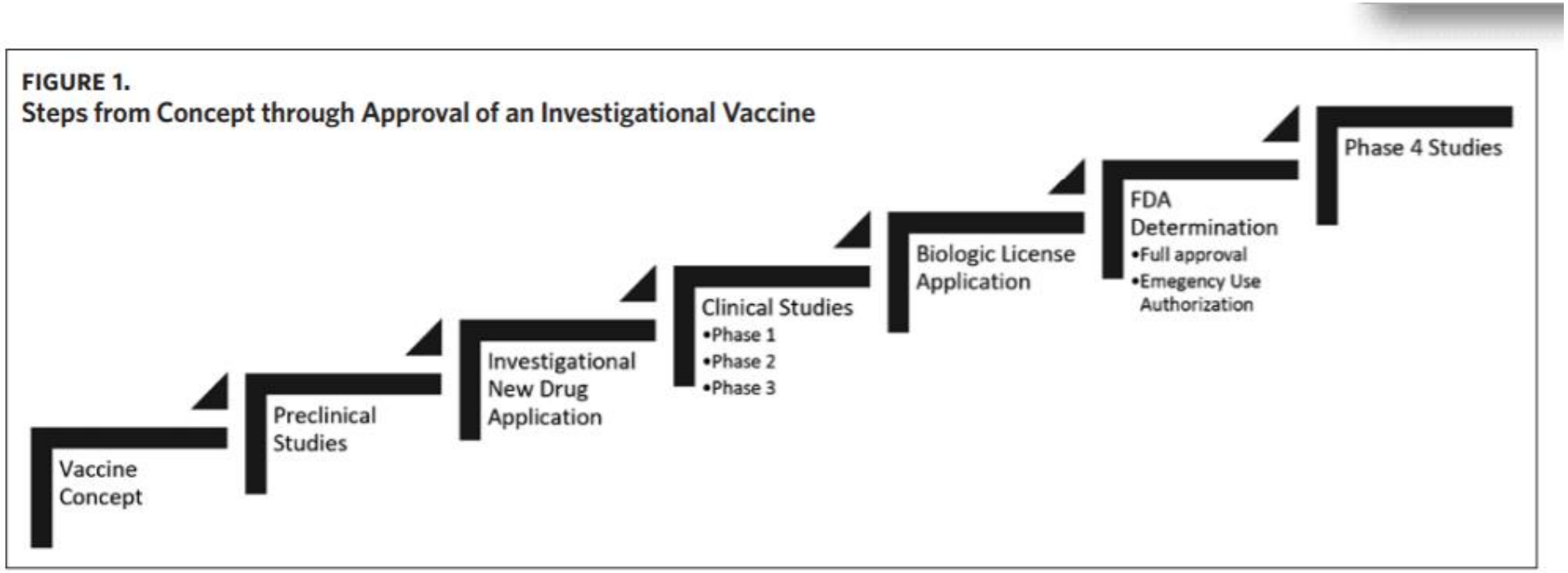
Randomized control trial – Similar to a cohort study except the exposure of interest is proscribed

Randomization accounts for known and unknown confounders

Considered the highest level of evidence

Required for licensure of vaccines and other pharmaceuticals

Stages of Vaccine Development



NCMJ 2021 vol. 82, no. 2: 141-144

Pre-Clinical Development

Develop rationale based on disease

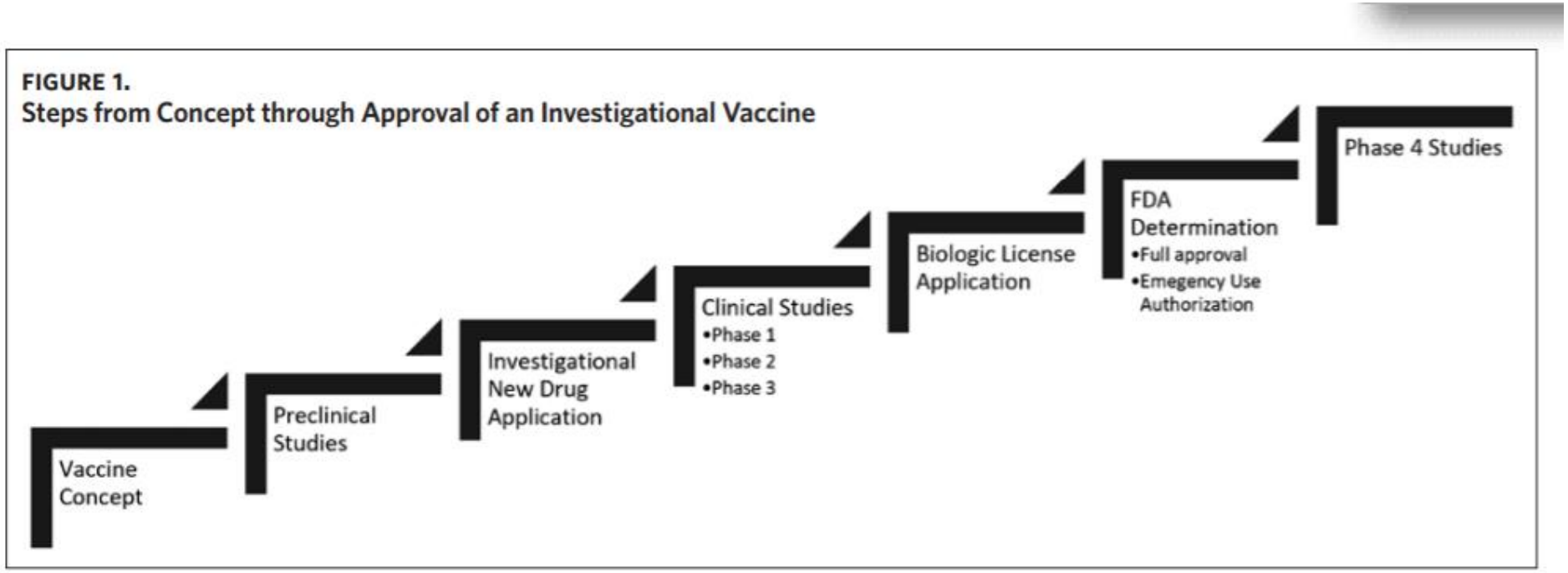
Identify an immunogen

Develop manufacturing process

Preclinical studies

- Acute toxicity
  - Escalating doses of candidate vaccine administered to animals by the route expected to be used in humans
    - Must include doses higher than those used in humans
    - Helps predict safe starting dose in humans
    - Assess for behavioral changes, injection-site inflammation, and laboratory evaluations
- In vivo pyrogenicity testing in animals (rabbits and/or guinea pigs)
- Safety studies (rats or possibly primates)

Stages of Vaccine Development



NCMJ 2021 vol. 82, no. 2: 141-144

Pre-licensure Human Subject Studies

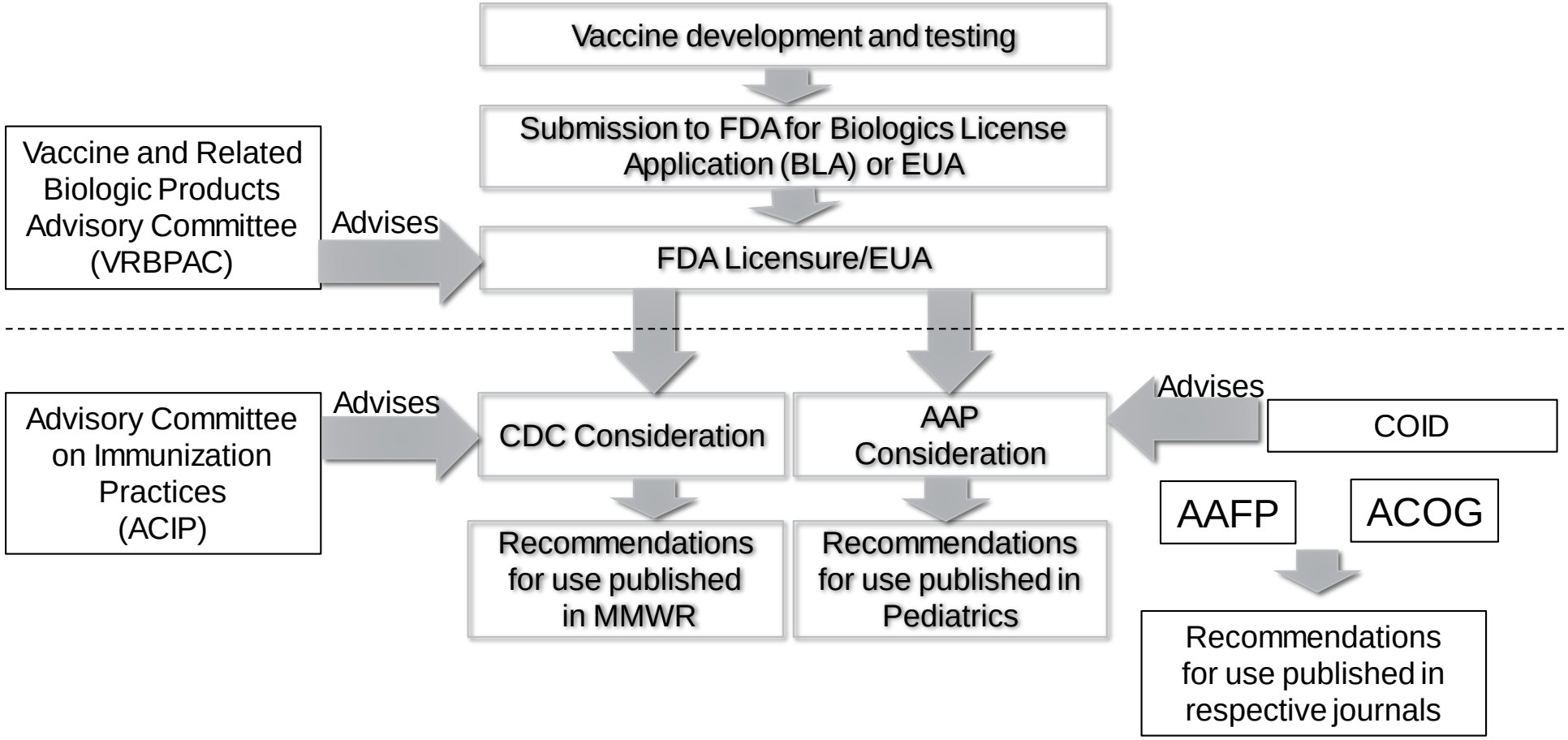
TABLE 1.
Phases of Clinical Evaluation of an Investigational Vaccine

Phase	Number and Type of Study Participants	Scientific Questions Asked
1	20 to 100 healthy adults	• Is the vaccine safe?
		• Is the vaccine tolerable?
		• What are the vaccine side effects in relation to the dose administered?
		• Does the vaccine cause the desired immune response?
2	Several hundred from target population	• What is the desired vaccine dose and dosing interval?
		• Is the desired immune response to the vaccine achieved?
		• What are the common short-term vaccine side effects observed?
3	Several hundred to tens of thousands from target population	• How effective and safe is the vaccine when comparing people who receive the vaccine to people who do not receive the vaccine?
		• What are the most common side effects?
		• Is the safety and immune response in study participants consistent across different lots of vaccine manufactures?
		• What is the effect on safety and immune response when the vaccine is co-administered with other vaccines?

Source. Adapted from: Centers for Disease Control and Prevention: Vaccines. Parents. CDC.gov website. https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine-h.pdf. Updated July 2018. Accessed December 12, 2020.

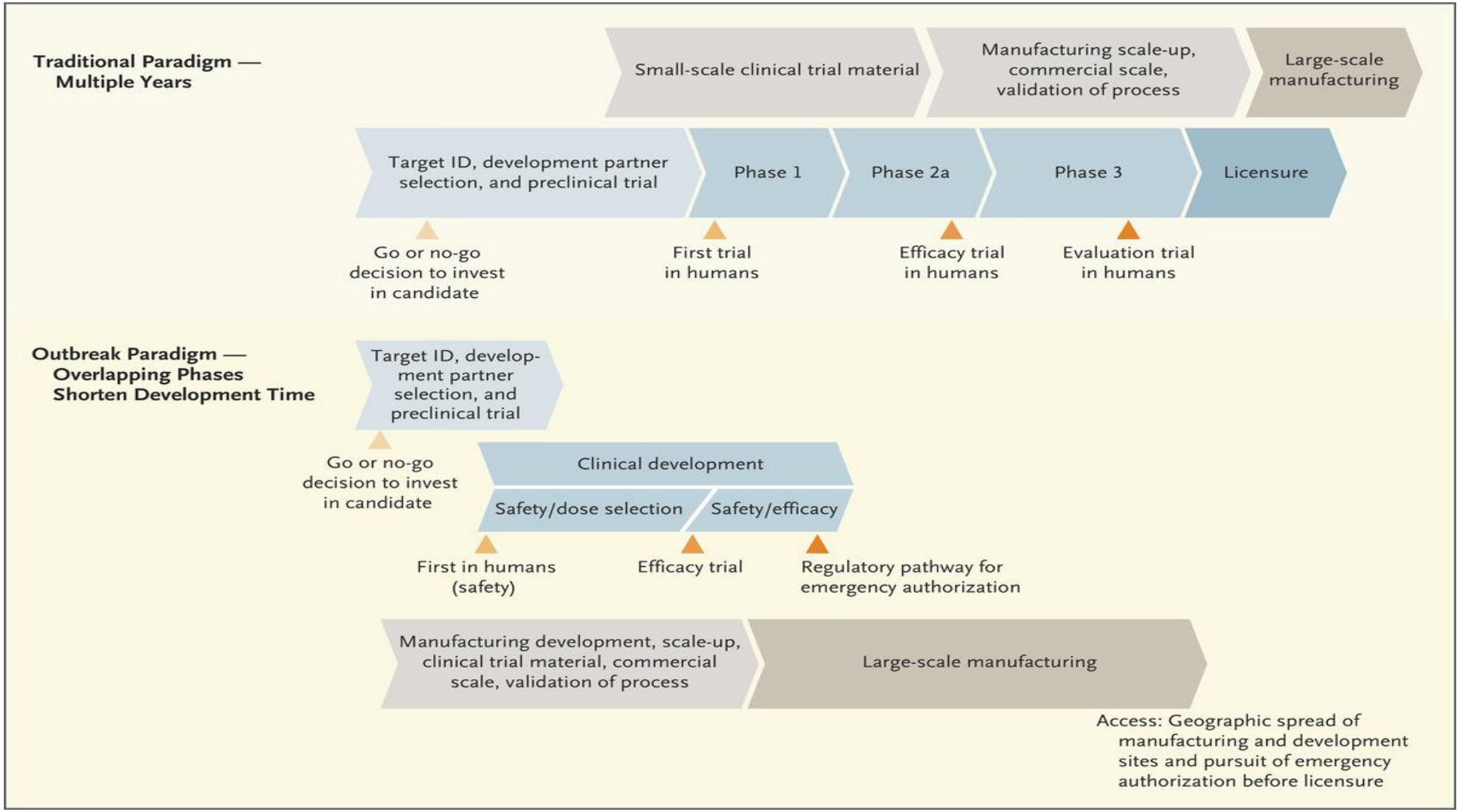
NCMJ 2021 vol. 82, no. 2: 141-144

From Science to Policy



Semin Pediatr Infect Dis 2002:13:148-154.

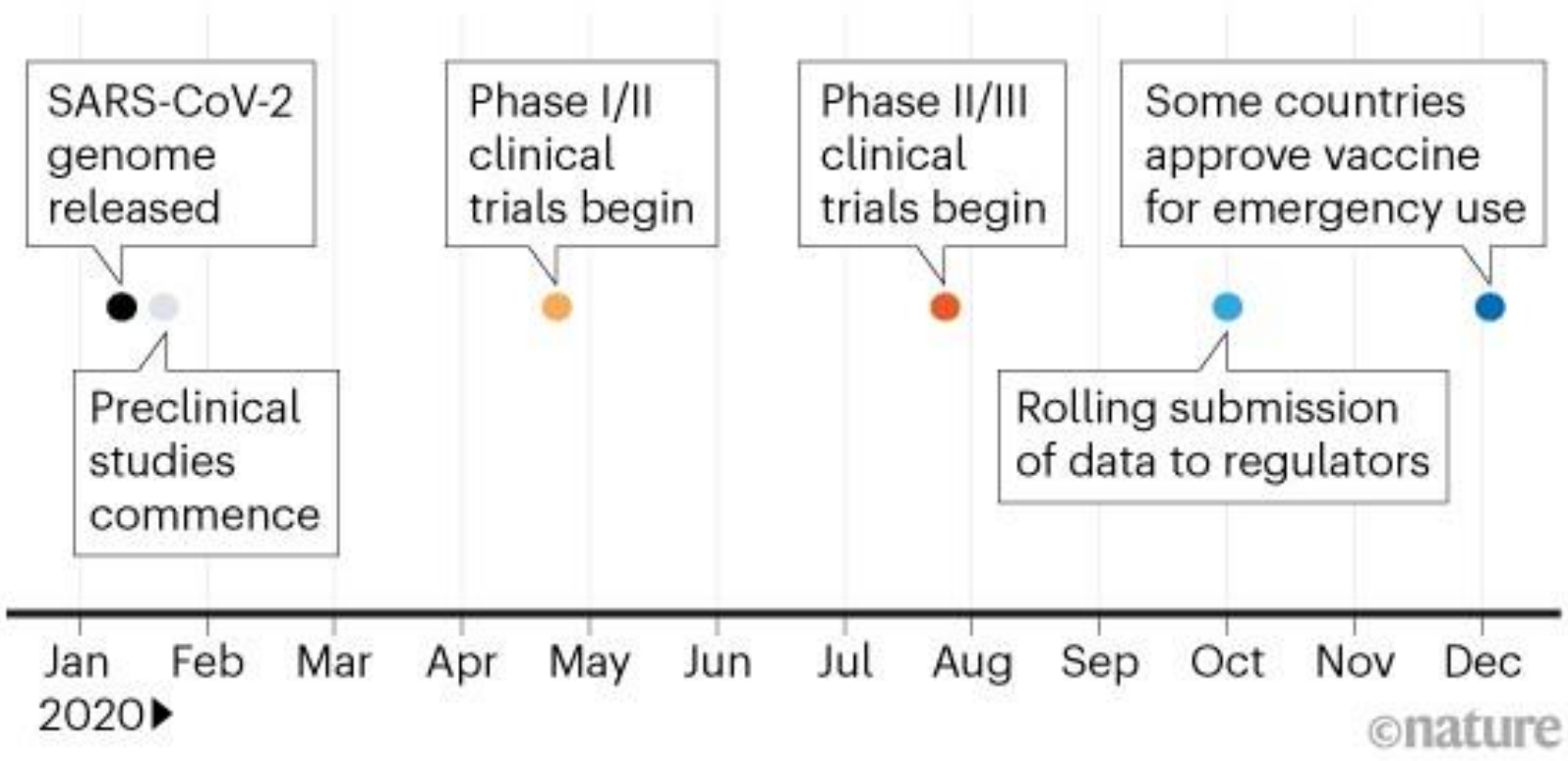
Traditional vs. Pandemic Development



N Lurie et al. N Engl J Med 2020;382:1969-1973.

A VACCINE IN A YEAR

The drug firms Pfizer and BioNTech got their joint SARS-CoV-2 vaccine approved less than eight months after trials started. The rapid turnaround was achieved by overlapping trials and because they did not encounter safety concerns.



Nature **589**, 16-18 (2021)

Currently licensed/authorized vaccines

mRNA vaccines

- Pfizer:
  - ≥ 16 (EUA December 2020, **full approval August 2021**)
  - 12 – 15 (EUA May 2021)
  - 5 – 11 (EUA October 2021)
- Moderna
  - ≥ 18 (EUA December 2020)

Vector vaccine

- Johnson and Johnson
  - ≥ 18 (EUA February 2021)

PFIZER VACCINE

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Main Outcomes

Efficacy: what is the incidence of infection in vaccinated versus unvaccinated individuals?

Immunogenicity: What is the immune response in vaccinated versus unvaccinated individuals?

Safety: What are the short- and long-term adverse events in vaccinated versus unvaccinated individuals?

Selected Inclusion Criteria

Male or female participants ≥12 years at randomization

Healthy participants who are determined by medical history, physical examination and clinical judgment of the investigator to be eligible for inclusion in the study.

- Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included

Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19

Selected Exclusion Criteria

Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19

Immunocompromised individuals with known or suspected immunodeficiency or individuals who receive treatment with immunosuppressive therapy

Pregnancy

Temporary Delay Criteria

Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:

- New or increased cough
- New or increased shortness of breath
- Chills
- New or increased muscle pain
- New loss of taste/smell
- Sore throat
- Diarrhea
- Vomiting

Temporary Delay Criteria

Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other non-study vaccine within 28 days, before study intervention administration

Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other non-study vaccine within 28 days, after study intervention administration

Receipt of short-term (< 14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intra-bursal, or topical (skin or eyes) corticosteroids are permitted

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	**Vaccination 1**	**Vaccination 2**	**1-Month Follow-up Visit**	**6-Month Follow-up Visit**	**12-Month Follow-up Visit**	**24-Month Follow-up Visit**	**Potential COVID-19 Illness Visit[a]**	**Potential COVID-19 Convalescent Visit**
Visit Window (Days)	**Day 1[b]**	**19 to 23 Days After Visit 1**	**28 to 35 Days After Visit 2**	**175 to 189 Days After Visit 2**	**350 to 378 Days After Visit 2**	**714 to 742 Days After Visit 2**	**Optimally Within 3 Days After Potential COVID-19 Illness Onset**	**28 to 35 Days After Potential COVID-19 Illness Visit**
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment[c]	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment[d]	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

Monitoring for Adverse Events

Adverse event – Any undesirable experience associated with the use of a medical product in a patient

- Graded for severity or intensity
- Assessed for relatedness to study product

Solicited Adverse Events

Local Injection Site Reactions

Monitored for specified period

Participants / LARs rate local site reactions following vaccination using electronic or paper diaries

- Pain – intensity (mild, moderate, severe)
- Tenderness - intensity (mild, moderate, severe)
- Swelling / Induration - intensity (mild, moderate, severe)
- Redness - intensity (mild, moderate, severe)

Recorded information is obtained from participants / LARs electronically or during telephone calls and clinic visits

Solicited Adverse Events

Local Injection Site Reactions

COVID-19 Vaccine Local Vaccination Site Reactions: ☐ RIGHT ARM ☐ LEFT ARM Grade 0 = **None** Grade 1 = **Mild** (noticeable but does not interfere with activity) Grade 2 = **Moderate** (interferes with activity but did not need a medical visit or absenteeism [i.e. missing work or school]) Grade 3 = **Severe** (significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]) Grade 4 = **Potentially Life Threatening** (requires an emergency room visit or hospitalization)							
Post-Vaccination Day	**Day 1 (Day of vaccination)**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Check if no symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms
Pain							
Swelling– size (mm)	mm	mm	mm	mm	mm	mm	mm
Redness- size (mm)	mm	mm	mm	mm	mm	mm	mm
Axillary swelling/tenderness							

Solicited Adverse Events

Systemic Reactions

- Monitored for specified period
- Daily temperature measurements and rating (mild, moderate, severe) of general body symptoms following vaccination using electronic or paper diary
- Age dependent assessments

Adult

- Fatigue / Malaise
- Body aches
- Joint aches
- Headache
- Nausea
- Vomiting
- Diarrhea

Young Children

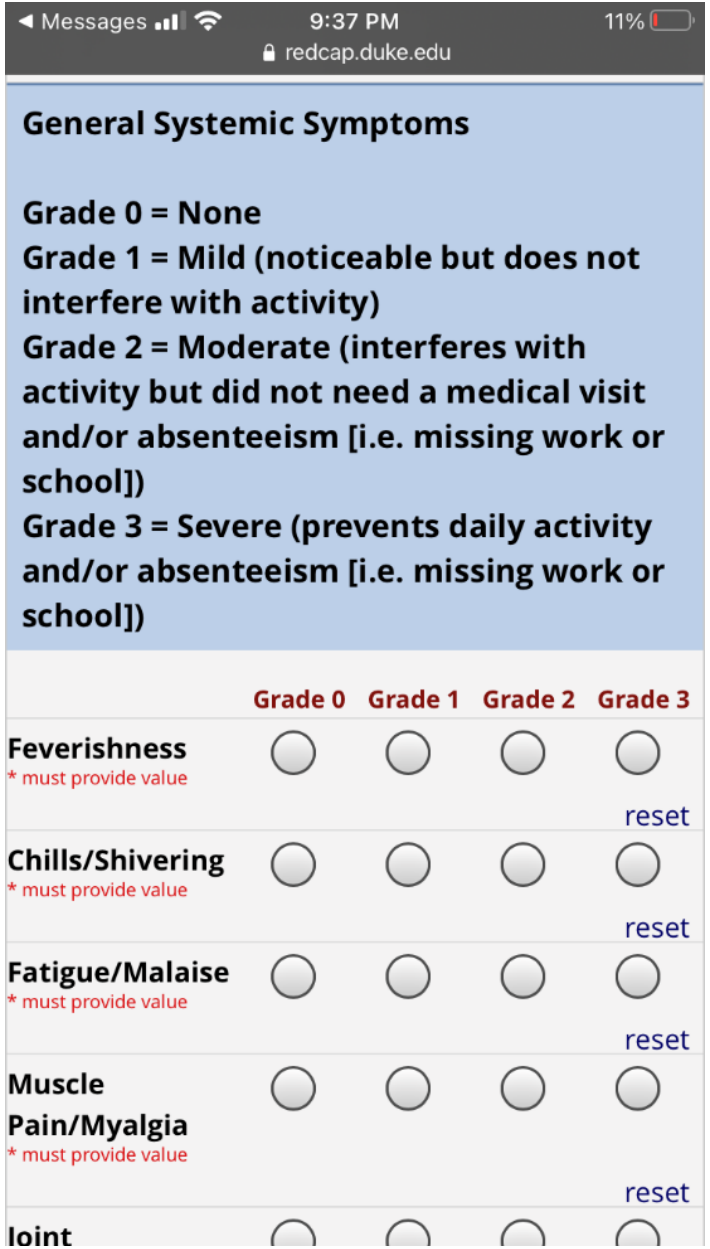
- Irritability
- Decreased appetite
- Lethargy
- Vomiting
- Diarrhea

- Recorded information is obtained from participants / LARs electronically or during telephone calls and clinic visits

Solicited Adverse Events

Systemic Reactions

Post-Vaccination Day	Day 1(Day of vaccination)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date (MM/DD/YYYY)	/ /	/ /	/ /	/ /	/ /	/ /	/ /
Oral Temperature °F	.	.	.	.	.	.	.
General Systemic Symptoms:							
Grade 0 = **None** Grade 1 = **Mild** (noticeable but does not interfere with activity) Grade 2 = **Moderate** (some interference with activity but did not need a medical visit or absenteeism [i.e. missing work or school]) Grade 3 = **Severe** (significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]) Grade 4 = **Potentially Life Threatening** (requires an emergency room visit or hospitalization)							
Check if no symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms	☐ No symptoms
Chills/Shivering							
Fatigue							
Body Aches/Muscle Pain							
Headache							
Joint pain							
Grade 0 = **None** Grade 1 = **Mild** (noticeable but does not interfere with activity or 1 – 2 episodes in 24 hours) Grade 2 = **Moderate** (some interference with activity > 2 episodes/24 hours) Grade 3 = **Severe** (significant; prevents daily activity and/or resulted in medical visit and/or absenteeism [i.e. missing work or school]) Grade 4 = **Potentially Life Threatening** (requires an emergency room visit or hospitalization)							
Nausea/Vomiting							


Messages
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redcap.duke.edu
General Systemic Symptoms
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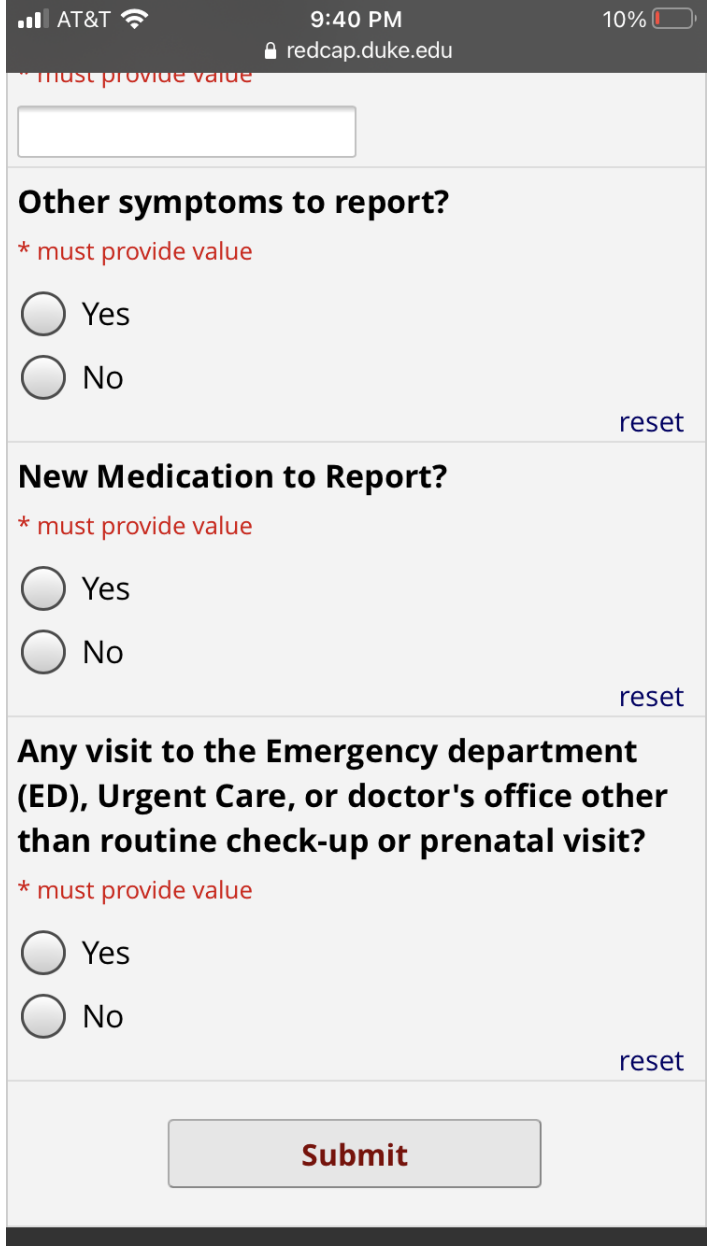
Grade 2 = Moderate (interferes with activity but did not need a medical visit and/or absenteeism [i.e. missing work or school])
Grade 3 = Severe (prevents daily activity and/or absenteeism [i.e. missing work or school])
Grade 0
Grade 1
Grade 2
Grade 3
Feverishness
* must provide value
reset
Chills/Shivering
* must provide value
reset
Fatigue/Malaise
* must provide value
reset
Muscle Pain/Myalgia
* must provide value
reset
Joint


AT&T
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10%
redcap.duke.edu
Other symptoms to report?
* must provide value
Yes
No
reset
New Medication to Report?
* must provide value
Yes
No
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Any visit to the Emergency department (ED), Urgent Care, or doctor's office other than routine check-up or prenatal visit?
* must provide value
Yes
No
reset
Submit

Unsolicited Adverse Events

Adverse events (time period specified)

Medically attended adverse events (time period specified)

Adverse events of special interest (time period specified)

Onset of a new chronic medical condition (time period specified)

Serious Adverse Events

Serious adverse event – an adverse event when the participant or patient outcome was:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious (Important Medical Events)

Need to be reported to the FDA

Adverse Events: Causality

Health problem occurs during a plausible time period following vaccination

Adverse event corresponds to those previously associated with a particular vaccine

The event conforms to a specific clinical syndrome whose association with vaccination has a strong biologic plausibility or occurs following natural disease

A laboratory result confirms the association

The event recurs on re-administration of vaccine

A controlled clinical trial demonstrates greater risk of a specific adverse event in those vaccinated when compared to control groups

A finding linking an adverse event to vaccine has been confirmed in other studies

Atkinson W, Wolfe S, Hamborsky J, Eds. 12th Ed., Second Printing. Washington DC: Public Health Foundation, 2012.

Main Outcomes

Efficacy against confirmed COVID-19 occurring from 7 days after the second dose

Immunogenicity: Non-inferiority in participants 12 to 15 years of age (and later 5 – 11) compared to participants 16 to 25 years of age

Safety: Percentage of patients with

- Local reactions for up to 7 days following each dose
- Systemic events for up to 7 days following each dose
- AEs from Dose 1 to 1 month after the second dose
- SAEs from Dose 1 to 6 months after the second dose

Efficacy Outcomes

Prior SARS-CoV-2 infection[b]	Vaccine	Placebo	VE% (95% CI)
No previous infection	0 cases	16 cases	100.0 (75.3-100.0)
With or without previous infection	0 cases	18 cases	100.0 (78.1-100.0)
All-available efficacy population[c]	3 cases	35 cases	91.4 (72.2-97.4)

[a] Positive SARS-CoV-2 PCR plus at least one COVID-19 symptom, at least 7 days after Dose 2
[b] By NAAT nasal swab at visit 1, 2, and any point up to 7 days after Dose 2
[c] Randomized and received at least 1 dose of vaccine
VE = vaccine efficacy, CI = confidence interval

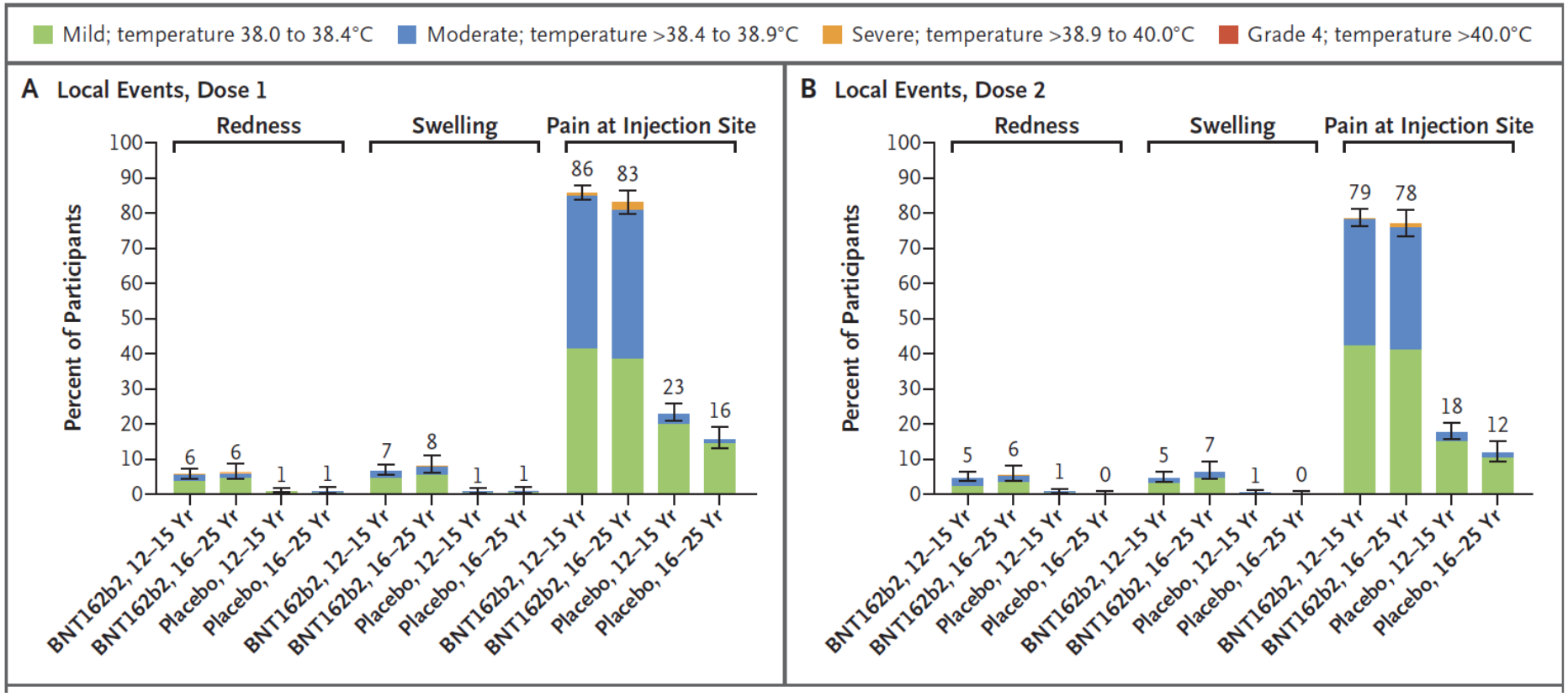
Immunogenicity Outcomes

Randomly selected subset of participants ages 12-15 (and later 5-11) vs ages 16-25 with no evidence of past SARS-CoV-2 infection

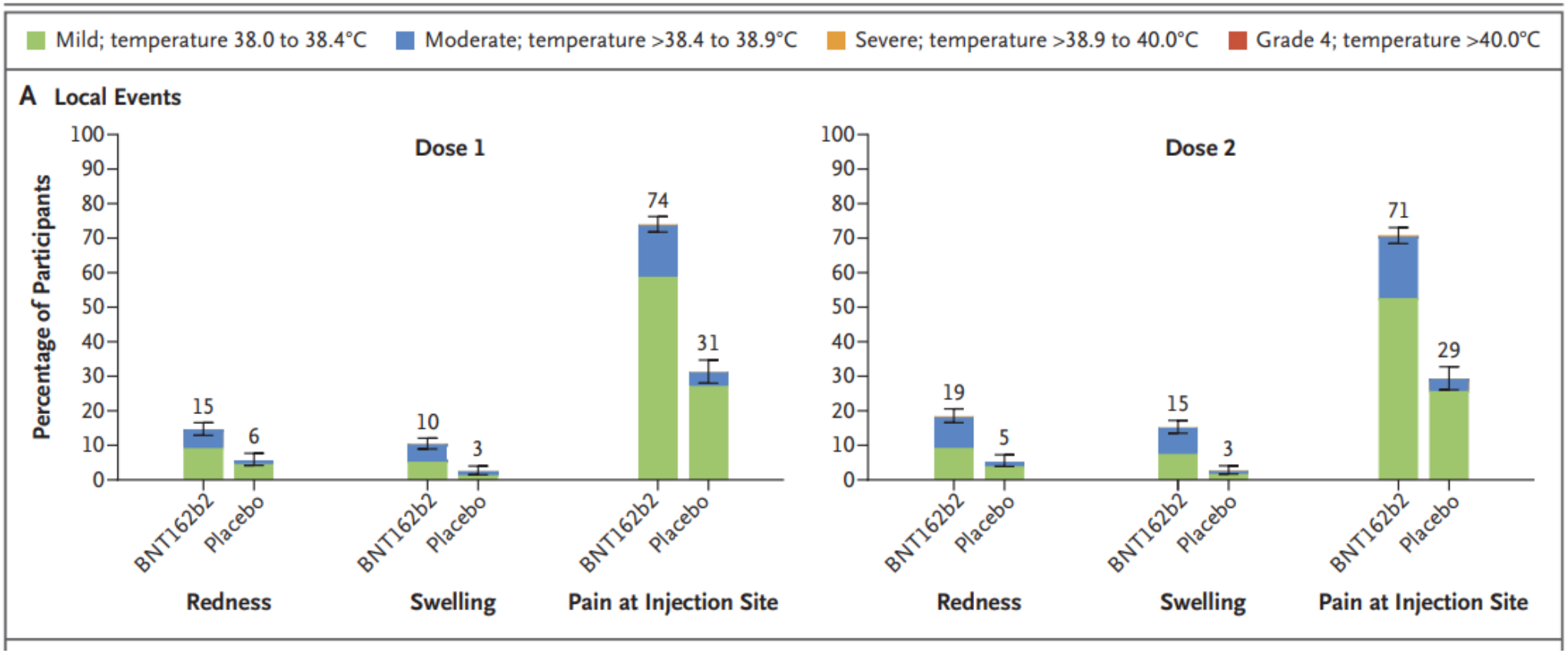
Measured immune response (SARS-CoV-2 50% neutralizing titers) 1 month after Dose 2

Both age-groups met non-inferiority objectives

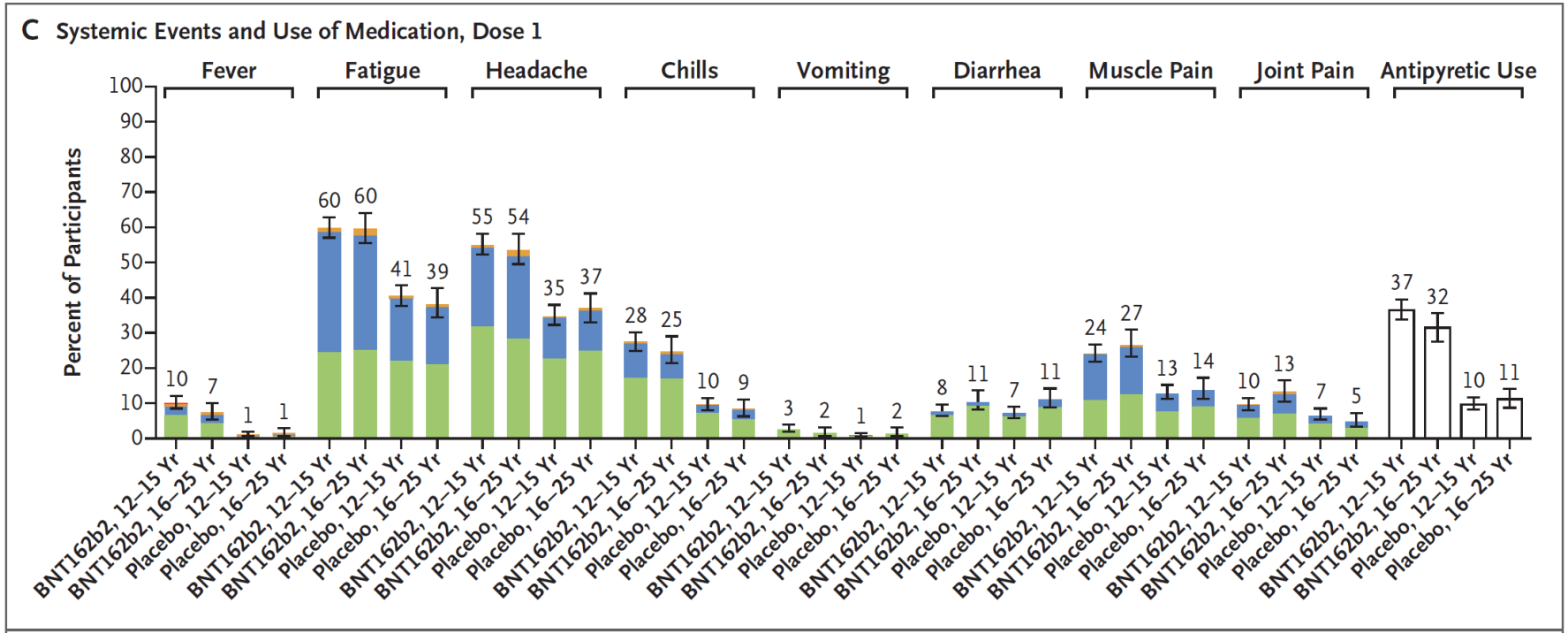
Local reactogenicity, 12-15

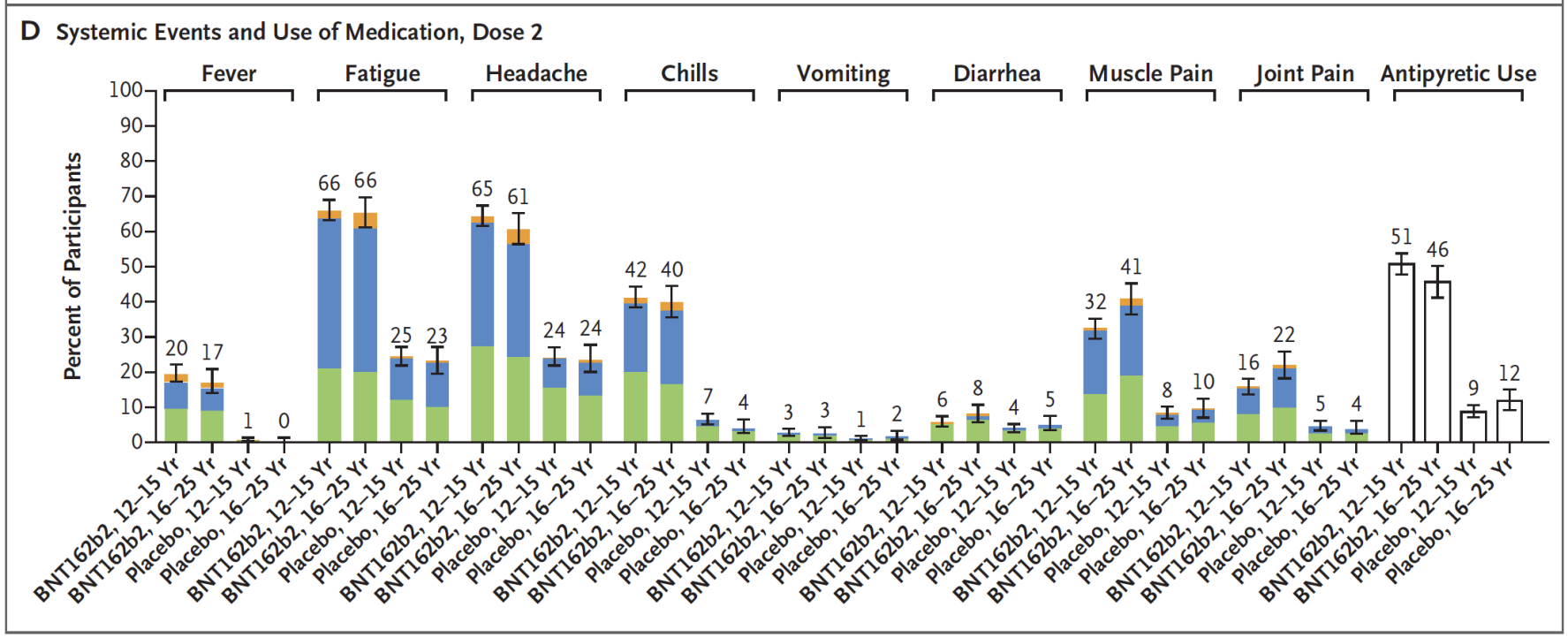


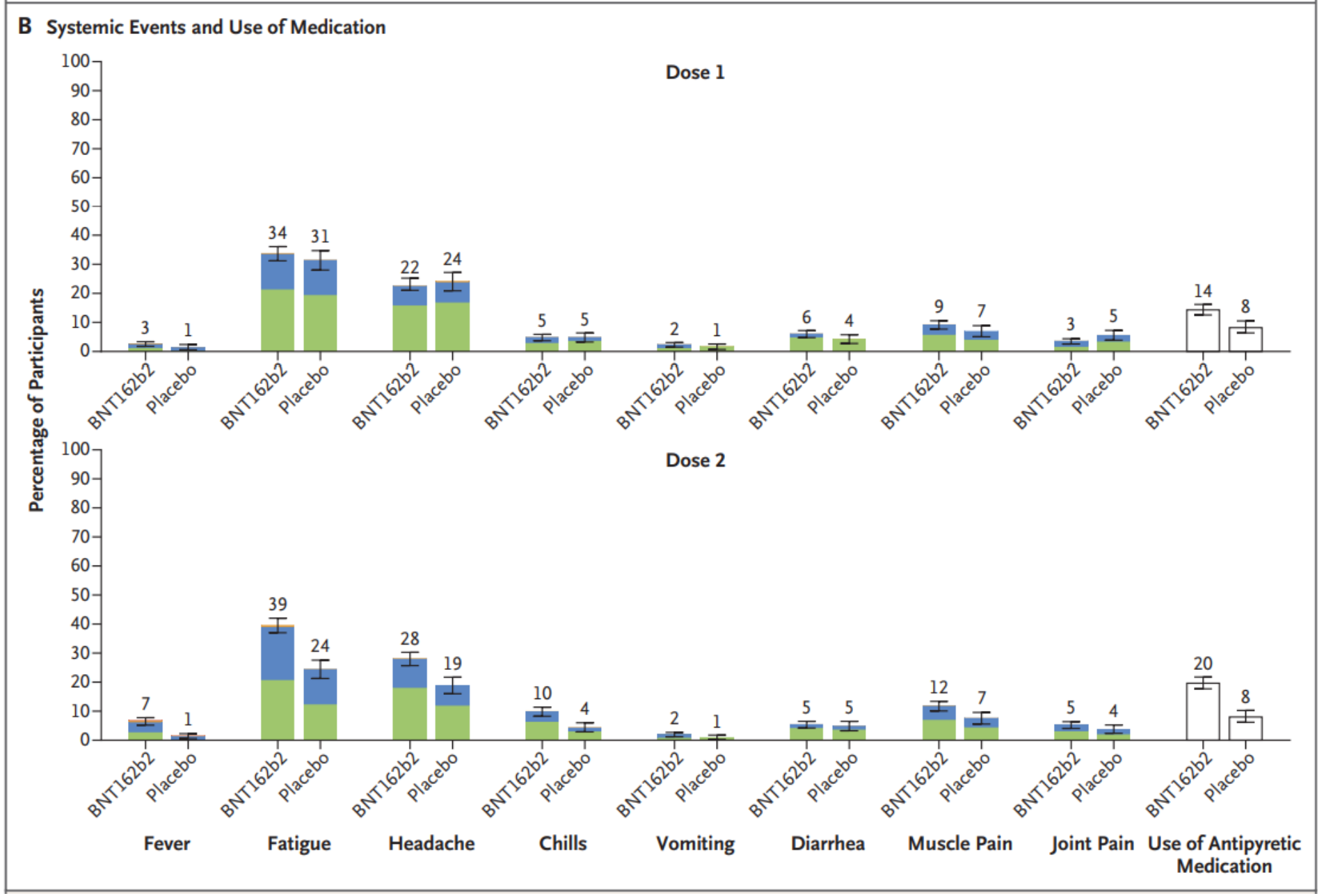
Local reactogenicity, 5-11



Walter et al, **NEJM** 2021






B Systemic Events and Use of Medication
Dose 1
Dose 2
Percentage of Participants
100
90
80
70
60
50
40
30
20
10
0
BNT162b2
Placebo
3 1
34 31
22 24
5 5
2 1
6 4
9 7
3 5
14 8
7 1
39 24
28 19
10 4
2 1
5 5
12 7
5 4
20 8
Fever
Fatigue
Headache
Chills
Vomiting
Diarrhea
Muscle Pain
Joint Pain
Use of Antipyretic Medication

MODERNA VACCINE

Duke University School of Medicine

Duke Vaccine & Trials Unit DVTU

Duke Center for Antimicrobial Stewardship and Infection Prevention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents

Kashif Ali, M.D., Gary Berman, M.D., Honghong Zhou, Ph.D., Weiping Deng, Ph.D., Veronica Faughnan, B.S., Maria Coronado-Voges, M.S., Baoyu Ding, M.S., Jacqueline Dooley, B.A., Bethany Girard, Ph.D., William Hillebrand, M.S., Rolando Pajon, Ph.D., Jacqueline M. Miller, M.D., Brett Leav, M.D., and Roderick McPhee, M.D., Ph.D.

ABSTRACT

BACKGROUND

The incidence of coronavirus disease 2019 (Covid-19) among adolescents between 12 and 17 years of age was approximately 900 per 100,000 population from April 1 through June 11, 2021. The safety, immunogenicity, and efficacy of the mRNA-1273 vaccine in adolescents are unknown.

METHODS

In this ongoing phase 2–3, placebo-controlled trial, we randomly assigned healthy adolescents (12 to 17 years of age) in a 2:1 ratio to receive two injections of the mRNA-1273 vaccine (100 μg in each) or placebo, administered 28 days apart. The primary objectives were evaluation of the safety of mRNA-1273 in adolescents and the noninferiority of the immune response in adolescents as compared with that in young adults (18 to 25 years of age) in a phase 3 trial. Secondary objectives included the efficacy of mRNA-1273 in preventing Covid-19 or asymptomatic severe acute respiratory syndrome coronavirus 2 infection.

RESULTS

A total of 3732 participants were randomly assigned to receive mRNA-1273 (2489 participants) or placebo (1243 participants). In the mRNA-1273 group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 93.1% and 92.4%, respectively), headache (in 44.6% and 70.2%, respectively), and fatigue (in 47.9% and 67.8%, respectively); in the placebo group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 34.8% or 30.3%, respectively), headache (in 38.5% and 30.2%, respectively), and fatigue (in 36.6% and 28.9%, respectively). No serious adverse events related to mRNA-1273 or placebo were noted. The geometric mean titer ratio of pseudovirus neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, −1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group.

CONCLUSIONS

The mRNA-1273 vaccine had an acceptable safety profile in adolescents. The immune response was similar to that in young adults, and the vaccine was efficacious in preventing Covid-19. (Funded by Moderna and the Biomedical Advanced Research and Development Authority; Teen COVE ClinicalTrials.gov number, NCT04649151.)

From Kool Kids Pediatrics, DM Clinical Research, Houston (K.A.); the Clinical Research Institute, Minneapolis (G.B.); and Moderna, Cambridge, MA (H.Z., W.D., V.F., M.C.-V., B.D., J.D., B.G., W.H., R.P., J.M.M., B.L., R.M.). Address reprint requests to Dr. McPhee at Moderna, 200 Technology Square, Cambridge, MA 02139, or at roderick.mcphee@modernatx.com.

Drs. Ali and Berman contributed equally to this article.

This article was published on August 11, 2021, at NEJM.org.

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Selected Inclusion Criteria

Male or female participants 12 - < 18 years at consent in good general health based on review of medical history and screening physical examination

BMI ≥ 3rd percentile

Selected Exclusion Criteria

Travel outside of the United States within 28 days prior to screening

Pregnancy

Prior COVID vaccine receipt or current treatment

Immunocompromising conditions

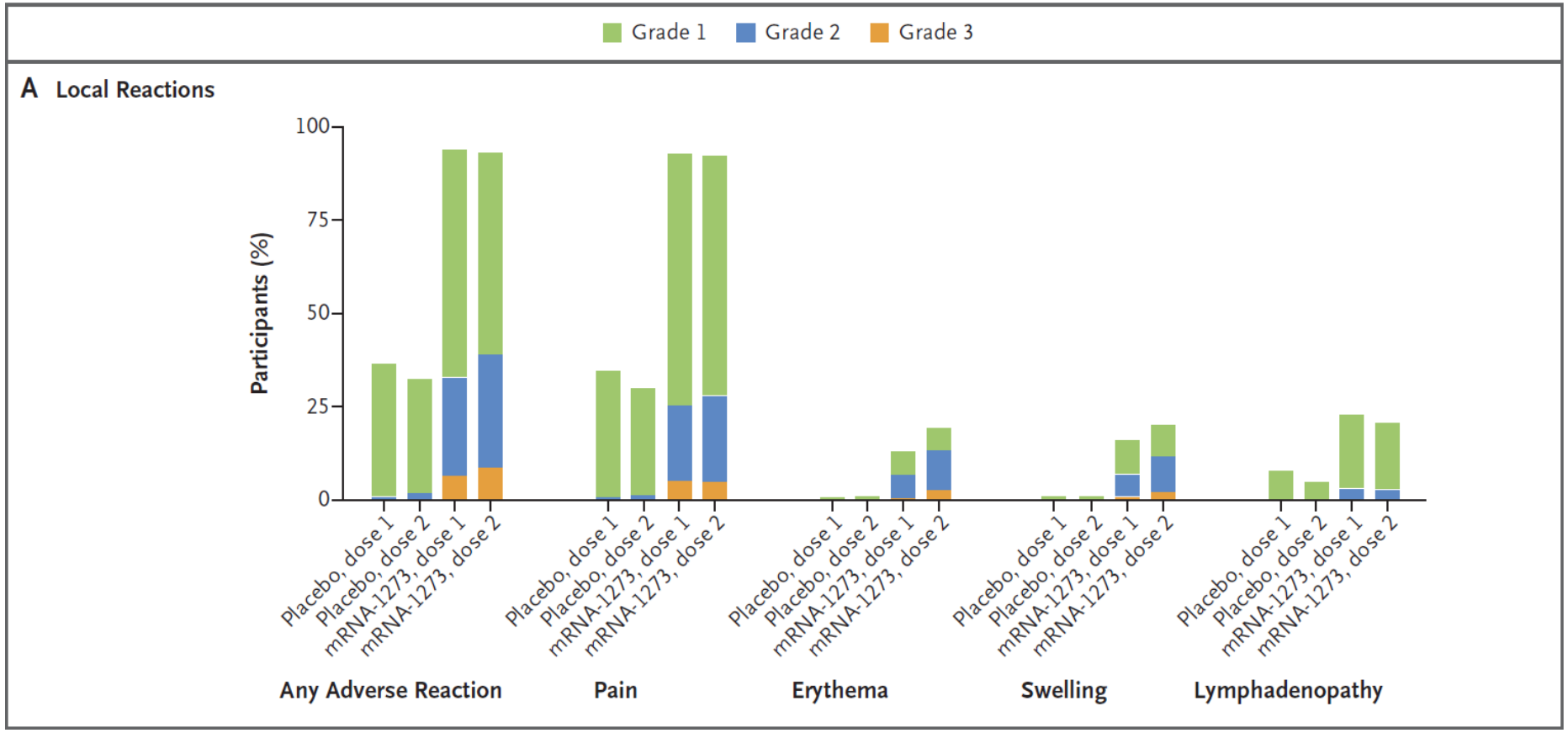
Other conditions that makes participation unsafe

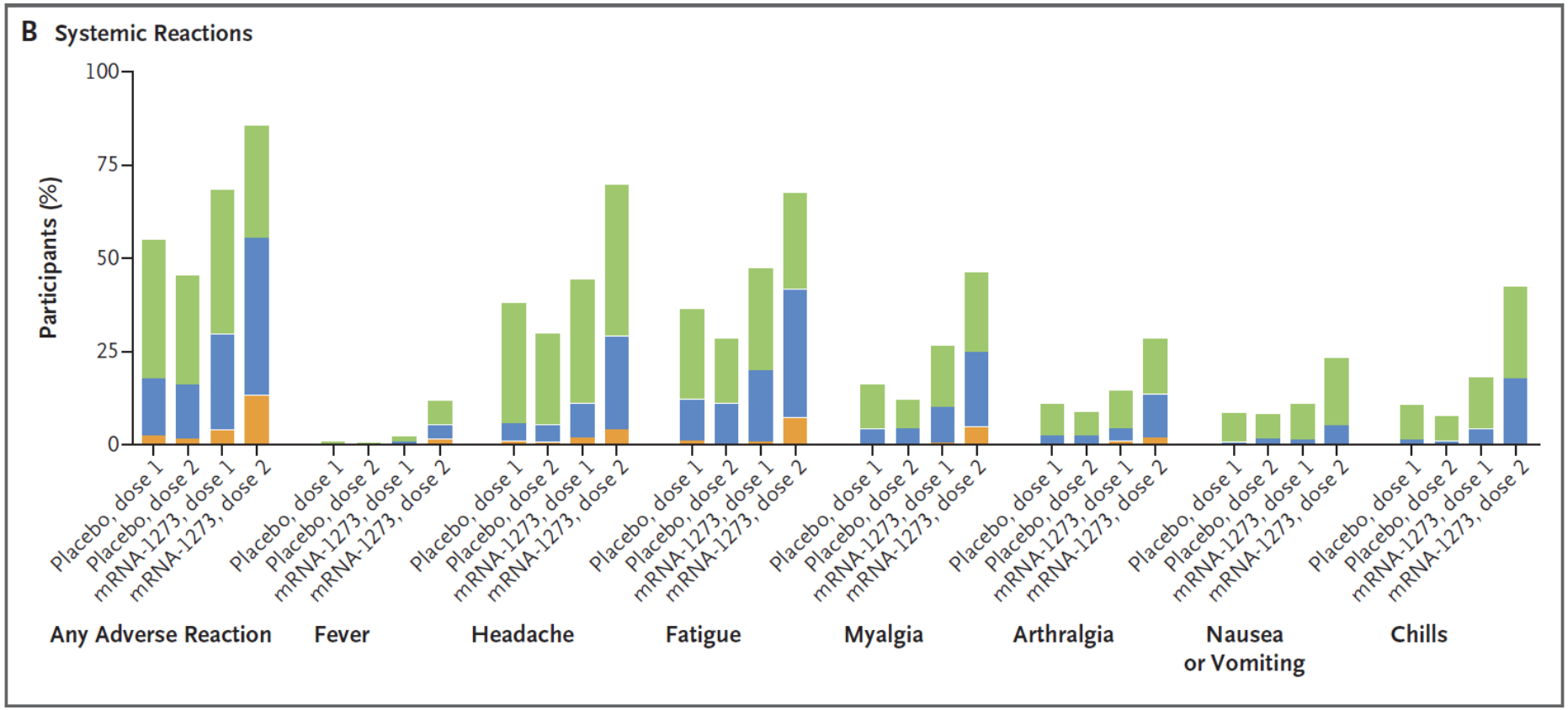
Temporary Delay Criteria

Current febrile illness (body temperature ≥100.4°F [≥38°C]) or other acute illness within 24 hours before enrollment

Licensed vaccine within 28 days prior to the first dose or planned receipt within 28 days following the last dose

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3, 6]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	±3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Blood sample for vaccine immunogenicity[9]		X				X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[10]		X		X		X			X			
Surveillance for COVID-19/ Illness visit[11]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X
Convalescent Visit[12]		X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[13]		X		X								
Review of eDiary data			X		X							
Follow-up safety telephone calls[14]								X		X		
Recording of unsolicited AEs		X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[15]		X	X	X	X	X	X		X	X		X


Grade 1
Grade 2
Grade 3
A Local Reactions
Participants (%)
100
75
50
25
0
Placebo, dose 1
Placebo, dose 2
mRNA-1273, dose 1
mRNA-1273, dose 2
Any Adverse Reaction
Pain
Erythema
Swelling
Lymphadenopathy


B Systemic Reactions
Participants (%)
100
75
50
25
0
Placebo, dose 1
Placebo, dose 2
mRNA-1273, dose 1
mRNA-1273, dose 2
Any Adverse Reaction
Fever
Headache
Fatigue
Myalgia
Arthralgia
Nausea or Vomiting
Chills

Randomized control trials: what we know

COVID vaccines are efficacious

COVID vaccines are immunogenic

No major safety concerns

Randomized control trials: what we don't know

- Impact of prior symptomatic infections
- Impact of concomitant vaccine receipt
- Immunogenicity in immunocompromised individuals
- Safety in pregnancy
- Impact of race

Diversity in Pediatric COVID vaccine trials

Pfizer 12 – 15: 85% white, 5% black, 12% Hispanic

Moderna 12- 15: 84% white, 3% black, 12% Hispanic

Pfizer 5 – 11: 79% white, 7% black, 21% Hispanic

POST-LICENSURE VACCINE SAFETY

Duke University School of Medicine

Duke Vaccine & Trials Unit DVTU

Duke Center for Antimicrobial Stewardship and Infection Prevention

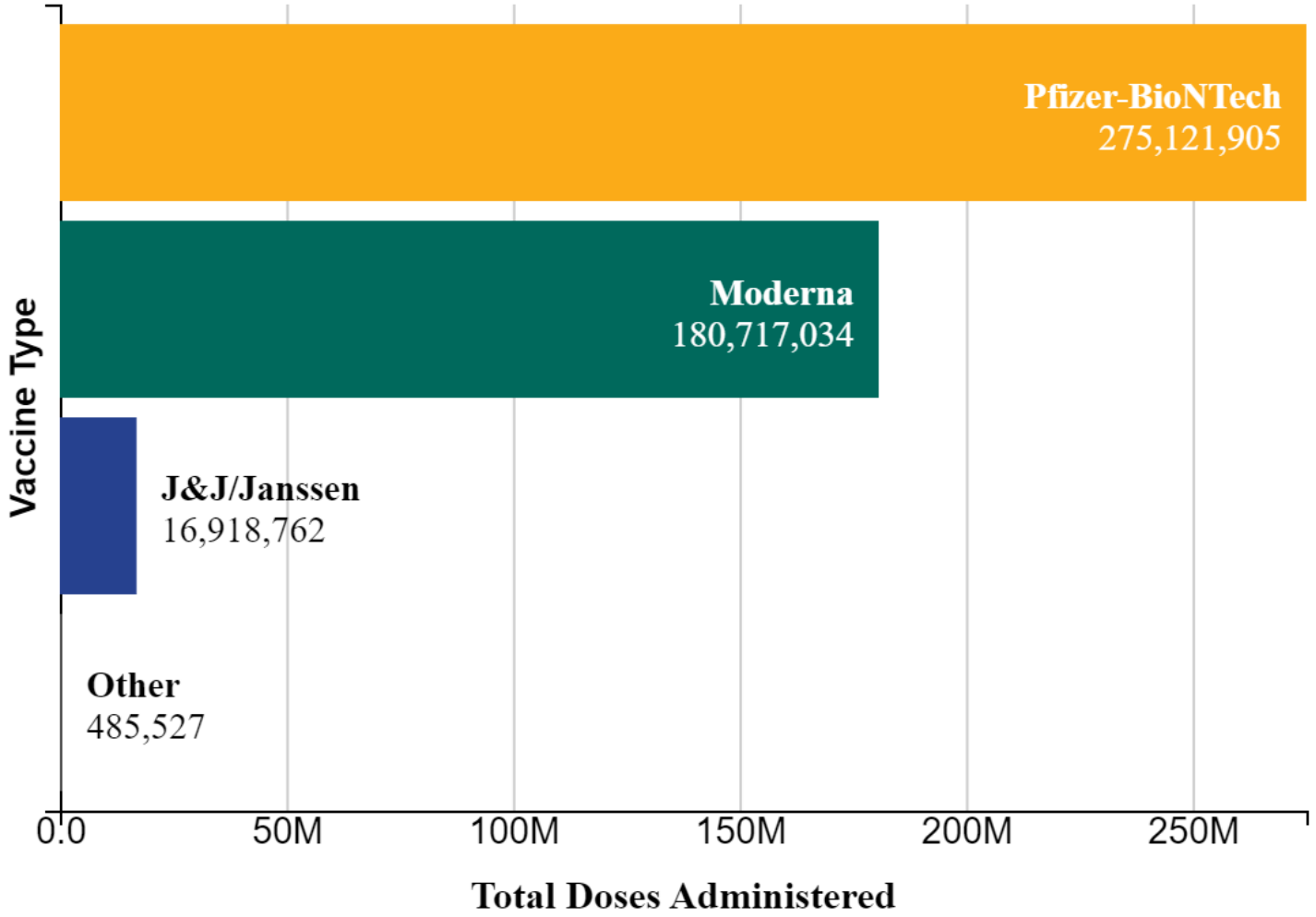
Post-licensure vaccine safety

Once a vaccine is approved for use in the population vaccine safety assessments continue. This is important to:

- Identify rare AEs that may not have been found in trials that “only” included 50,000 people
- Identify AEs that may occur in individuals who were excluded from the trials.

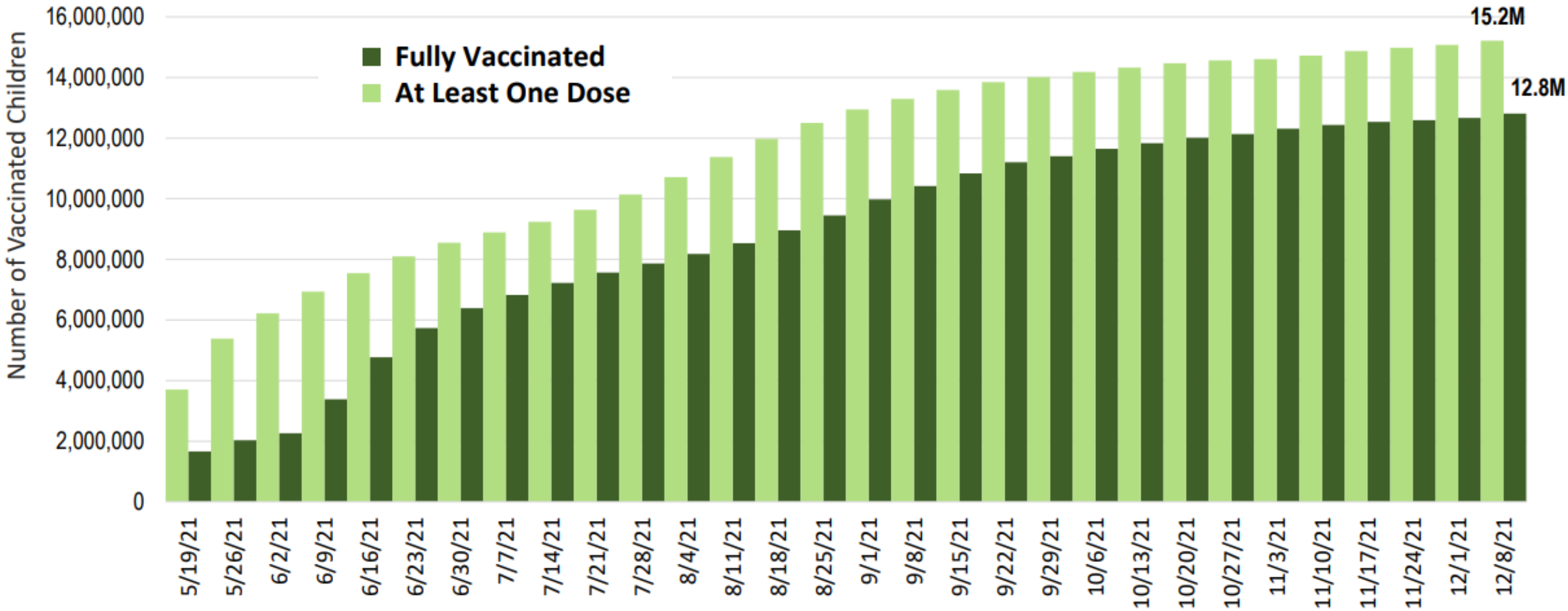
Currently, almost 500 million doses administered

U.S. COVID-19 Vaccine Administration by Vaccine Type



Cumulative Number of US COVID-19 Vaccine Recipients Ages 12-17

5.19.21 to 12.8.21



Source: AAP analysis of data series titled "COVID -19 Vaccinations in the United States, Jurisdiction". CDC COVID -19 Data Tracker (URL: https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc). Idaho information not available. Check state's web sites for additional or more recent information.

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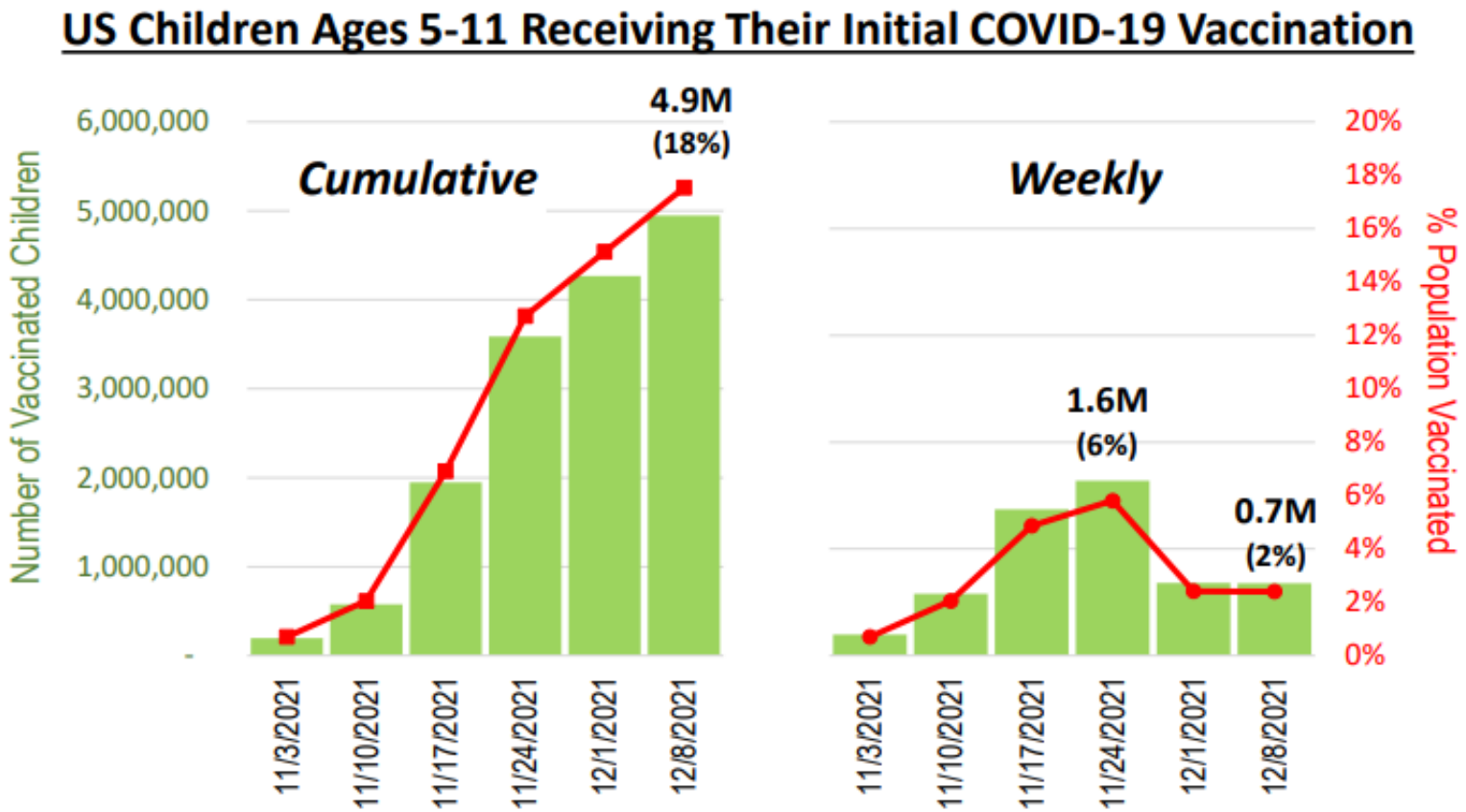
COVID-19 Vaccinations for US Children Ages 5-11

Weeks ending 11.3.21 to 12.8.21

As of December 8:

4.9 million (18%)
US children ages 5-11 had received at least **one dose** of COVID-19 vaccine

Per public-use data
From the CDC



Source: AAP analysis of data series titled "COVID -19 Vaccinations in the United States, Jurisdiction". CDC COVID -19 Data Tracker (URL: https://data.cdc.gov/Vaccinations/COVID-19-Vaccinations-in-the-United-States-Jurisdi/unsk-b7fc). Idaho information not available. Check state's web sites for additional or more recent information.

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Post-licensure vaccine safety

There are several long-standing post-licensure mechanisms:

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Clinical Immunization Safety Assessment (CISA)

VAERS

www.vaers.hhs.gov

A passive surveillance system that allows anyone (health care providers, patients or their families) to report unexpected signs or symptoms after vaccine receipt

VAERS functions as an “early warning system”

Importantly, there is no comparison group, only patients who received a vaccine and had an adverse event are included. VAERS data are hypothesis generating but can be used to design other more rigorous studies to explore causation

VAERS data DO NOT imply causation in and of themselves

Adolescent VAERS reports

9,246 reports of adverse events in adolescents

- About 1 per 1000 doses administered
- 8,383 (91%) nonserious events
- 863 (9.3%) serious events

Symptom, sign, diagnostic result, or condition	% Reporting
Nonserious reports (n = 8,383)	
Dizziness	21.2
Syncope	14.4
Nausea	10.4
Headache	10.0
Fever	8.3
Loss of consciousness	7.5
Excessive sweating	7.4
Fatigue	7.2
Pallor	7.1
Product administered to patient outside of indicated age range	7.0
Product storage error	6.4
Vomiting	6.4
Difficulty breathing	5.3
Chest pain	4.9
Pain	4.6
Serious reports, including reports of death† (n = 863)	
Chest pain	56.4
Increased troponin	41.7
Myocarditis	40.3
Increased c-reactive protein	30.6
Negative SARS-CoV-2 test result	29.4
Fever	28.3
Normal echocardiogram	26.9
Abnormal electrocardiogram	25.6
Headache	22.2
Difficulty breathing	21.4
Elevated electrocardiogram ST segment	20.5
Normal chest radiograph	19.7
Intensive care	18.1
Vomiting	17.0
Nausea	16.6

Hause et al, MMWR, 8/6/21

Myocarditis data in VAERS

	Female			Male		
Age (years)	Cases	Doses administered	Rate per million doses	Cases	Doses administered	Rate per million doses
12 – 17	19	2,189,726	8.68	128	2,039,871	62.75
18 – 24	23	5,237,262	4.39	219	4,337,287	50.49
25 – 29	7	4,151,975	1.69	59	3,625,574	16.27

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf

VAERS: Strengths and Limitations

Strengths

- National data
- Rapid signal detection
- Can detect rare adverse events (AE)
- Generates hypotheses for further study
- Data are available to the public http://vaers.hhs.gov/index

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an AE
- Lack of unvaccinated comparison group

VAERS website: http://vaers.hhs.gov

Adolescent V-safe reports

Event	% of v-safe enrollees reporting reaction or health impact*			
	Age 16–17 yrs, dose (no.)		Age 12–15 yrs, dose (no.)	
	Dose 1 (66,350)	Dose 2 (41,040)	Dose 1 (62,709)	Dose 2 (38,817)
Any injection site reaction	**62.7**	**64.4**	**63.9**	**62.4**
Itching	5.7	6.3	5.8	5.5
Pain	60.2	62.0	61.2	59.9
Redness	3.4	4.9	4.1	5.3
Swelling	7.7	9.9	7.5	8.9
Any systemic reaction	**55.7**	**69.9**	**48.9**	**63.4**
Abdominal pain	4.7	8.5	4.1	7.0
Myalgia	25.4	40.7	21.4	31.4
Chills	8.3	26.2	6.8	21.1
Diarrhea	4.2	4.9	3.1	3.3
Fatigue	34.1	52.3	27.4	44.6
Fever	9.9	31.0	9.3	29.9
Headache	29.8	50.6	25.2	43.7
Joint pain	7.9	18.2	6.3	12.4
Nausea	10.2	19.8	7.5	14.8
Rash	1.2	1.1	1.2	1.2
Vomiting	1.1	2.3	1.0	2.6
Any health impact	**11.0**	**28.6**	**10.6**	**25.4**
Unable to perform normal daily activities	9.0	24.7	9.3	23.1
Unable to work or attend school	3.7	11.6	2.4	6.1
Needed medical care	0.5	0.6	0.5	0.8
Telehealth	0.1	0.2	0.1	0.2
Clinic	0.2	0.2	0.2	0.3
Emergency department visit	0.1	0.2	0.1	0.2
Hospitalization	0.02	0.03	0.02	0.04

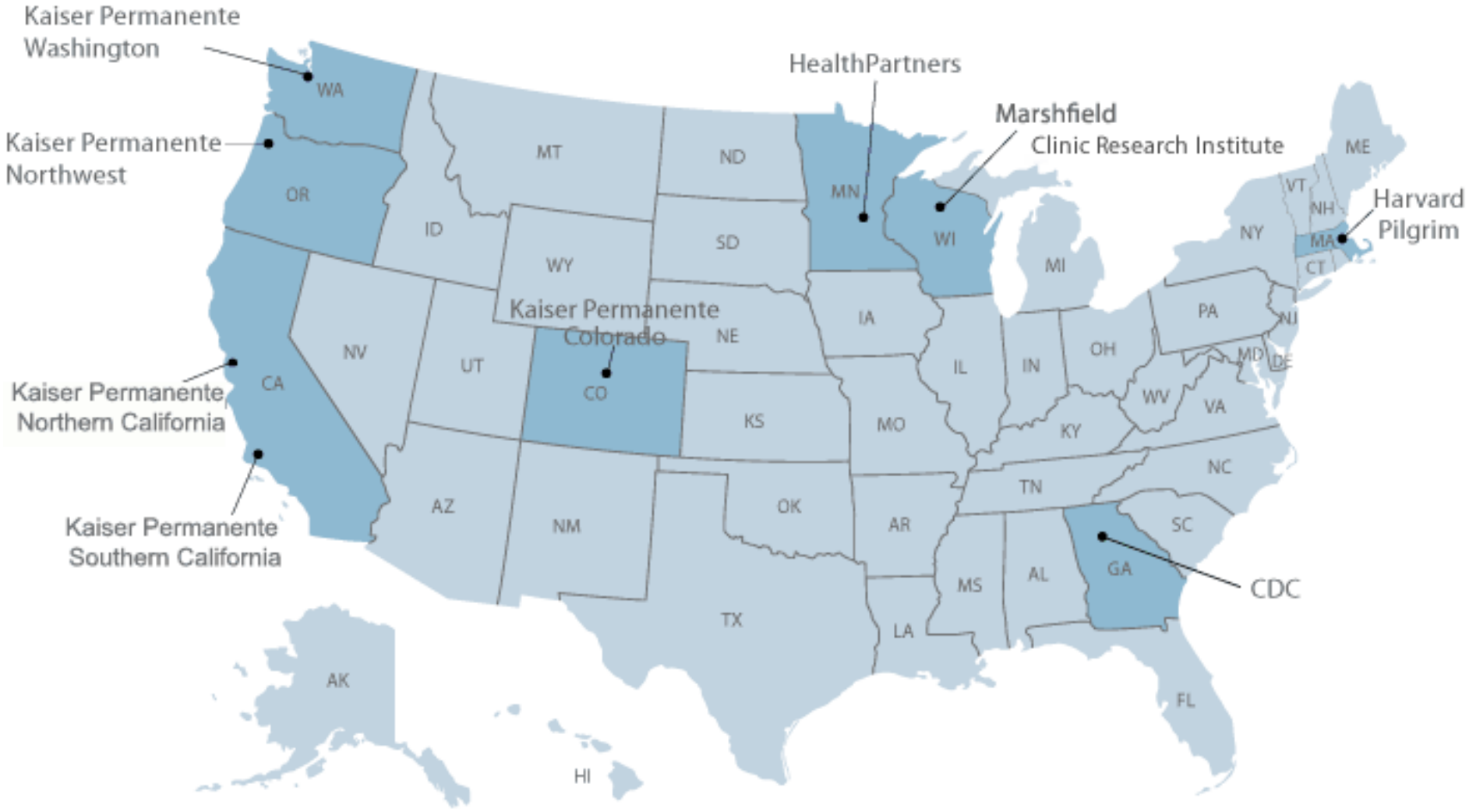
Hause et al, MMWR, 8/6/21

Vaccine Safety Datalink

One way to conduct a more epidemiologically rigorous vaccine safety study involves the Vaccine Safety Datalink (VSD)

VSD is a partnership between the CDC and several geographically diverse managed care organization. VSD includes clinical data for nearly 10 million individuals each year

VSD data are updated weekly and allow for a better understanding of causation by comparing rates of an adverse event of concern among individuals who received a vaccine as compared to those who did not



Duke Center for
Antimicrobial Stewardship
and Infection Prevention

Research

JAMA | Original Investigation

Surveillance for Adverse Events After COVID-19 mRNA Vaccination

Nicola P. Klein, MD, PhD; Ned Lewis, MPH; Kristin Goddard, MPH; Bruce Fireman, MA; Ousseny Zerbo, PhD; Kayla E. Hanson, MPH; James G. Donahue, DVM, PhD; Elyse O. Kharbanda, MD, MPH; Allison Naleway, PhD; Jennifer Clark Nelson, PhD; Stan Xu, PhD; W. Katherine Yih, PhD, MPH; Jason M. Glanz, PhD; Joshua T. B. Williams, MD; Simon J. Hambidge, MD, PhD; Bruno J. Lewin, MD; Tom T. Shimabukuro, MD, MPH, MBA; Frank DeStefano, MD, MPH; Eric S. Weintraub, MPH

IMPORTANCE Safety surveillance of vaccines against COVID-19 is critical to ensure safety, maintain trust, and inform policy.

OBJECTIVES To monitor 23 serious outcomes weekly, using comprehensive health records on a diverse population.

DESIGN, SETTING, AND PARTICIPANTS This study represents an interim analysis of safety surveillance data from Vaccine Safety Datalink. The 10 162 227 vaccine-eligible members of 8 participating US health plans were monitored with administrative data updated weekly and supplemented with medical record review for selected outcomes from December 14, 2020, through June 26, 2021.

EXPOSURES Receipt of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) COVID-19 vaccination, with a risk interval of 21 days for individuals after vaccine dose 1 or 2 compared with an interval of 22 to 42 days for similar individuals after vaccine dose 1 or 2.

MAIN OUTCOMES AND MEASURES Incidence of serious outcomes, including acute myocardial infarction, Bell palsy, cerebral venous sinus thrombosis, Guillain-Barré syndrome, myocarditis/pericarditis, pulmonary embolism, stroke, and thrombosis with thrombocytopenia syndrome. Incidence of events that occurred among vaccine recipients 1 to 21 days after either dose 1 or 2 of a messenger RNA (mRNA) vaccine was compared with that of vaccinated concurrent comparators who, on the same calendar day, had received their most recent dose 22 to 42 days earlier. Rate ratios (RRs) were estimated by Poisson regression, adjusted for age, sex, race and ethnicity, health plan, and calendar day. For a signal, a 1-sided $P < .0048$ was required to keep type I error below .05 during 2 years of weekly analyses. For 4 additional outcomes, including anaphylaxis, only descriptive analyses were conducted.

RESULTS A total of 11 845 128 doses of mRNA vaccines (57% BNT162b2; 6 175 813 first doses and 5 669 315 second doses) were administered to 6.2 million individuals (mean age, 49 years; 54% female individuals). The incidence of events per 1 000 000 person-years during the risk vs comparison intervals for ischemic stroke was 1612 vs 1781 (RR, 0.97; 95% CI, 0.87-1.08); for appendicitis, 1179 vs 1345 (RR, 0.82; 95% CI, 0.73-0.93); and for acute myocardial infarction, 935 vs 1030 (RR, 1.02; 95% CI, 0.89-1.18). No vaccine-outcome association met the prespecified requirement for a signal. Incidence of confirmed anaphylaxis was 4.8 (95% CI, 3.2-6.9) per million doses of BNT162b2 and 5.1 (95% CI, 3.3-7.6) per million doses of mRNA-1273.

CONCLUSIONS AND RELEVANCE In interim analyses of surveillance of mRNA COVID-19 vaccines, incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination. While CIs were wide for many outcomes, surveillance is ongoing.

Editorial

Supplemental content

During the study period:

11.8 million doses of mRNA vaccine administered to 6.2 million individuals

6.7 million Pfizer, 5.1 million Moderna

The 8 participating health plans include 12.5 million people (3.6% of US population)

Multiple comparators are used in this surveillance system. Main outcome for this study was incidence rate in days 1-21 as compared to days 22-42

Table 1. Outcomes for Rapid Cycle Analysis of COVID-19 mRNA Vaccines

Outcomes	Risk interval, d	Setting	Exclude if COVID-19 positive in the interval before vaccination, d[a]
Comparative analyses	1-21		
Acute disseminated encephalomyelitis		Emergency department, inpatient	NA
Acute myocardial infarction		Emergency department, inpatient	30
Appendicitis		Emergency department, inpatient	NA
Bell palsy		Emergency department, inpatient, outpatient	30
Cerebral venous sinus thrombosis		Emergency department, inpatient	30
Convulsions/seizures		Emergency department, inpatient	30
Disseminated intravascular coagulation		Emergency department, inpatient	42
Encephalitis/myelitis/ encephalomyelitis		Emergency department, inpatient	30
Guillain-Barré syndrome		Emergency department, inpatient	NA
Immune thrombocytopenia		Emergency department, inpatient, outpatient	30
Kawasaki disease		Emergency department, inpatient	NA
Myocarditis/pericarditis		Emergency department, inpatient	30
Pulmonary embolism		Emergency department, inpatient	30
Stroke			
Hemorrhagic		Emergency department, inpatient	30
Ischemic		Emergency department, inpatient	30
Thrombosis with thrombocytopenia syndrome[b]		Emergency department, inpatient	30
Thrombotic thrombocytopenic purpura		Emergency department, inpatient	30
Transverse myelitis		Emergency department, inpatient	NA
Venous thromboembolism		Emergency department, inpatient, outpatient	30
Descriptive monitoring only	Monitoring period, d		
Acute respiratory distress syndrome	0-84	Emergency department, inpatient	42
Anaphylaxis	0-1	Emergency department, inpatient	NA
Multisystem inflammatory syndrome in children/adults	0-84	Emergency department, inpatient	NA
Narcolepsy/cataplexy	0-84	Emergency department, inpatient, outpatient	NA

- 183 reported cases of anaphylaxis
  - 171 adjudicated
  - 55 confirmed
    - Almost all in women
    - Median 10 (IQR 5 – 20) min
    - 4.8 cases per million doses

None of these conditions met signal criteria

Myocarditis

No signal in overall cohort

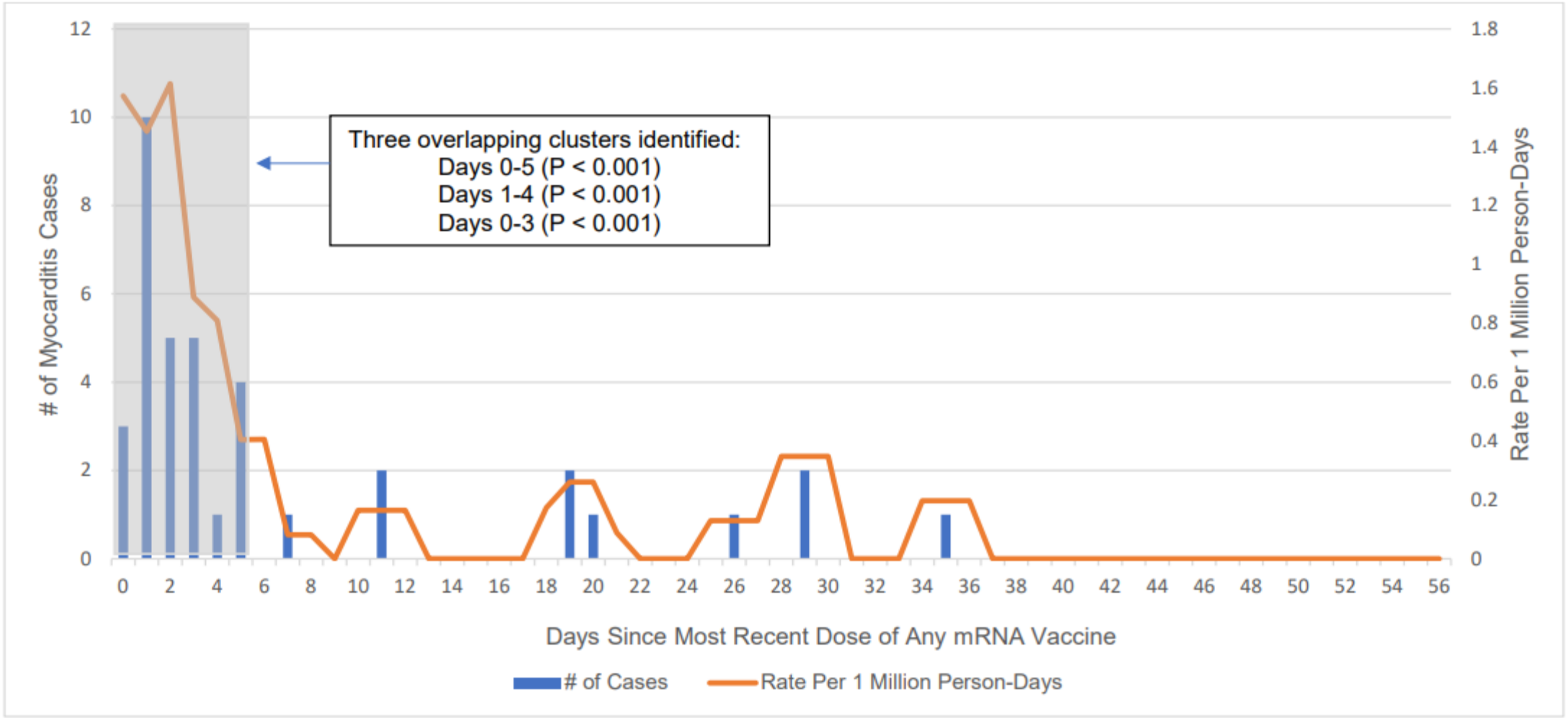
Post-hoc review of members 12-29

34 cases of confirmed myocarditis/pericarditis

Median 24 years (13 - 29)

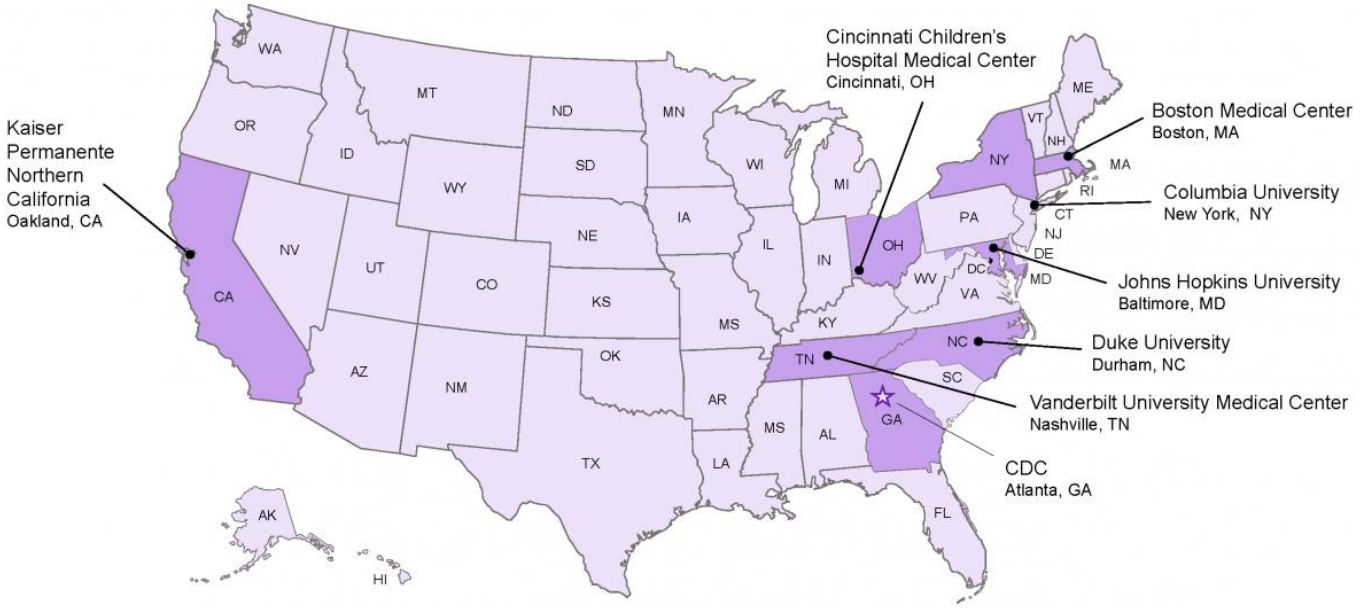
Mostly (85%) male

Most (82%) hospitalized – median length of stay 1 day



Blue bars denote number of cases of medical-record confirmed myocarditis/pericarditis during days 0-56 after either dose of an mRNA vaccine. Orange line represents the rate of confirmed myocarditis/pericarditis per 1 million person-days. The rate is a moving 3 day mean. Clusters were identified using Kulldorff's scan statistic [17].

Clinical Immunization Safety Assessment (CISA)



A longstanding partnership between CDC and seven medical research centers that provides expert consultation and conducts clinical research on vaccine-associated health risks

Dedicated CISA COVIDVax program launched December 2020

Since December, there have been daily check-ins (7 days a week) to discuss emergent vaccine safety concerns from across the US

Several trials underway/planned:

- Maternal and pediatric cohorts
- RCT of concomitant vs serial vaccine

Summary

- The vaccine development process includes multiple stages and review processes. These were modified to maximize efficiency during COVID vaccine development, but no corners cut
- Based on published clinical trials, COVID-19 vaccines are efficacious, safe and immunogenic
- Post-licensure (EUA) safety surveillance has identified rare adverse events after COVID vaccines
  - Anaphylaxis
  - Myocarditis
  - TTS

QUESTIONS?

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