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COVID-19 Vaccination for Children Aged 6 months to 5 Years

Monkeypox, Worldwide, 2022

Genevieve Buser, MDCM
Providence St Vincent
19 July 2022

Conflicts of interest

- Grant from Gilead Foundation for Hepatitis C prevalence study

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COVID-19 vaccination "Little" Pediatric update ACIP 17 June 2022

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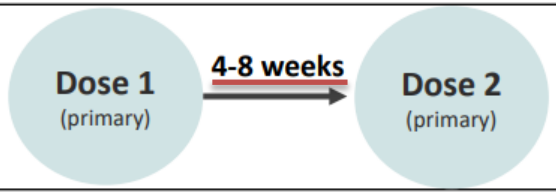
New Emergency Use Authorization

Children who are NOT moderately or severely immunocompromised

Pfizer-BioNTech
(6 months–4 years)

Moderna
(6 months–5 years)



Children who ARE moderately or severely immunocompromised

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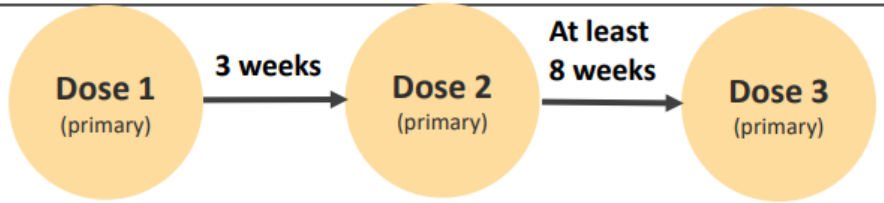
(6 months–4 years)



Moderna
(6 months–5 years)

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Moderna vaccine
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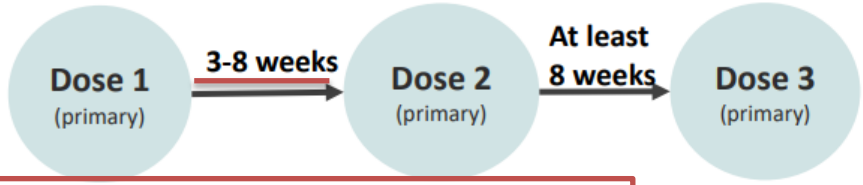

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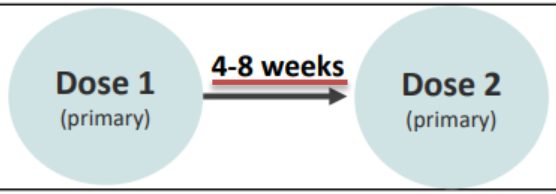
(6 months–5 years)



Children who ARE moderately or severely immunocompromised

Pfizer-BioNTech
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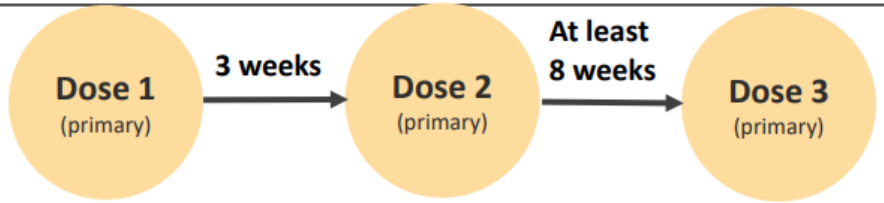


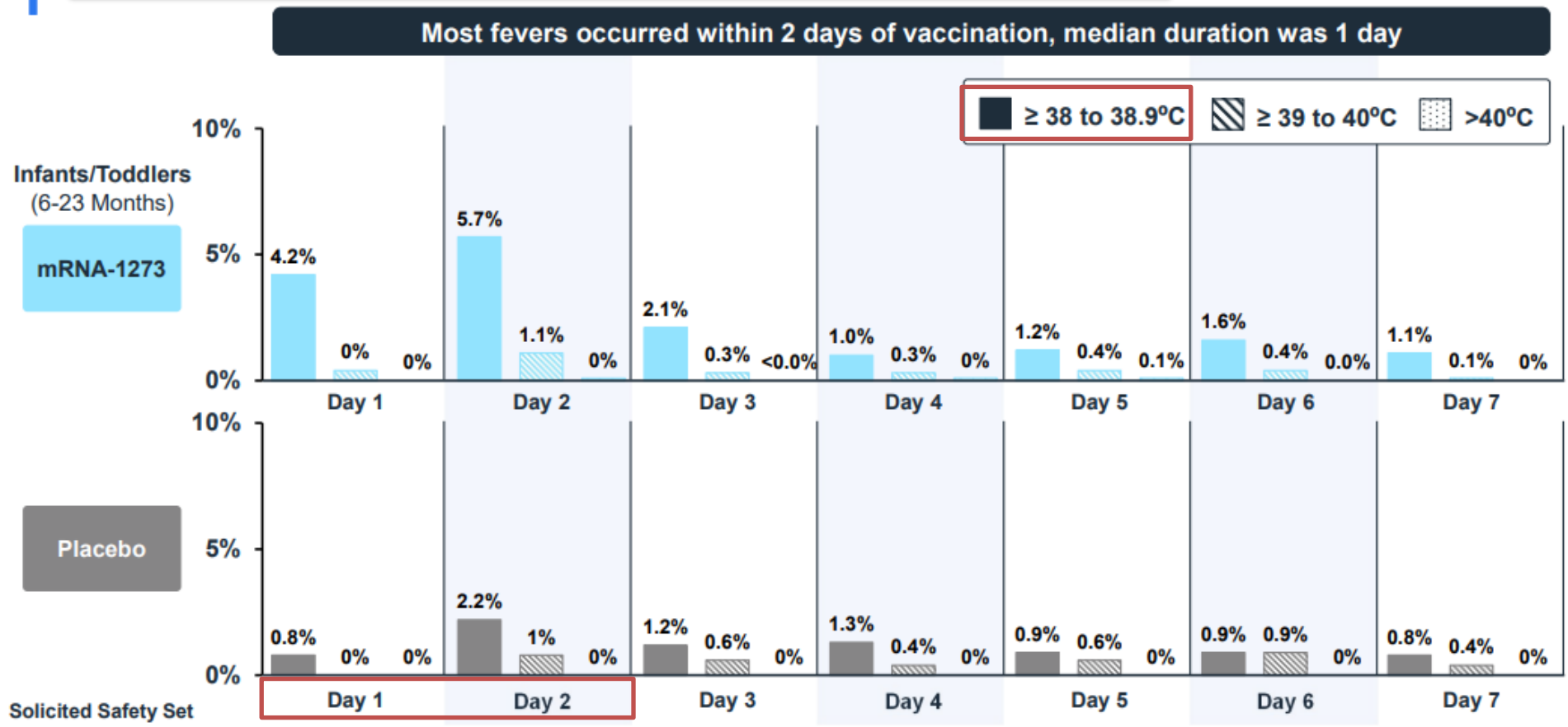
Moderna
(6 months–5 years)

Moderna safety and efficacy in age 6m–5y

- Data presented by ModernaTx
- Safety N>6,400 25µg 6m–5yr x 12 months (data thru May 2022)
  - Solicited, unsolicited (28d), serious & MIS-C (1 yr)
  - Asked specifically about s/s of myocarditis/pericarditis
  - Median follow-up post-dose 2: 2.5 months
- Met immunogenicity endpoints, equivalent to 18–25yo
  - 6-8% baseline seropositive or day1 SARS-CoV-2 +PCR:
    - >>>higher geometric mean post-vaccine
    - Slightly more fever after dose 1; no diff after dose 2

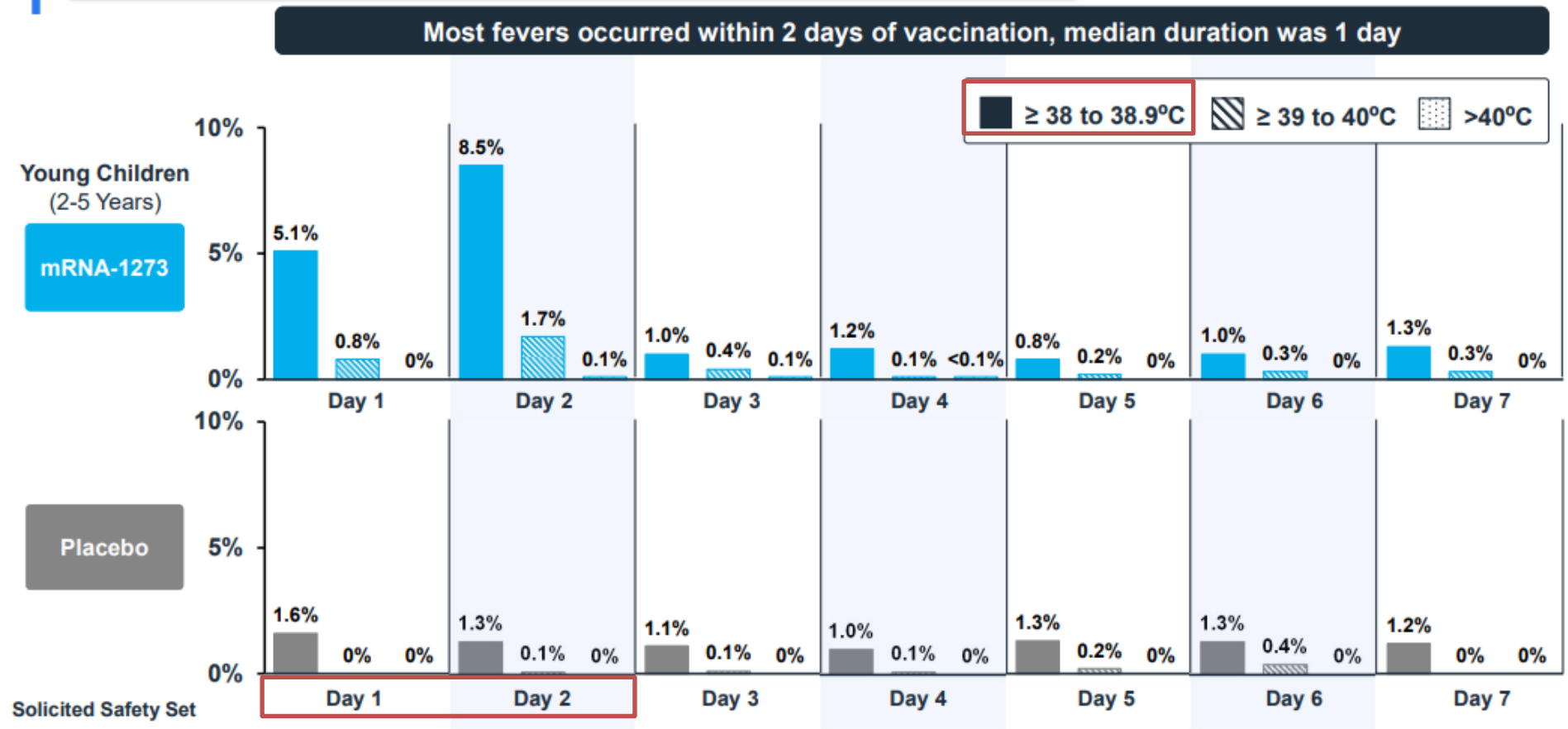
Fevers by Day and Temperature, Post-Dose 2

Study 204 (Part 2): Infants/Toddlers (6-23 Months)



Fevers by Day and Temperature, Post-Dose 2

Study 204 (Part 2): Young Children (2-5 Years)



Fevers (>40°C or >104°F) within 7 Days of Any Injection

Study 204: Infants/Toddlers (6-23 Months) and Young Children (2-5 Years)

	Young Children (2-5 Years) 25 µg		Infants/Toddlers (6-23 Months) 25 µg	
After Any Dose	**mRNA-1273** N = 3,016	**Placebo** N = 1,007	**mRNA-1273** N = 1,758	**Placebo** N = 585
Fever, % (n)	**0.4%** (11)	**0.2%** (2)	**0.2%** (4)	**0.2%** (1)

- Duration of peak temperature >40°C lasted <1 day
- 15 events in vaccine recipients
  - 6 had symptoms of concurrent viral infections
- One febrile seizure considered related to vaccination reported in a 17- month old 2 days postdose 1
  - Fever to 103.1ºF
  - Child developed a maculopapular rash 2 days after the febrile seizure
  - Received 2nd dose without event

Sensitivity Analyses of Efficacy Against Symptomatic COVID-19

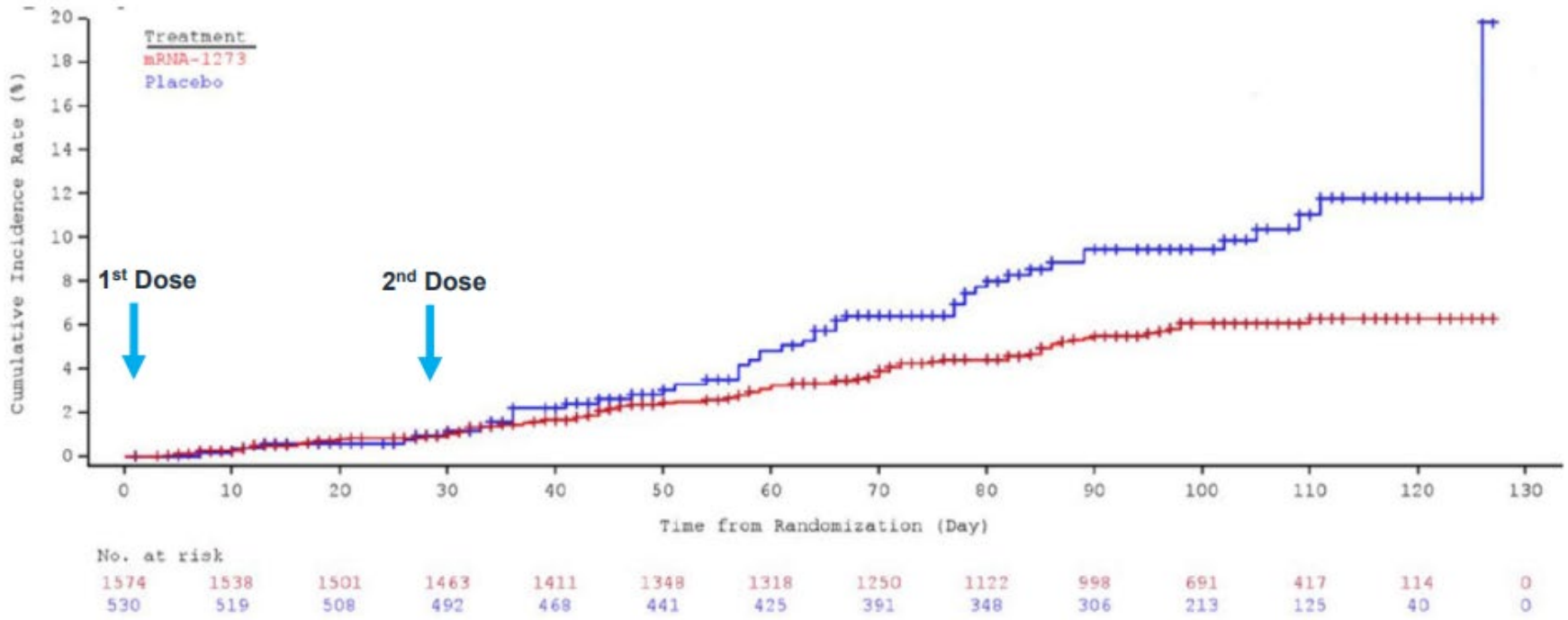
Study 204 (Part 2): Infants / Toddlers (6 - 23 Months), Per Protocol, ≥14 Days Post-Dose 2

	mRNA-1273 25 µg	Placebo
CDC case definition of COVID-19		
Cases, n/N (%)	74/1,512 (4.9%)	52/513 (10.1%)
Incidence rate per 1000 person-years (95% CI)	202	434
VE (%) based on incidence rate (95% CI)	**53.5%** (32.4, 67.9)	
301 case definition of COVID-19		
Cases, n/N (%)	51/1,512 (3.4%)	30/513 (5.8%)
Incidence rate per 1000 person-years (95% CI)	138	246
VE (%) based on incidence rate (95% CI)	**43.7%** (8.5, 64.8)	

CDC case definition: 1 systemic or 1 respiratory symptom + **any positive COVID-19 test (including home tests)**
301 case definition: 2 systemic or 1 respiratory symptom + **any positive COVID-19 test (including home tests)**

Cumulative Incidence Curve of COVID-19 Starting after Dose 1 (CDC Case Definition)

Study 204 (Part 2): Infants & Toddlers (6-23 Months), miTT1 Set



Efficacy Against Symptomatic COVID-19 During Omicron Period

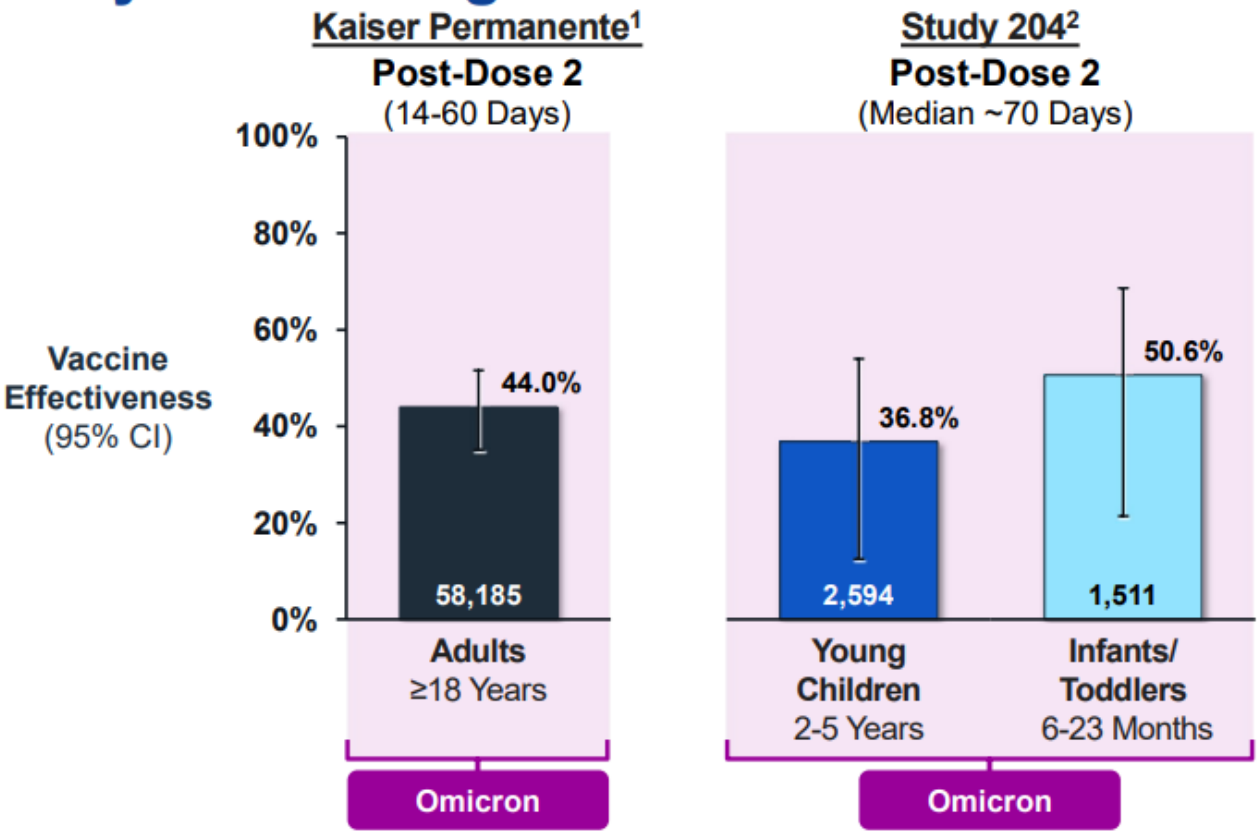
Study 204 (Part 2): Young Children (2 - 5 Years), Per Protocol, ≥14 Days Post-Dose 2

	mRNA-1273 25 µg	Placebo
CDC case definition of COVID-19		
Cases, n/N (%)	119 / 2,594 (4.6%)	61 / 858 (7.1%)
Incidence rate per 1000 person-years (95% CI)	175 (145, 209)	277 (212, 356)
VE (%) based on incidence rate (95% CI)	**36.8%** (12.5, 54.0)	
301 case definition of COVID-19		
Cases, n/N (%)	71 / 2,594 (2.7%)	43 / 858 (5.0%)
Incidence rate per 1000 person-years (95% CI)	104 (81, 131)	194 (140, 261)
VE (%) based on incidence rate (95% CI)	**46.4%** (19.8, 63.8)	

CDC case definition: 1 systemic or 1 respiratory symptom + positive RT-PCR
301 case definition: 2 systemic or 1 respiratory symptom + positive RT-PCR

71 days median follow-up post-dose 2 in Part 2 for both groups combined

Real-World Effectiveness (Kaiser Permanente) Compared to Study 204 During Omicron Period



1. Tseng HF et al, 2022; Vaccine Effectiveness against infection
2. Study 204 – Vaccine Efficacy based on CDC Definition

Summary of Moderna COVID-19 Vaccine

Study 204: Infants, Toddlers and Young Children (6 Months - 5 Years)

Safety (Primary Objective)	▪ mRNA-1273 was generally well-tolerated in this age group
	  ▪ Local and systemic reactions lower than older children and adults
	  ▪ Fever in ~25% of participants, mostly grade 1-2, short duration
	▪ 1 related SAE of fever/seizure within 28 days

Immunogenicity (Primary Objective)	▪ Pre-specified immunogenicity objectives met
	▪ Vaccine immunogenic, GMCs and seroresponse rates non-inferior to young adults
	  ▪ *Children (2-5 years):* GMC ratio 1.01 & difference in seroresponse rates -0.4
	  ▪ *Infants/Toddlers (6-23 months):* GMC ratio 1.28 & difference in seroresponse rates 0.7
	▪ Vaccine effectiveness successfully inferred based on immunogenicity

Efficacy (Secondary Objective)	▪ Demonstrated efficacy against COVID-19, 14 days after dose 2, during Omicron period
	  ▪ *Children (2-5 years):* 36.8% (CDC definition) & 46.4% (Study 301 definition)
	  ▪ *Infants/Toddlers (6-23 months):* 50.6% (CDC definition) & 31.5% (Study 301 definition)
	▪ Consistent with adult effectiveness against Omicron
	▪ Boosters are under evaluation

Moderna upcoming studies

- Roll-over study for age 6m–5y to give Omicron vaccine booster started late June
  - >3m interval from last vaccine dose
- Baby CoV <6m: no details, but likely to down-dose
- Testing for T-cell responses: will be testing collected blood

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Pfizer vaccine
Ages 6 months through 4 years

New Emergency Use Authorization

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Pfizer-BioNTech
(6 months–4 years)

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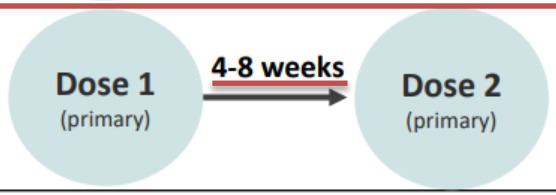

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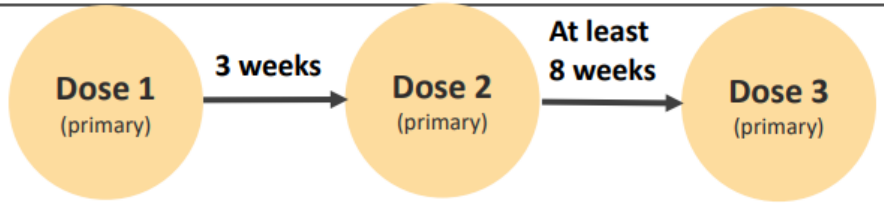

Moderna
(6 months–5 years)

Pfizer safety and efficacy in age 6m–4y

- Data presented by Pfizer
- Safety N≈4,000 3µg 6m–4yr (data thru Apr 2022)
  - Solicited, unsolicited (28d), serious & MIS-C (1 yr)
  - Asked specifically about s/s of myocarditis/pericarditis
  - Median follow-up post-dose 3: 1.3 months*
- Met immunogenicity endpoints, equivalent to 16–25yo
  - 6-23m: 8% baseline seropositivity; 2-5y: 13% baseline*
  - Required 3 doses in age 2 to <5y;
  - Median interval dose 2→3: 16wks 6-23m, 11wks 2-4y*
  - Only a portion blinded for 3rd dose*
  - 3 doses best Omicron immunity both groups

*areas of concern

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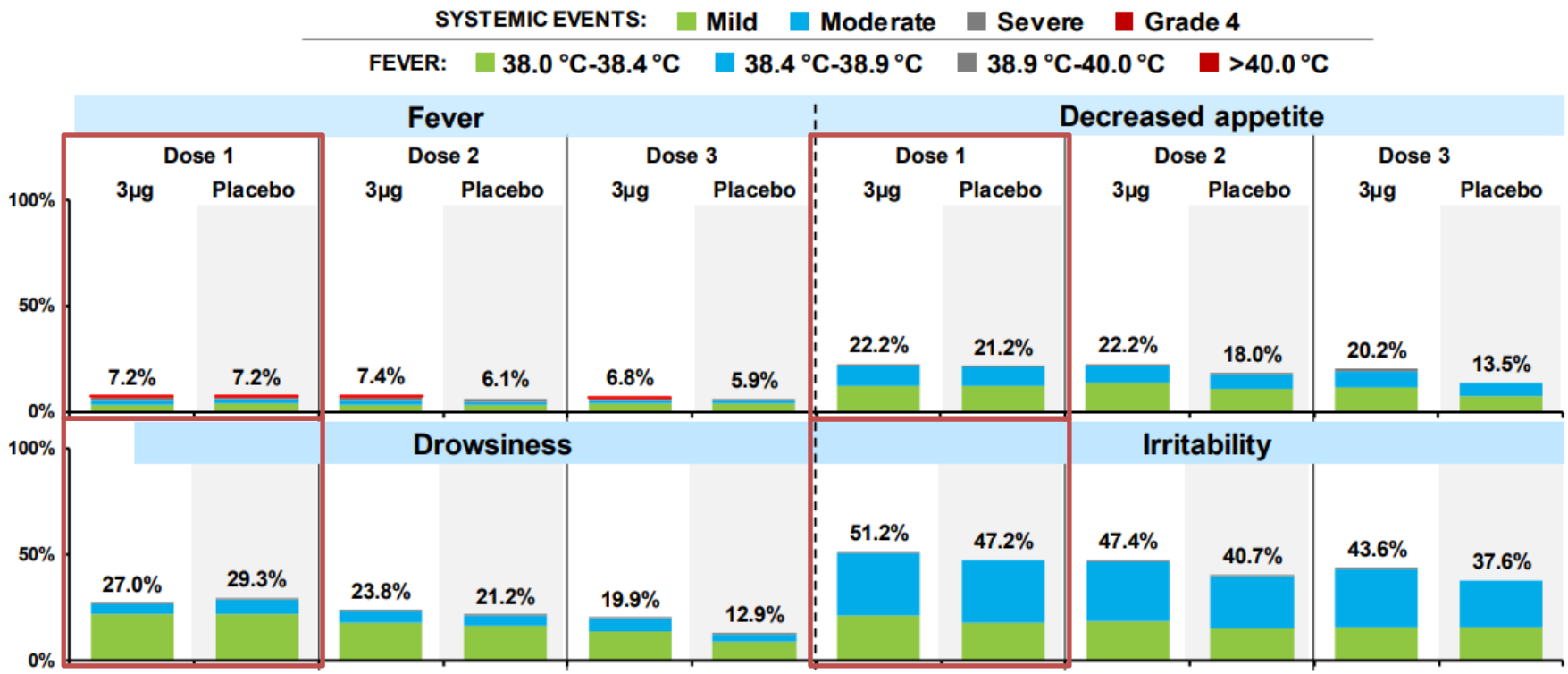
AGE
6 mo. to <2

Systemic Events Within 7 Days After Each Dose Mostly Mild to Moderate

Similar incidence seen between BNT162b2 and placebo



Decreased appetite severity definition: Mild=decreased interest in eating; Moderate=decreased oral intake; Severe=refusal to feed; Grade 4=ER visit or hospitalization
Drowsiness severity definition: Mild=increased/prolonged sleeping; Moderate: slightly subdued; Severe=Disabling/not interested in daily activity; Grade 4=ER visit or hospitalization
Irritability severity definition: Mild=easily consolable; Moderate=requires increased attention; Severe=inconsolable; Grade 4 =ER visit or hospitalization
Dose 1: N= 1768; Dose 2: N= 1738; Dose 3: N=535

CC-1

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AGE
6 mo. to <5

Few Adverse Events of Special Interest (AESIs) Were Reported

- **FDA AESIs (both age groups):**
  - Predominant categories were potential angioedema and hypersensitivity comprising mainly urticarias and rashes
  - Similar incidence between BNT162b2 and placebo for these categories
- **CDC Defined AESIs:**
  - No vaccine related anaphylaxis
  - No myocarditis/pericarditis
  - No Bell's palsy (or facial paralysis/paresis)
  - No MIS-C

CC-1

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AGE
6 mo. to <5

Vaccine Efficacy from 7 Days After Dose 2 to Before Dose 3

Evaluable Population

	6 months to <5 years		2 to <5 years		6 months to <2 years	
	Case Split (BNT162b2:Placebo)	VE (95% CI)	Case Split (BNT162b2:Placebo)	VE (95% CI)	Case Split (BNT162b2:Placebo)	VE (95% CI)
Without prior evidence of SARS-CoV-2 infection	163:113	28.3% (8.0%, 43.9%)	90:69	35.9% (11.0%, 53.7%)	73:44	16.1% (-24.9%, 43.1%)
With or without prior evidence of SARS-CoV-2 infection	173:120	27.0% (7.1%, 42.5%)	97:73	34.3% (9.7%, 52.0%)	76:47	15.6% (-24.2%, 42.1%)

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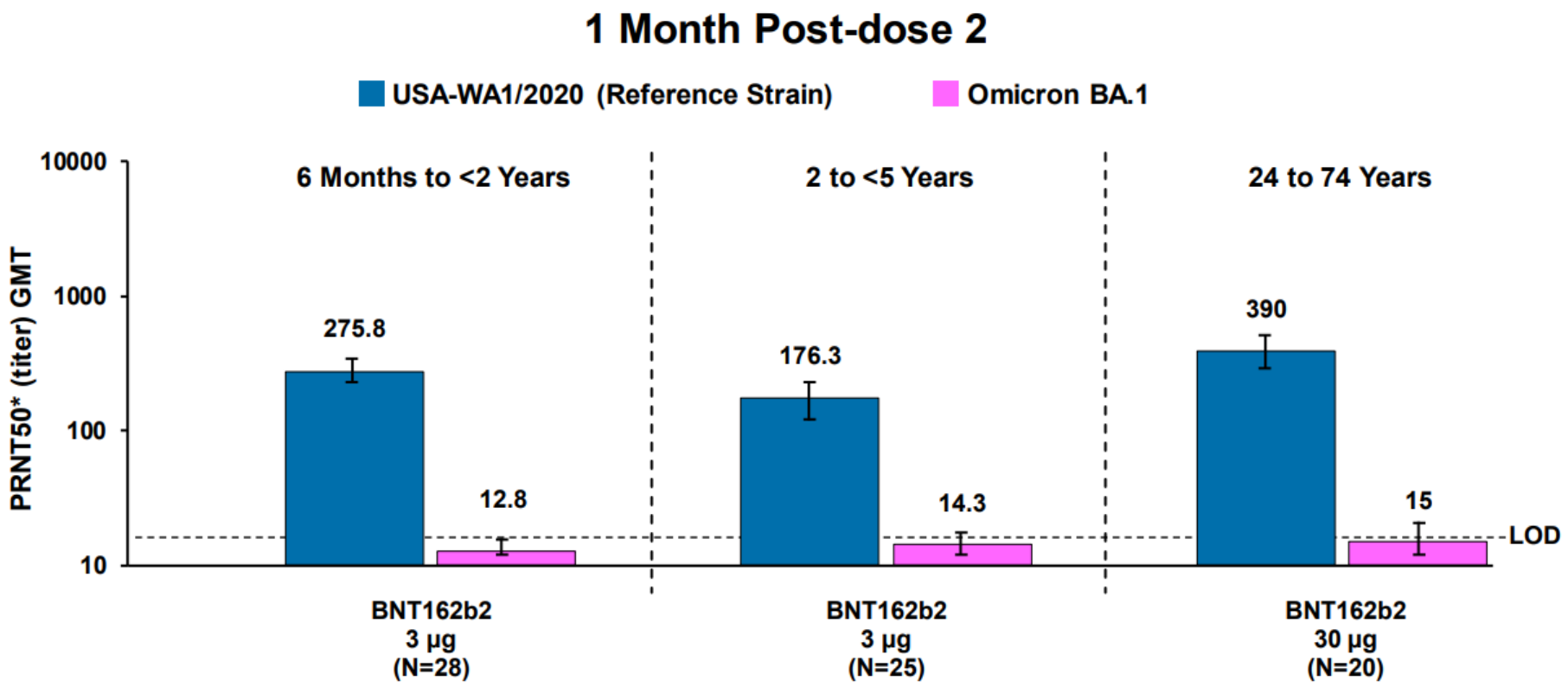
AGE
6 mo. to <5

Robust Immune Response After 2 Doses to Reference Strain with Low Immune Responses to Omicron



*PRNT50 = 50% Plaque Reducing neutralizing titers

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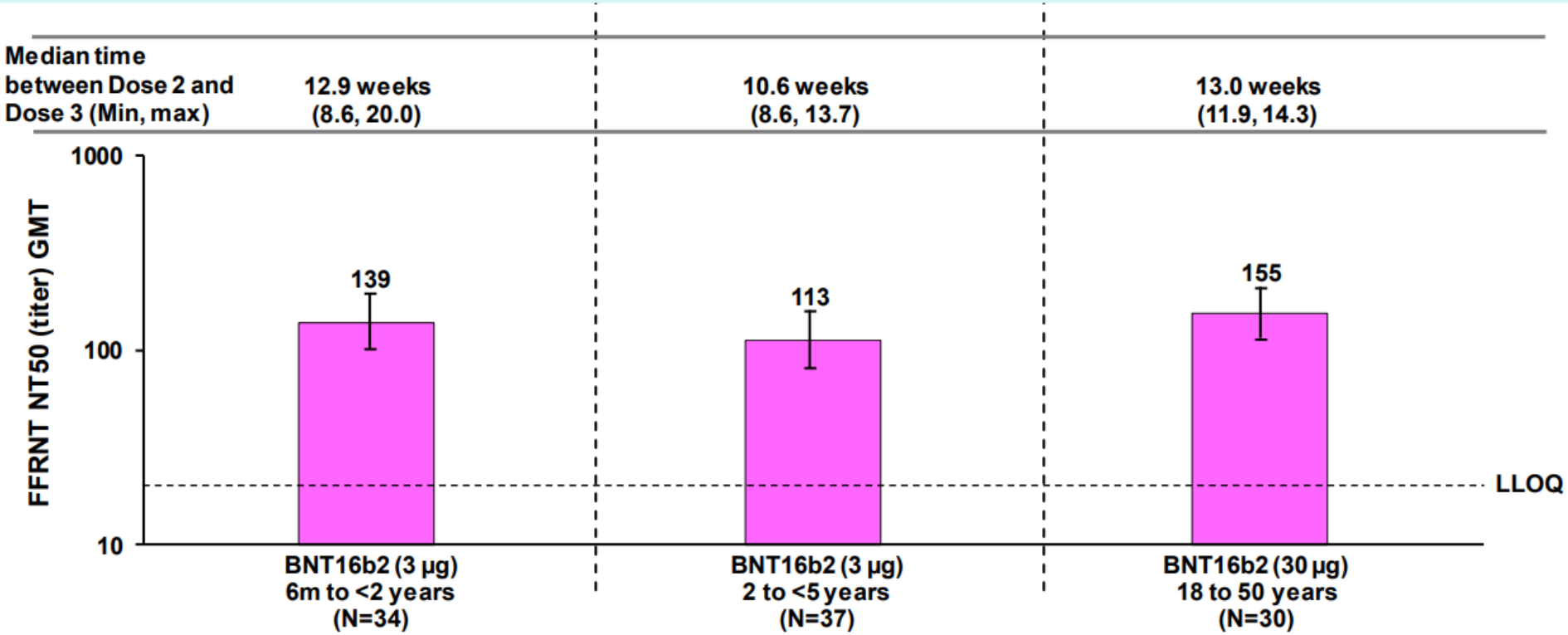
AGE
6 mo. to <5

Similar Neutralizing Responses to Omicron Observed Across Age Groups One Month After The 3rd Dose

Subjects WITHOUT evidence of existing or preexisting SARS-CoV-2 infection



CC-2

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AGE
6 mo. to <5

Vaccine Efficacy 80% Post-dose 3 During a Period When Omicron Was Predominant

Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 3

	BNT162b2 (3 µg)		Placebo			
	n / N *	Surveillance Time (n)	n / N *	Surveillance Time (n)	VE (%)	(95% CI)
6 months to <5 years	3 / 992	0.086 (758)	7 / 464	0.039 (348)	80.3 **	(13.9, 96.7)
2 to <5 years	2 / 606	0.056 (481)	5 / 280	0.025 (209)	82.3	(-8.0, 98.3)
6 months to <2 years	1 / 386	0.030 (277)	2 / 184	0.015 (139)	75.5	(-370.1, 99.6)

All the cases post-dose 3 occurred after February 7, 2022 and were confirmed to be omicron

CDC review noted: *Underpowered; **~30% of participants were seropositive at baseline; could over-estimate the efficacy of vaccine (S. Oliver, ACIP 17 June 2022, slide 44)

Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint

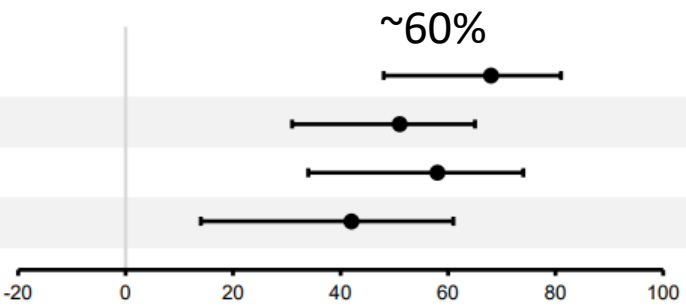
Post-authorization vaccine effectiveness

Overcoming COVID-19 platform

2 doses of Pfizer-BioNTech vaccine against hospitalization, Dec 19, 2021-Apr 27, 2022

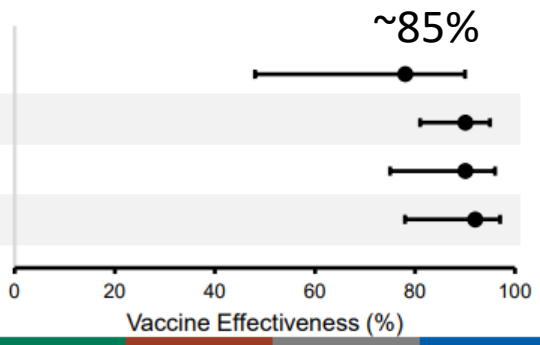
	No. vaccinated COVID-19 patients/Total COVID-19 patients (%)	Adjusted VE % (95% CI)
5–11 years*	25/325 (8)	68 (48-81)
12–18 years	109/286 (38)	51 (31-65)
2–22 weeks since vaccination	42/219 (19)	58 (34-74)
23–45 weeks since vaccination	67/244 (27)	42 (14-61)

*median time from vaccination to hospitalization is 37 days



2 doses of Pfizer-BioNTech vaccine against MIS-C, Jul 1, 2021-Apr 7, 2022

	No. vaccinated MIS-C patients/Total no. MIS-C patients (%)	Median (IQR) days from 2nd dose to MIS-C	Adjusted VE (95% CI)
5–11 years	10/144 (7)	44 (32-56)	78 (48-90)
12–18 years	14/160 (9)	120 (57-169)	90 (81-95)
28-120 days since vaccination	7/153 (5)	60 (42-89)	90 (75-96)
≥121 days since vaccination	7/131 (5)	172 (138-215)	92 (78-97)



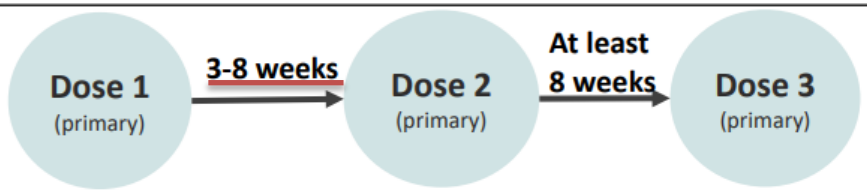
Gaps in knowledge

- Longer follow-up after 3rd dose:
  - Rare adverse side effects in this age group
- Role of longer intervals between vaccine doses
- Vaccine (real-world) effectiveness
  - Vs. severe disease and MIS-C?
- Most recommend to delay vaccination at least 3 months after natural SARS-CoV-2 infection

New Emergency Use Authorization

Children who are NOT moderately or severely immunocompromised

Pfizer-BioNTech
(6 months–4 years)



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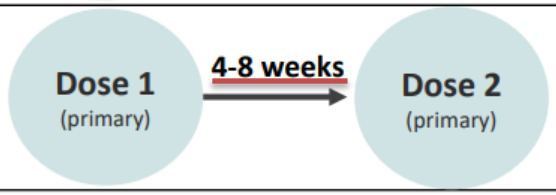

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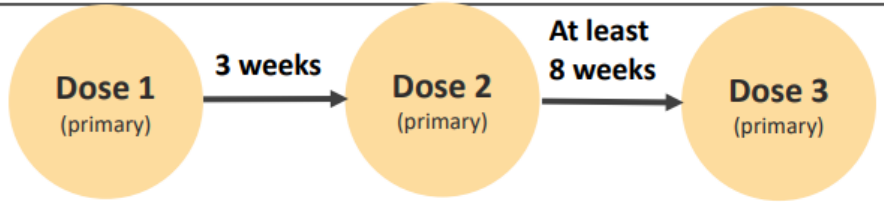

Moderna
(6 months–5 years)

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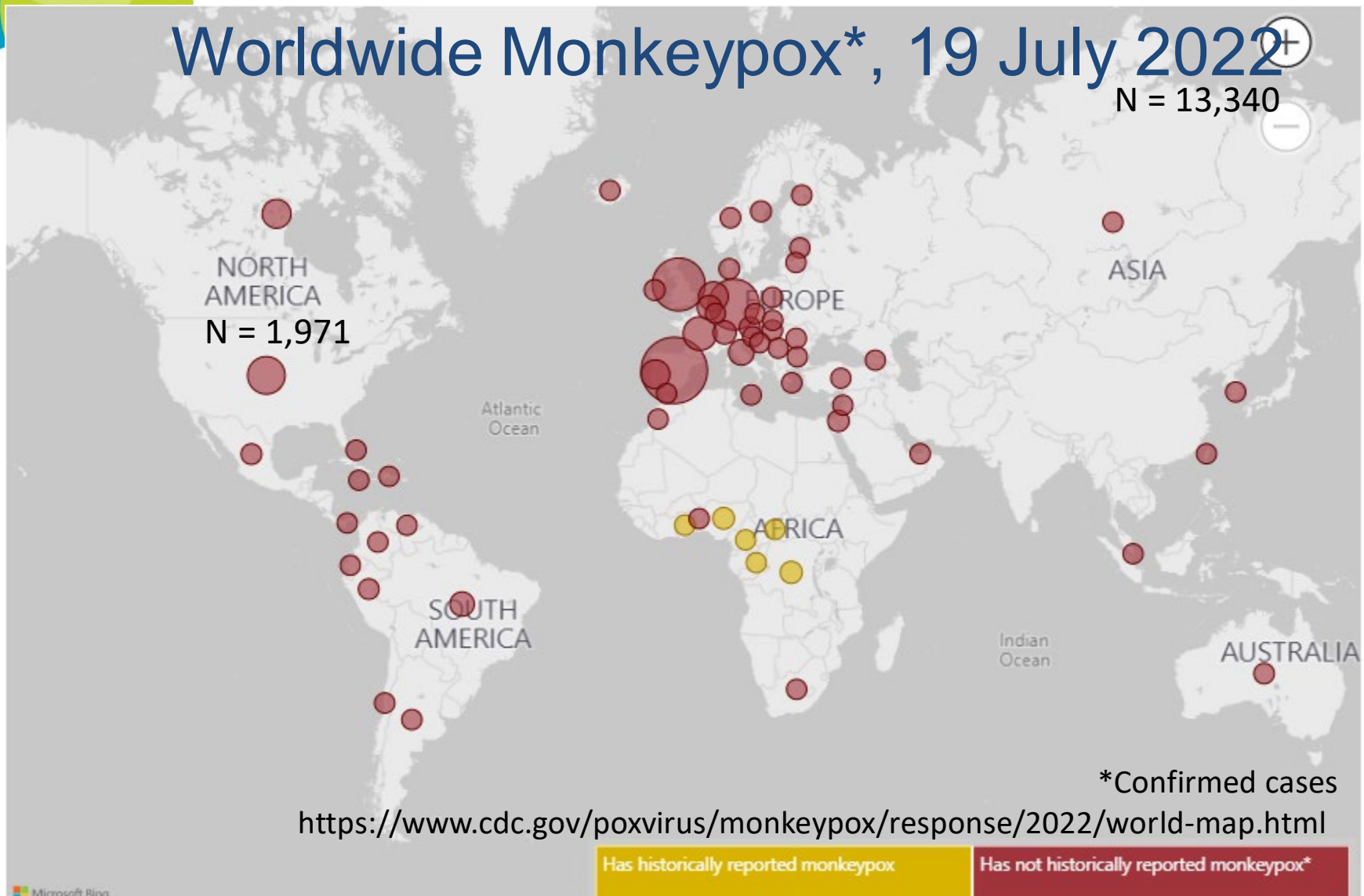
Monkeypox, Worldwide, 2022

Worldwide Monkeypox*, 19 July 2022



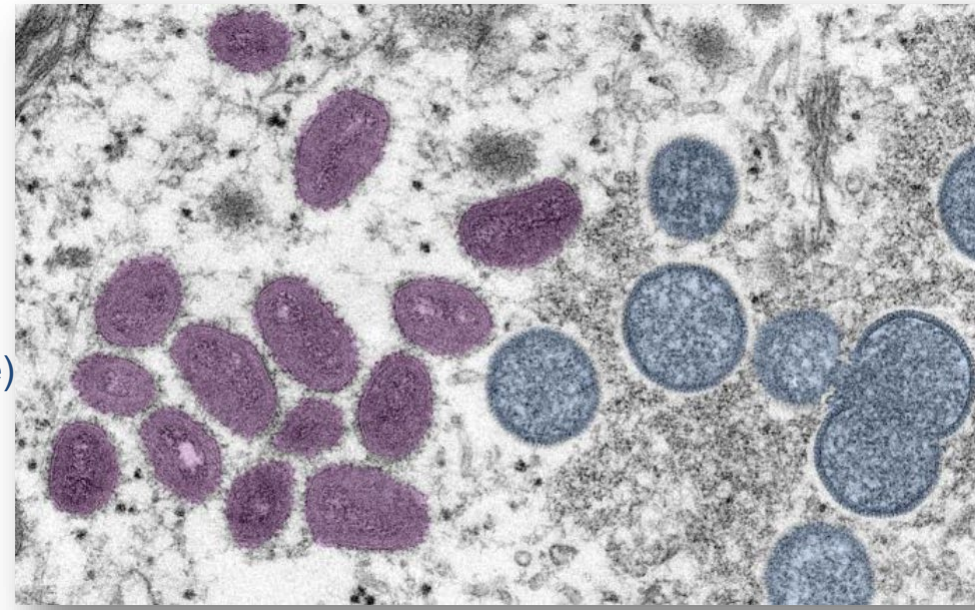
*Confirmed cases

https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html

Current worldwide outbreak details:

- Index cases in UK: 7, 12, 16 May 2022
  - Travel-associated: 1
  - Family cluster of unknown etiology: 3
  - STI clinics: 4
- US index case: 17 May 2022, MA via Canada
  - 305 cases; 28 states, DC (28 June)
  - 271 male sex at birth; 5 female sex at birth
  - 36 yrs (20–76 years)
  - 99% male to male sexual contact
  - CC: tenesmus
- Importation → local transmission

Oregon cases



- As of 19 Jul 2022
- 25 cases (4 confirmed, 21 presumptive)
- Onset June 7 to July 10
- 25 males
- Counties: Lane (7), Multnomah (12), Washington (5), Clackamas (1)
- Evidence of community transmission
- Expect more cases: currently in incubation period of “super-spreader” events

https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/DISEASESAZ/Pages/Orthopoxviruses.aspx

CDC Photos. Monkeypox virus particles. **Photo Credit:** Cynthia S. Goldsmith, Russell Regnery

What do we know about monkeypox?

- Large Family: *Poxviridae*; Genus: *Orthopoxvirus*
- Ancient double-stranded DNA virus family
- Historical: Zoonotic reservoir, imported animals, travel
- Current: Intimate human contact + travel
- Variants to Nigerian 2017 strain (aka West African clade III)
- Transmission: R_0?
  - Close contact with lesions or body fluid, including sexual transmission (2019 Ogoina D et al, PLoS ONE)
  - Contaminated patient environment or items
  - Respiratory droplets

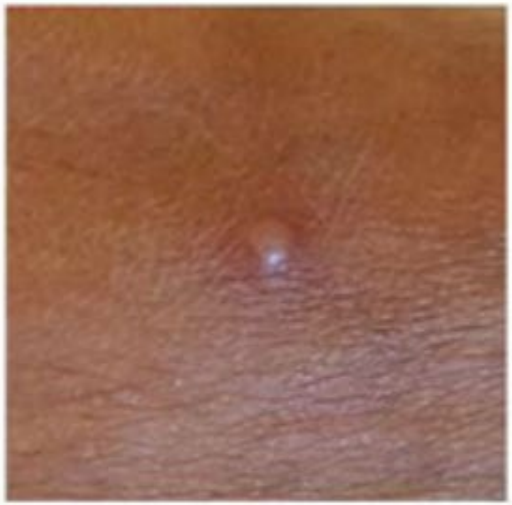
Alakunle E et al. Viruses 2020

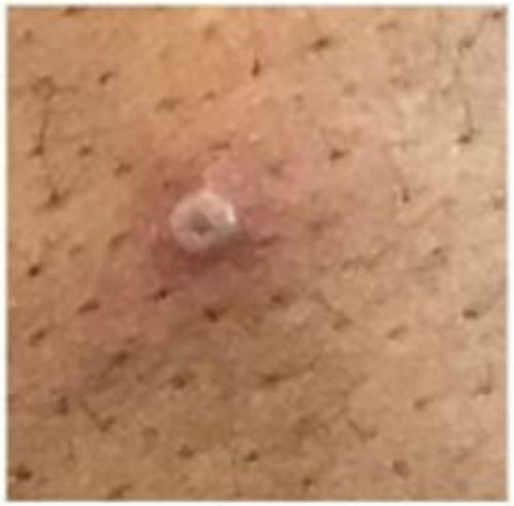
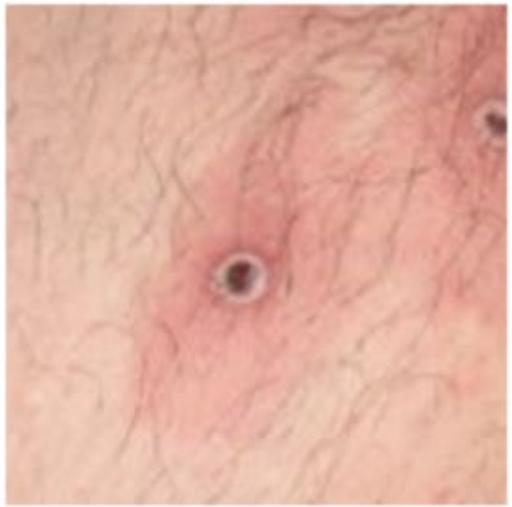
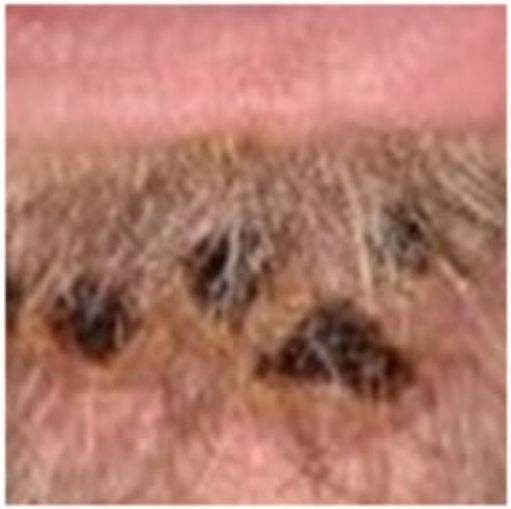
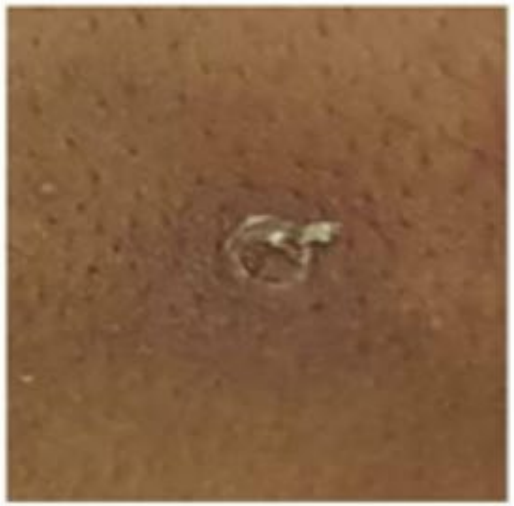
What does monkeypox look like?

- Incubation: 7-14 days (range: 4-21)
- Prodrome: Fever, headache, myalgia, lymphadenopathy, chills, exhaustion
- Rash 1–10 days later face → body: Deep pea-sized papule → pustule → umbilication → scab → healing
- Duration: 2-4 weeks
- Current outbreak has non-classical features:
  - Fewer lesions, more isolated crops
  - Absent fever, lymphadenopathy or delayed after rash
  - Co-infections with other sexually transmitted infections

More Monkeypox Rash Photos

Photo credit: UK Health Security Agency



https://www.cdc.gov/poxvirus/monkeypox/symptoms.html

Examples of Monkeypox Rashes

Photo Credit: NHS England High Consequence Infectious Diseases Network

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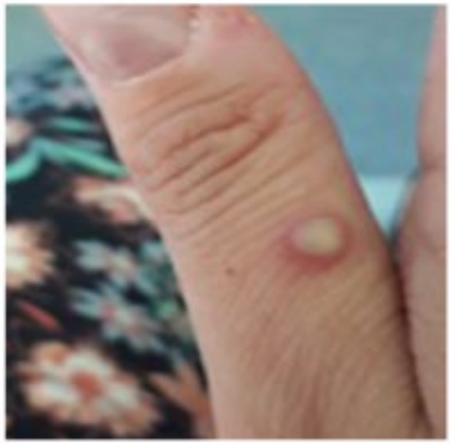

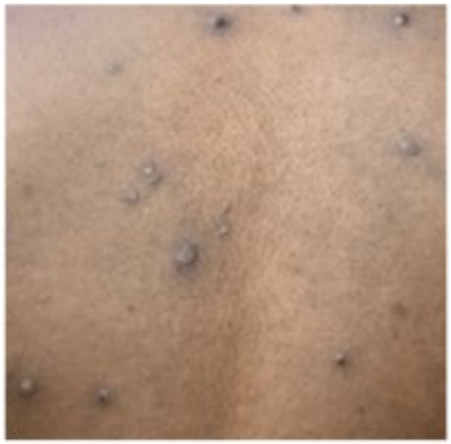

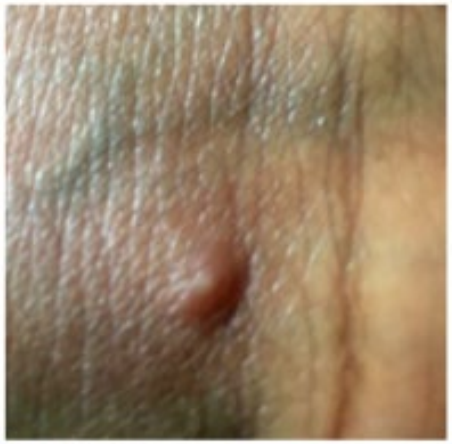

https://www.cdc.gov/poxvirus/monkeypox/symptoms.html

Monkeypox differential

- Syphilis (“the great pox”)
- Herpes
- Shingles or Varicella (varicella zoster)
- Molluscum contagiosum
- Staphylococcal pustule, folliculitis
- Wart, human papilloma virus
- Chancroid
- Lymphogranuloma venereum
- Granuloma inguinale
- Vaccinia (e.g., from live virus vaccine inoculation)
- Orf virus, sporotrichosis…
- Friction blister

Outcomes

- 1970s: 83% <10 years old, rare secondary transmission
  - <8 years, pregnant, immunocompromised risk for death
- 2017-2019 Nigerian outbreak*, N=21
  - 17 adults, **17 males**
  - Age range 6-45 years (**med 29**, IQR 22, 33)
  - 13 hospitalized, 8 outpatient
  - One pregnant women, 1st trimester, **fetal demise**
  - **10/21 with genital ulcers**
  - 8 with lab testing: 2 HIV+, 2 VDRL+, 2 VZV+
  - One suicide
  - **High secondary transmission rate:"[…] noteworthy that a substantial number of our cases who [*sic]* were young adults in their reproductive age presenting with genital ulcers, as well as concomitant syphilis and HIV infection."**

*final 68 confirmed, 197 suspected

Ogoina et al 2019 PLoS ONE

Case definitions

- Confirmed: *Monkeypox virus* DNA or culture
- Probable: *Orthopoxvirus* DNA or Ig M positive*
- Suspect: New characteristic rash OR epi + clinical suspicion
- Epidemiology: Within last 21 days:
  - Contact with persons with confirmed or probable or suspect monkeypox (including social networks)
  - Travel
  - Contact with wild animals (dead or alive) endemic to Africa

*without exposure to vaccine

What to do if you suspect monkeypox?

- Don gown, gloves, mask (prefer N95), eye protection
- Mask patient, keep exam room door closed, universal precautions
- Ask about epidemiologic exposures, contacts, risk (e.g., HIV positive)
- Perform thorough skin and mucosal exam for rash
- *Get photos*
- Call local health department to review epi & report suspect case
- Testing: *Orthopoxvirus* testing RT-PCR at OSPHL or Private Lab
- Test for other sexually transmitted disease
- PEP or treatment: Consult with LHD/OHA; they consult with CDC
- Have patient document all close contacts last 21 days
- Educate: No close/sexual contact until lesions completely gone (follow-up)
- Exposed: No sexual/close contact x 21 days from last exposure
- Avoid close contact with animals

Medical countermeasures

- Vaccines
  - JYNNEOS (IMVAMUNE, IMVANEX, MVA)
    - Live, attenuated, non-replicating vaccinia virus
  - ACAM2000
    - Live, replicating vaccinia virus
- Treatment
  - Tecovirimat
  - Vaccinia Immune Globulin IV
  - Cidofovir
  - New drugs

Who gets monkeypox vaccine?

- Pre-exposure prophylaxis:
  - Laboratorians or clinicians who test for or work with orthopoxviruses
  - Certain healthcare and public health response team members designated by public health authorities
- Post-exposure prophylaxis:
  - High degree of exposure: PEP recommended
  - Intermediate: Shared clinical decision-making
  - Low: brief and PPE, PEP not recommended
- Contraindications: Atopic dermatitis, immunosuppression, pregnancy, aged <1 yr, and others

https://emergency.cdc.gov/coca/calls/2022/. Accessed 29 June 2022

New vaccine strategy: (PEP)++

- Monkeypox vaccine post-exposure prophylaxis
- Vaccinate now people with risk factors for recent exposure
- PEP without the confirmed exposure piece
- Being used in Montreal, UK
- Focus on communities using HIV PrEP

https://emergency.cdc.gov/coca/calls/2022/. Accessed 29 June 2022

Medical countermeasures

- Vaccines
  - JYNNEOS (IMVAMUNE, IMVANEX, MVA)
    - Live, attenuated, non-replicating
  - ACAM2000
    - Live, replicating
- Treatment
  - Tecovirimat
  - Vaccinia Immune Globulin IV
  - Cidofovir
  - New drugs

What can be used to treat monkeypox?

- Those with expanded IND for use for MPXV, available via CDC from the national stockpile
  - Tecovirimat
    - Antiviral for smallpox, ≥3kg
    - Blocks release of intracellular virus from cell
  - Vaccinia virus IG
  - Cidofovir
    - Inhibits viral DNA polymerase
- Trifluridine eye drops (Viroptic, used for HSV disease)
- Brincidofovir: for smallpox; IND under development

Who gets treatment?

- In consultation state health department (who consults CDC)
- Severe disease:
  - Hemorrhagic, confluent lesions, sepsis, encephalitis
- Risk of severe disease:
  - Young age, pregnant or breastfeeding, atopic dermatitis, severe immune compromise
- In special sites:
  - Eyes, mouth, genitals, anus

How can we prevent spread of MPXV?

- Avoid all contact with lesions. Even scabs are infectious
- Do not share sleeping areas, linens, clothes, cups, utensils
- *Hand hygiene*
- Respiratory and contact precautions
- Travel to endemic countries:
  - Harm reduction with sexual contacts
  - Don’t eat “bush meat”
  - Don’t import wild animals and rodents
- Avoid encroachment on wild lands
- Don’t feed the squirrels

What don't we know?

- Natural history of current clinical presentation?
- Is there an asymptomatic but contagious state?
- Why is this outbreak different?
- How much protection from prior smallpox vaccination?
- How much will vaccines prevent infection or disease?
- How will disease epidemiology change over time?
- Is monkeypox filling a vacant immunologic niche?

What to do if you suspect monkeypox?

- Don gown, gloves, mask (prefer N95), eye protection
- Mask patient, keep exam room door closed, universal precautions
- Ask about epidemiologic exposures, contacts, risk (e.g., HIV positive)
- Perform thorough skin and mucosal exam for rash
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Oregon Health Authority Resources

Disease Reporting

What is required?

For Health Care Providers and Clinical Laboratories

Health care providers and clinical laboratories are required by law to report confirmed, probable (presumptive) and suspect cases of hMPXV to the state epidemiologist on-call **immediately, day or night** at 971-673-1111.

- Information on isolation for patients tested for hMPXV (pdf) Patient home isolation guidance

For Local Health Departments

- Monkeypox (hMPXV) Investigative Guidelines (pdf)
- CDC Orthopox Case Investigation Form (Short form) (pdf) Case investigation form
- Submitting specimens to OSPHL for Orthopox (monkeypox) testing (pdf) Specimen collection details

See Also

- Monkeypox (hMPXV) Frequently Asked Questions (pdf) FAQs
- Monkeypox (hMPXV) Frequently Asked Questions (Spanish) (pdf)
- OHA's letter to Community Based Organizations (CBOs) (pdf)
- OHA's letter to Community Based Organizations (CBOs) (Spanish) (pdf)
- Guidance for People Exposed to hMPXV (pdf) (July 13, 2022)
- Monkeypox (hMPXV) community letter (pdf) LGBQT community letter
- CDC's situation summary for 2022 Monkeypox Outbreak
- Social card: what to know about hMPXV in Oregon (English)
- Social card: what to know about hMPXV in Oregon (Spanish)

https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/DISEASESAZ/Pages/Orthopoxviruses.aspx

References, Monkeypox

- https://www.cdc.gov/poxvirus/monkeypox/
- Ogoina D, Izibewule JH, Ogunleye A et al. The 2017 human monkeypox outbreak in Nigeria—Report of outbreak experience and response in the Niger Delta University teaching Hospital, Bayelsa State, Nigeria. PLoS ONE. 2019;14:1-12. doi: 10.1371/journal.pone.0214229.
- Alakunle E, Moens U, Nchinda G, et al. Monkeypox virus in Nigeria: Infection Biology, Epidemiology, and Evolution. Viruses 2020, 12, 1257; doi:10.3390/v12111257.Line 4
- https://www.cdc.gov/poxvirus/monkeypox/clinicians/faq.html
- Isidro J, Borges V, Pinto M et al. Phylogenomic characterization andsigns of microevloution in the 2022 multi-country outbreak of monkeypox virus. Nature 2022; pre-print only.
- https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/DISEASESAZ/Pages/Orthopoxviruses.aspx

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More info:
www.cdc.gov/monkeypox

When to Refer

- Monkeypox: report to public health
- COVID vaccines: send me a message or call!

Questions?

- Phone number: 503-216-6050
- Fax number: 971-282-0102
- Genevieve.buser@providence.org

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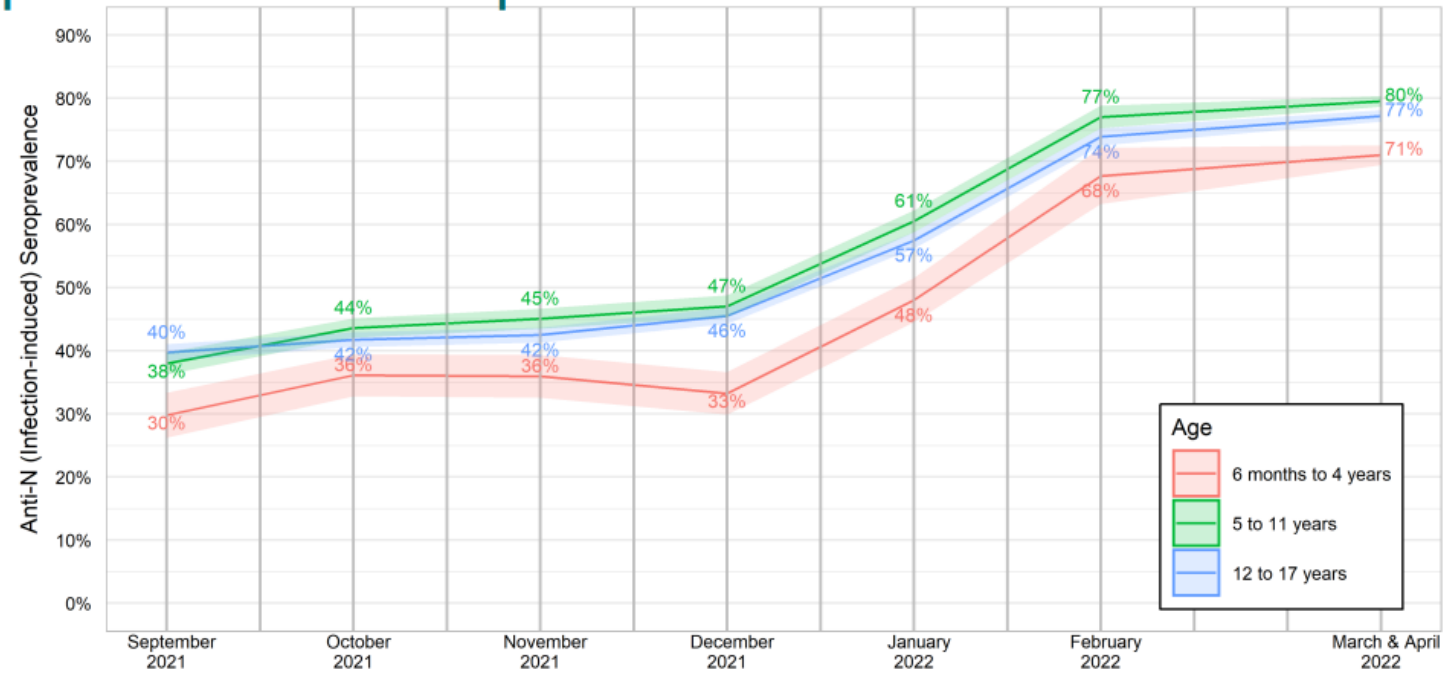
EXTRA SLIDES

Seroprevalence of infection-induced SARS-CoV-2 antibodies among children ages 6 months–17 years — National Commercial Lab Seroprevalence Study

September 2021– April 2022



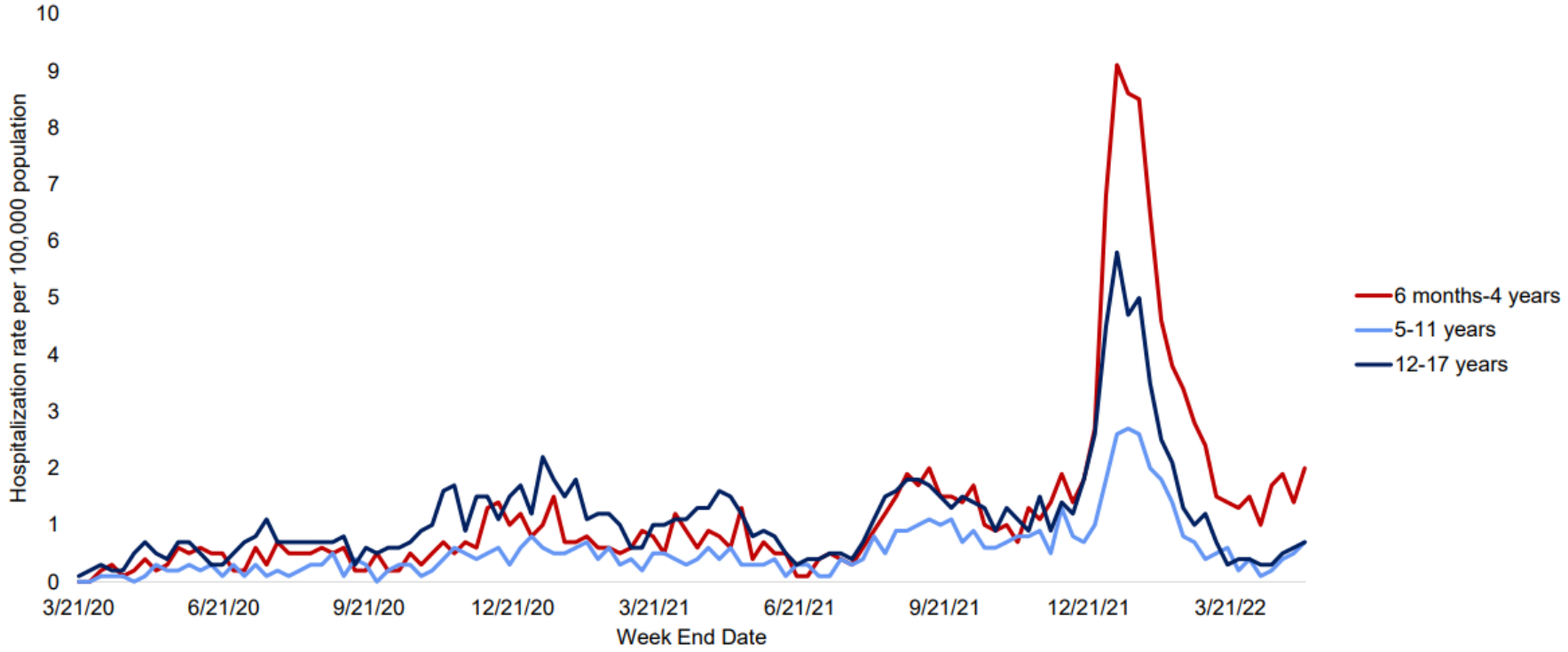
Shading indicates confidence intervals for each trend line.

Data updated for March/April 2022, based on Clarke K, Kim Y, Jones J et al. Pediatric Infection-Induced SARS-CoV-2 Seroprevalence Estimation Using Commercial Laboratory Specimens: How Representative Is It of the General U.S. Pediatric Population? (April 26, 2022). SSRN: https://ssrn.com/abstract=4092074 or http://dx.doi.org/10.2139/ssrn.4092074

COVID-19-associated hospitalizations among children and adolescents 6 months–17 years, COVID-NET

March 2020 – March 2022

Ages 6m-4y: 86% admitted primary for COVID-19.



Source: COVID-NET, https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html. Accessed May 21, 2022.

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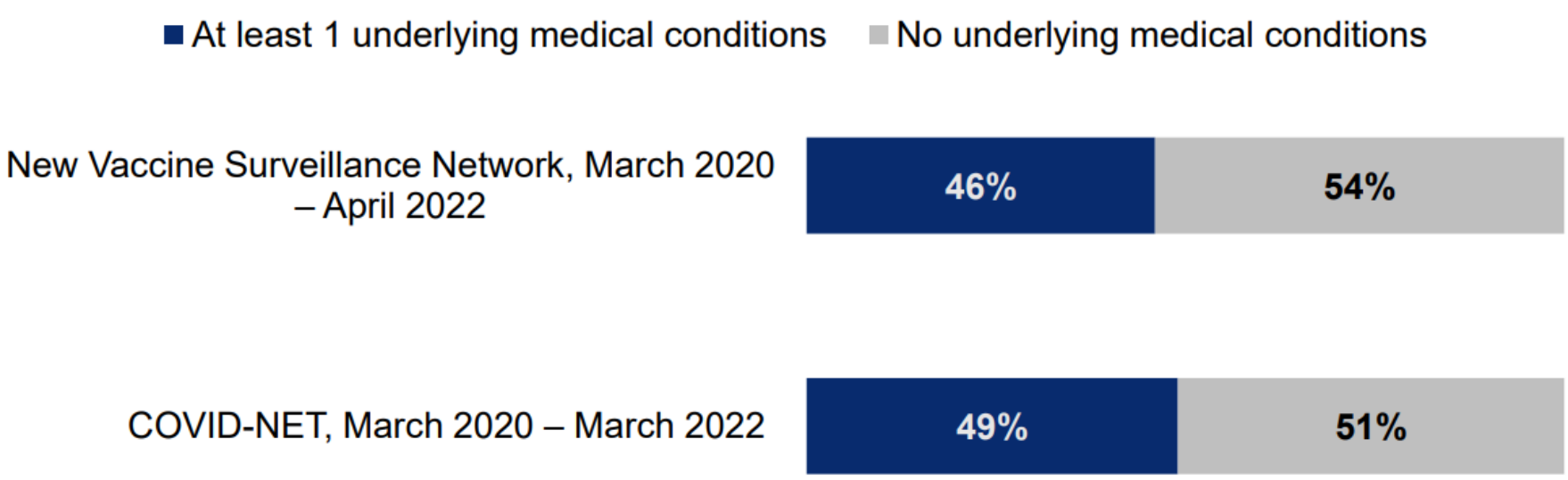
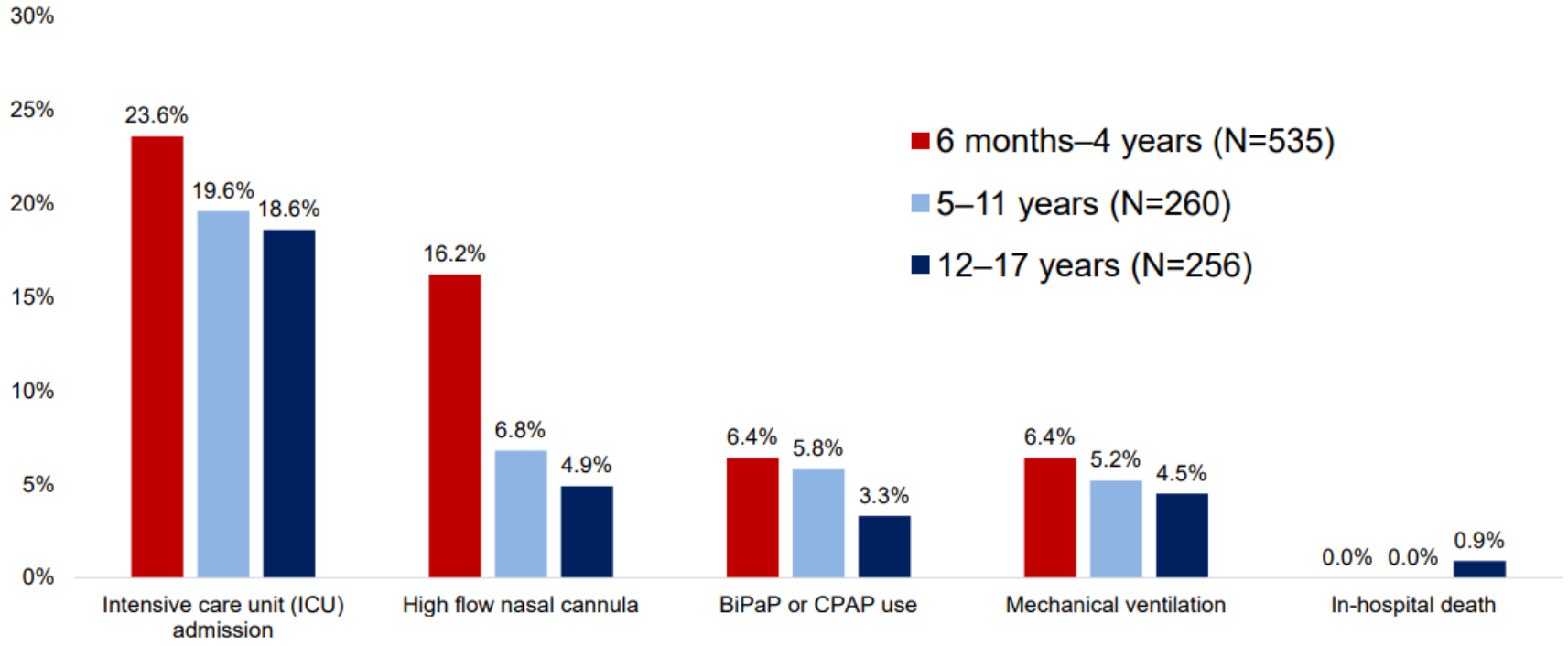
Percent of children ages 6 months–4 years with COVID-19 associated hospitalization with underlying health conditions



Source: 1. New Vaccine Surveillance Network. Preliminary data as of May 25, 2022, reflecting data from March 2020–April 2022
2. COVID-NET data. Accessed May 21, 2022, reflecting data from March 2020–March 2022

Severity of COVID-19-associated hospitalizations among children and adolescents 6 months–17 years, COVID-NET, December 19, 2021 – March 31, 2022 (Omicron period)

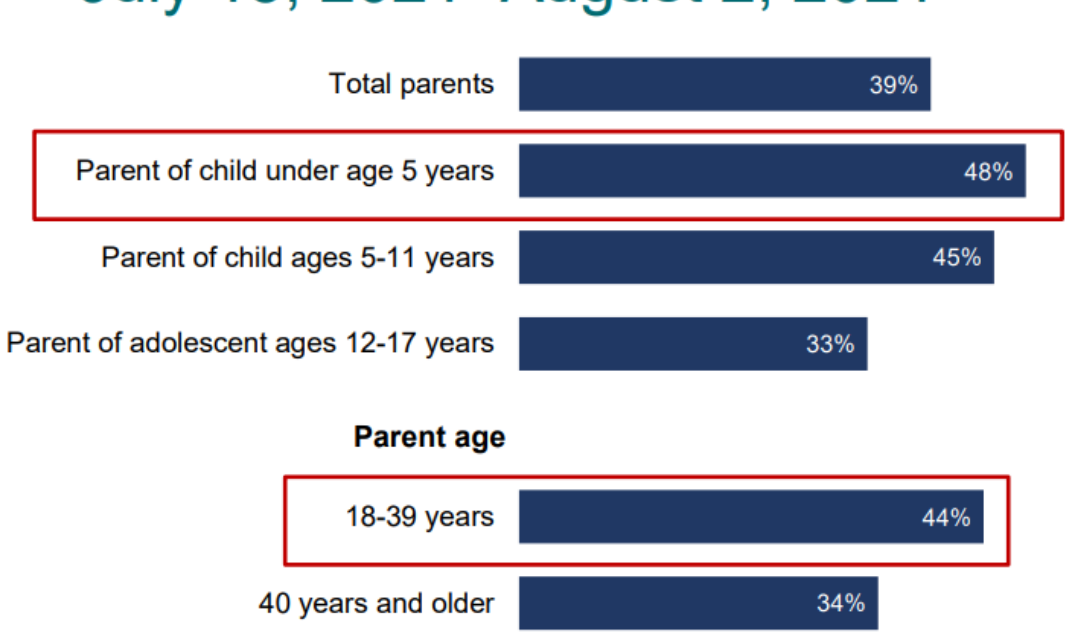


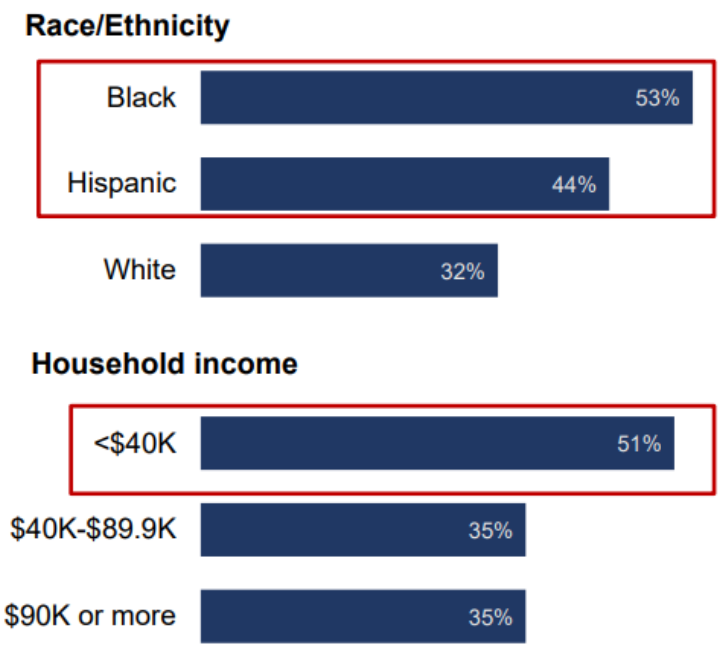
BiPAP: bilevel positive pressure, CPAP: continuous positive pressure

Source: COVID-NET data. Accessed May 21, 2022.

Percent of parents who say: In the past year, they or another adult in their household left a job or changed work schedules to take care of their children

July 15, 2021–August 2, 2021





Source: KFF COVID-19 Vaccine Monitor: The Impact Of The Coronavirus Pandemic On The Wellbeing Of Parents And Children | KFF. Accessed May 24, 2022.

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Other Pediatric Vaccine Preventable Diseases:

Hospitalizations per Year Prior to Recommended Vaccines

	Hepatitis A[1]	Varicella[2] (Chickenpox)	Vaccine-type Invasive Pneumococcal Disease[3]	COVID-19[4]
Age	**5–14 years**	**0–4 years**	**0–4 years**	**6 months–4 years**
Time period	2005	1993–1995	1998–1999	Year 1: April 2020–March 2021 Year 2: April 2021–March 2022
Hospitalization Burden (Annual rate per 100,000 population)	**<1**	**29-42**	**40** [5]	Year 1: **29.8** Year 2: **89.3**

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5603a1.htm

[2] Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. Pediatrics. 2004;114(3):786-792. doi:10.1542/peds.2004-0012

[3] Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 2005 Sep 16;54(36):893-7. PMID: 16163262.

[4] COVID-NET data, Accessed May 21, 2022.

[5] Vaccine-type invasive pneumococcal disease annual rate for children <5 years in 1998-1999 was 80 per 100,000, of which about 50% were hospitalized.

PROVIDENCE Children's Health

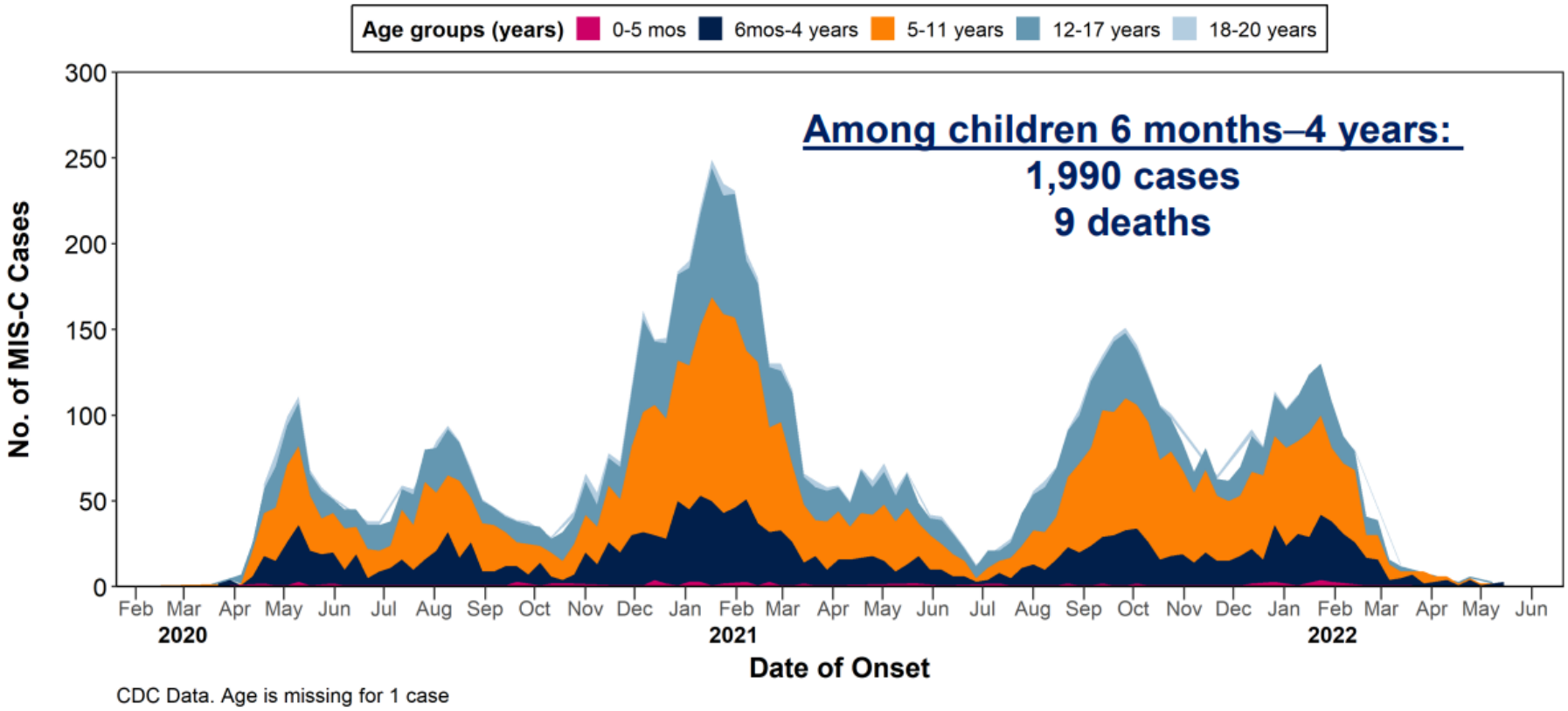
Pediatric vaccine preventable diseases: Deaths per year in the United States prior to recommended vaccines

	Hepatitis A[1]	Meningococcal (ACWY)[2]	~~Varicella[3]~~	~~Rubella[4]~~	~~Rotavirus[5]~~	COVID-19[6]
Age	**<20 years**	**11–18 years**	**5–9 years**	**All ages**	**<5 years**	**6 months – 4 years**
Time period	1990–1995	2000–2004	1990–1994	1966–1968	1985–1991	Jan 2020–May 2022
Average deaths per year	**3**	**8**	~~**16**~~	~~**17**~~	~~**20**~~	**86**

[1]Vogt TM , Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis2008; 197:1282–8.
[2]National Notifiable Diseases Surveillance System with additional serogroup and outcome data from Enhanced Meningococcal Disease Surveillance for 2015-2019.
[3]Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. J Infect Dis. 2000;182(2):383-390. doi:10.1086/315714
[4]Roush SW , Murphy TV; Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007; 298:2155–63.
[5] Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. J Infect Dis. 1996 Sep;174 Suppl 1:S5-11.
[6] https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Counts-by-Age-in-Years/3apk-4u4f/data. Accessed May 14, 2022

Weekly MIS-C case counts among persons ages 0–20 years by age group (N=8,525)

February 1, 2020 – May 31, 2022



CDC Data. Age is missing for 1 case

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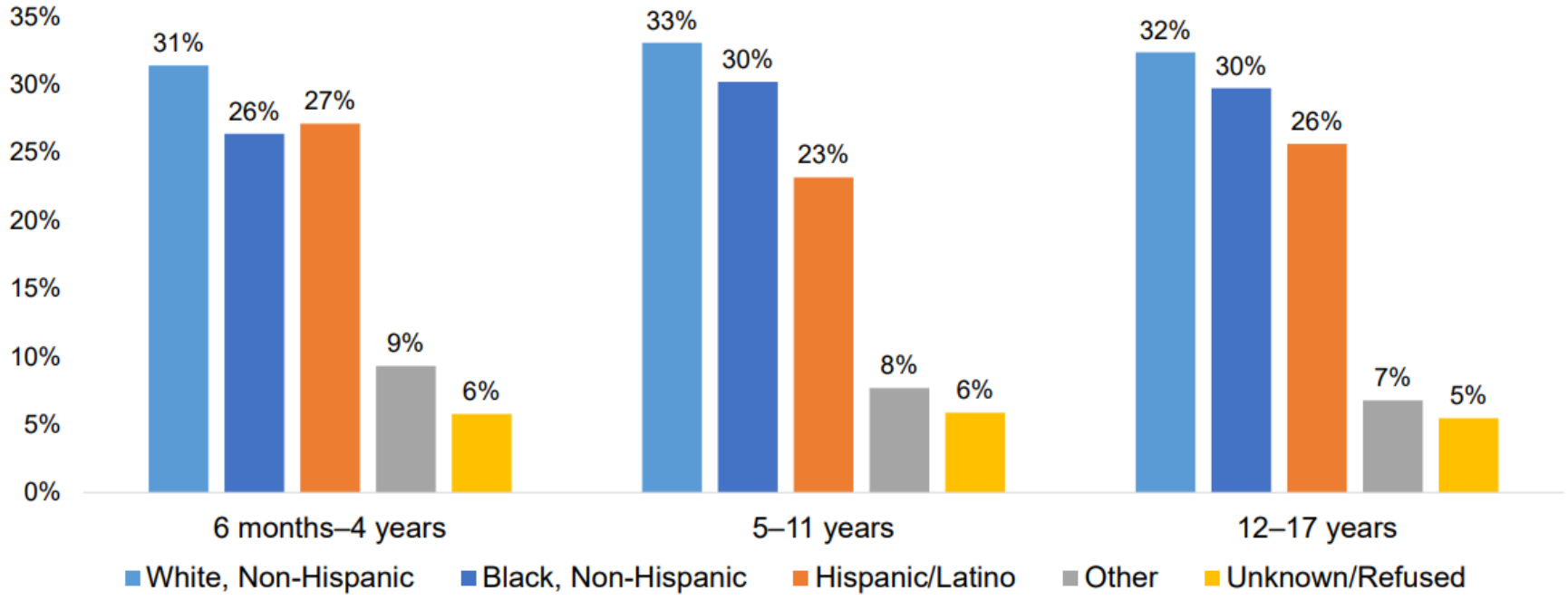
MIS-C patients by race & ethnicity for children and adolescents ages 6 months–17 years by age group

February 1, 2020 – May 31, 2022



Age is missing for 1 case.

Source: CDC data. Accessed June 7, 2022

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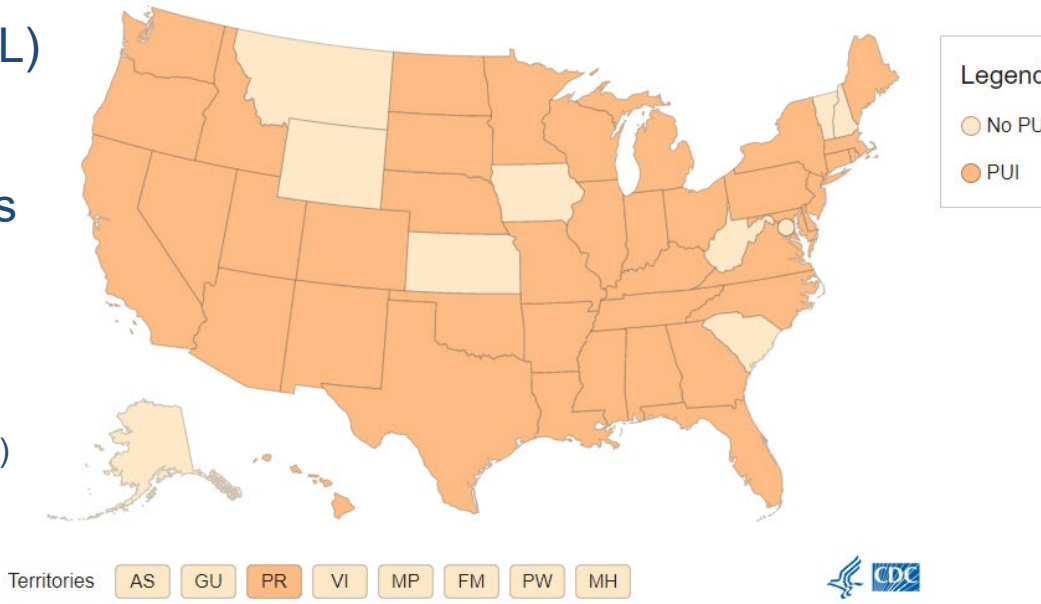
Children's Health

Hepatitis of unknown etiology among children

Person Under Investigation Definition

- Children aged <10 yrs
- Elevated ALT or AST (>500 U/L)
- No known etiology (with or without adenovirus testing results and independent of the results)
- Since October 2021
- N = 332 (1 in Oregon) (6 Jul 2022)
- Typical syndrome: nausea, vomiting, diarrhea, then jaundice
- US hepatitis NOS: ~500-600 cases/per year; about 31% without etiology



What we know as of 27 April 2022

- England, Scotland:
  - 3yr median age; 65% 3–5 yrs old
  - 54% female; 87% white
  - Increase in acute hepatitis NOS admissions and liver transplantations, as compared to prior years
  - Increase in adenovirus cases: 200-300/wk Nov 2021–Mar 2022 vs 50–150/wk pre-pandemic (also enterovirus, hMPV, Rhinovirus, Norovirus, RSV)
- US (Alabama)
  - Median 2yr (1.1–6.5yr)
  - 778% female, 100% White, 67% Hisp
  - Sporadic

ECDC, 28 April 2022; COCA, 19 May 2022

What we know as of 27 April 2022

- UK: 111 cases
  - 40 of 53 (75%) tested positive adenovirus (11 subtyped to 41F)
  - 10 of 61 (16%) tested positive SARS-CoV-2 on admission
  - No common exposures (food, medicines, travel, toxins)
  - Sporadic, ~10% liver transplantations, NO link to COVID-vaccinations
  - Background incidence of adenovirus detections in fecal samples among children aged 1–4 yrs increased in this time period
- EU/EEA: 55 cases
  - N=11 adenovirus
- US: 12 cases
  - 9 in Alabama (2 liver tx), 9+ adenovirus 41, all neg COVID, n=6 liver bx: HAdV not detected in IHC, no viral inclusions on EM

ECDC, 28 April 2022

What we don't know

- What is causing this?
  - A cofactor affecting young children which is rendering normal mild adenovirus infections more severe or causing them to trigger immunopathology.

    The cofactor may be:
    - a. susceptibility, for example due to lack of prior exposure to adenoviruses during the pandemic
    - b. a prior infection with SARS-CoV-2 or another infection, including an Omicron restricted effect
    - c. a coinfection with SARS-CoV-2 or another infection
    - d. a toxin, drug or environmental exposure

ECDC, 28 April 2022

What we are doing

- In children presenting with severe hepatitis, perform comprehensive testing per GI consult:
  - Infectious:
    - Adenovirus NAAT/PCR (whole blood, stool, respiratory)
    - SARS CoV-2 (NP, Spike & Nucleocapsid antibodies)
    - Hepatitis A, B, C, E (Ab, PCR)
    - HSV, VZV, EBV, CMV, HIV, enterovirus, parechovirus, etc
    - Respiratory panel
    - Stool culture (if epi suggests)
    - Leptospirosis (if epi suggests)
  - Metabolic, autoimmune, toxins, other non-infectious ☺

References

- European Centre for Disease Prevention and Control. Increase in severe acute hepatitis cases of unknown aetiology in children – 28 April 2022. ECDC: Stockholm; 2022.
- COCA Clinician Call 19 May 2022 https://emergency.cdc.gov/coca/calls/2022/callinfo_051922.asp
- CDC Website https://www.cdc.gov/ncird/investigation/hepatitis-unknown-cause/hcp.html. Accessed 13 Jul 2022