Data and clinical considerations for additional doses in immunocompromised people

Sara Oliver MD, MSPH

ACIP Meeting

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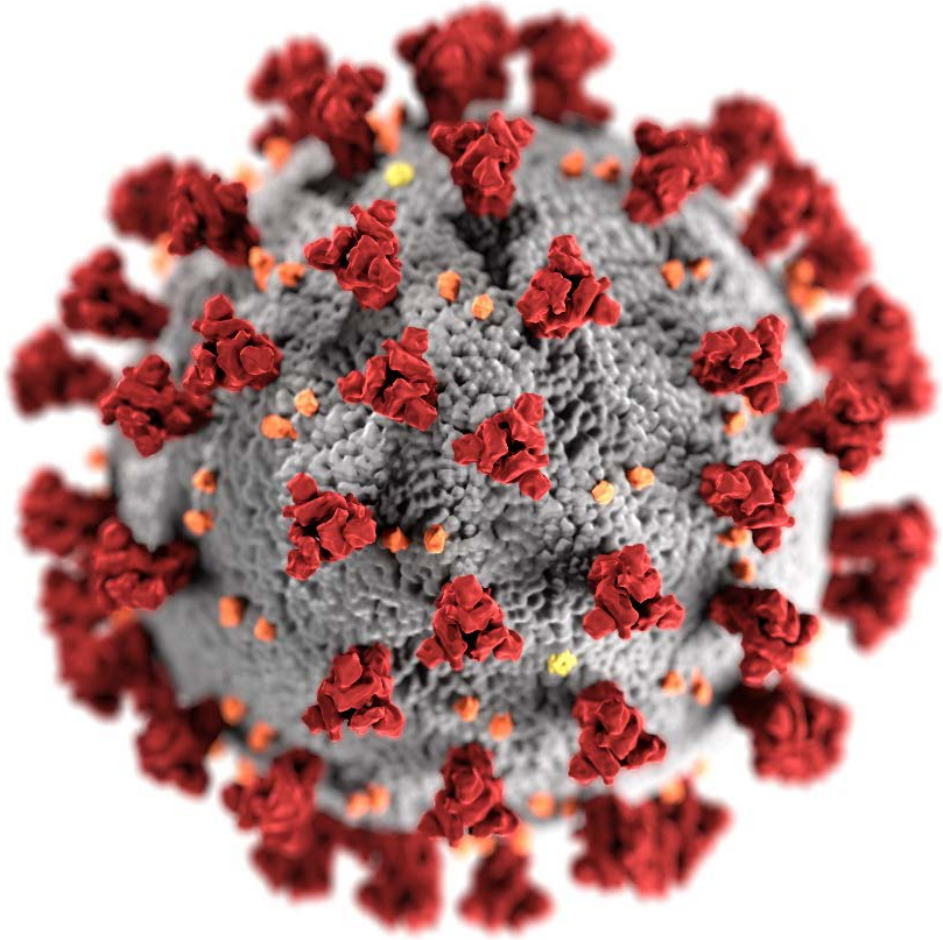


cdc.gov/coronavirus

Outline

1) COVID-19 vaccine response among immunocompromised people

2) Response to an additional dose of COVID-19 vaccine among immunocompromised people

3) Frequently asked questions about vaccination of immunocompromised people

Additional doses in immunocompromised people

Review data:
Assess safety, immunogenicity, and implementation

FDA

Regulatory allowance:
EUA amendment would allow recommendations under EUA

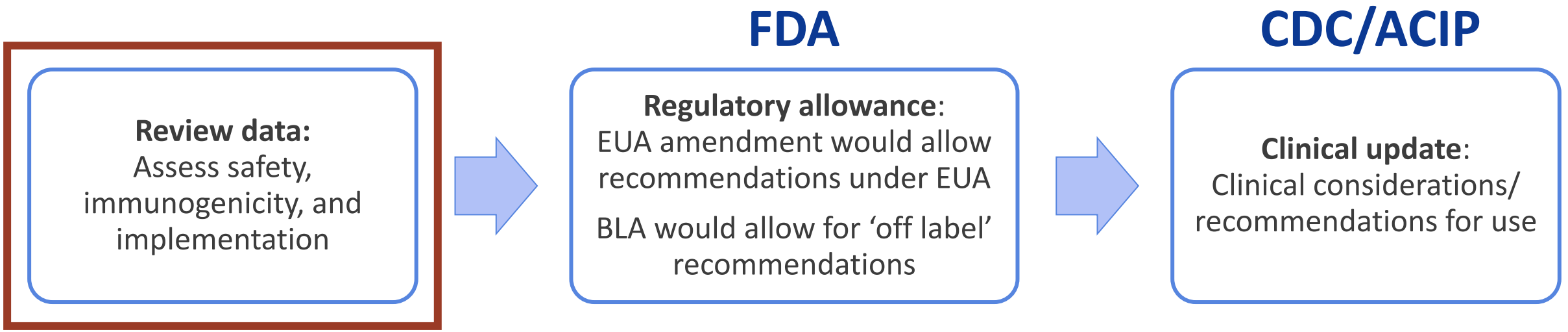
BLA would allow for 'off label' recommendations

CDC/ACIP

Clinical update:
Clinical considerations/ recommendations for use

EUA= Emergency Use Authorization; BLA= Biologics License Application

Additional doses in immunocompromised people



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COVID-19 vaccine response in immunocompromised people:

What do we know now?

Immunocompromised people and SARS-CoV-2 infection

- Immunocompromised people comprise ~2.7% of U.S. adults[1]
  - Solid tumor and hematologic malignancies
  - Receipt of solid-organ or hematopoietic stem cell transplant
  - Severe primary immunodeficiencies
  - Persons living with HIV
  - Treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids

1. Harpaz et al. Prevalence of Immunosuppression Among U.S. Adults, 2013. JAMA 2016

Immunocompromised people and SARS-CoV-2 infection

- More likely to get severely ill from COVID-19[1,2]
- Higher risk for:
  - Prolonged SARS-CoV-2 infection and shedding[3-7 14-16]
  - Viral evolution during infection and treatment (hospitalized patients)[3,6,8-10,14,17]
  - Low antibody/neutralization titers to SARS-CoV-2 variants[12]
- More likely to transmit SARS-CoV-2 to household contacts[11]
- More likely to have breakthrough infection:
  - **44%** of hospitalized breakthrough cases are immunocompromised people in US study[13]
  - **40%** of hospitalized breakthrough cases are immunocompromised people in Israeli study[18]

See reference slide at end

mRNA vaccine effectiveness (VE) studies among immunocompromised populations

- VE: 7-27 days after 2nd dose of Pfizer-BioNTech vaccine[1]
  - **71%** (CI 37-87%) among immunosuppressed* people vs. **90%** (CI 83-96%) overall: **SARS-CoV-2 infection**
  - **75%** (CI 44-88%) among immunosuppressed people vs. **94%** (CI 87-97%) overall: **symptomatic COVID-19**

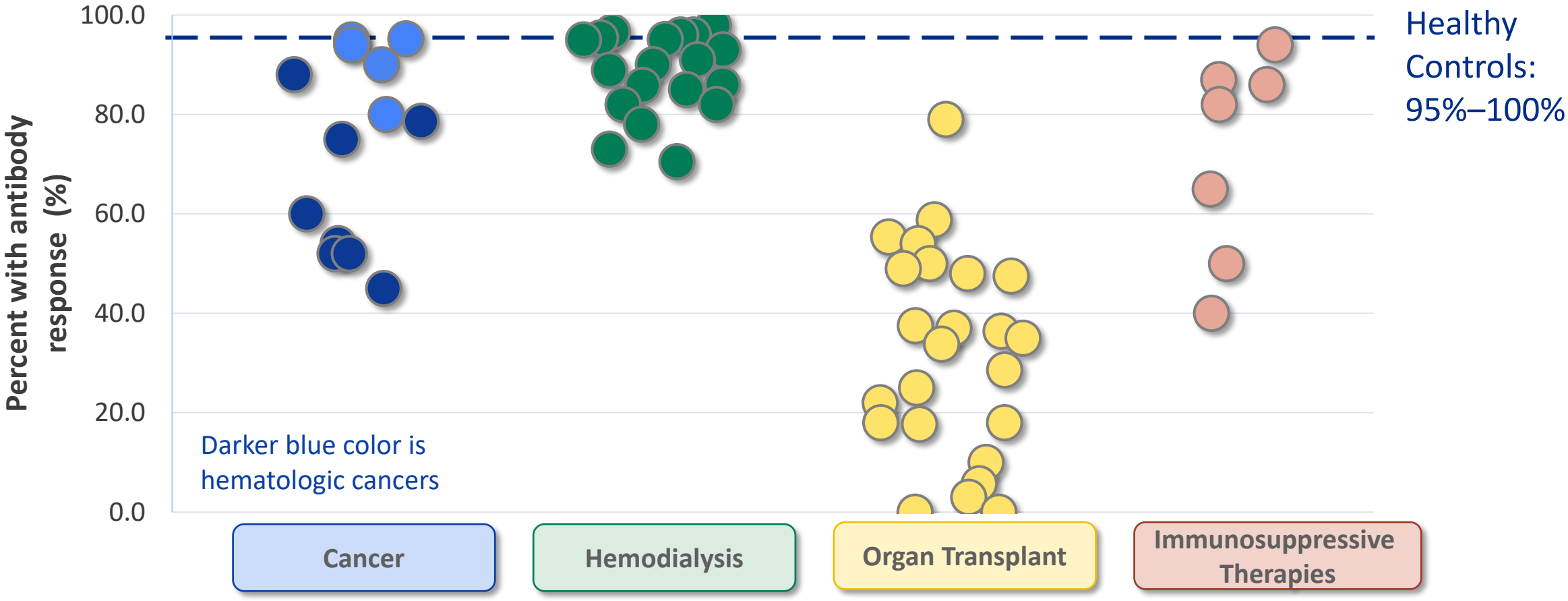
- VE: ≥7 days after 2nd dose of mRNA vaccine[2]
  - **80%** among people with inflammatory bowel disease on immunosuppressive meds: **SARS-CoV-2 infection**
  - VE of **25%** was noted after 1st dose of mRNA vaccine for **SARS-CoV-2 infection**

- VE: ≥14 days after 2nd dose of mRNA vaccine[3]
  - **59%** (CI 12-81%) among immunocompromised people vs. **91%** (CI 86-95%) without immunocompromise: **COVID-19 hospitalization**[3]

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438; **2.** Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf; **3.** Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)



- Studies that compared response after 1st and 2nd dose demonstrated poor response to dose 1
- Antibody measurement and threshold levels vary by study protocol

See reference list at end

Response to an additional dose of COVID-19 vaccine in immunocompromised people:

The emerging data

Comparing evidence 3rd mRNA COVID-19 vaccine dose in immunosuppressed people with seropositive response

Study	Patient Population	2nd Dose			3rd Dose Seronegative after 2nd dose		
		Sample Size	Seronegative N (%)	Seropositive N (%)	Sample Size	Seronegative N (%)	Seropositive N (%)
Kamar et al.	Recipients of solid-organ transplant	99	59 (60)	40 (40)	59	33 (56)	**26 (44)**
Werbel et al.*	Recipients of solid-organ transplant	30	24 (80)	6 (20)	24	16 (67)	**8 (33)**
Longlune et al.	Patients on hemodialysis	82	13 (16)	69 (84)	12	7 (58)	**5 (42)**
Maxime et al.	Patients on hemodialysis	106	66 (62)	40 (38)	12	6 (50)	**6 (50)**

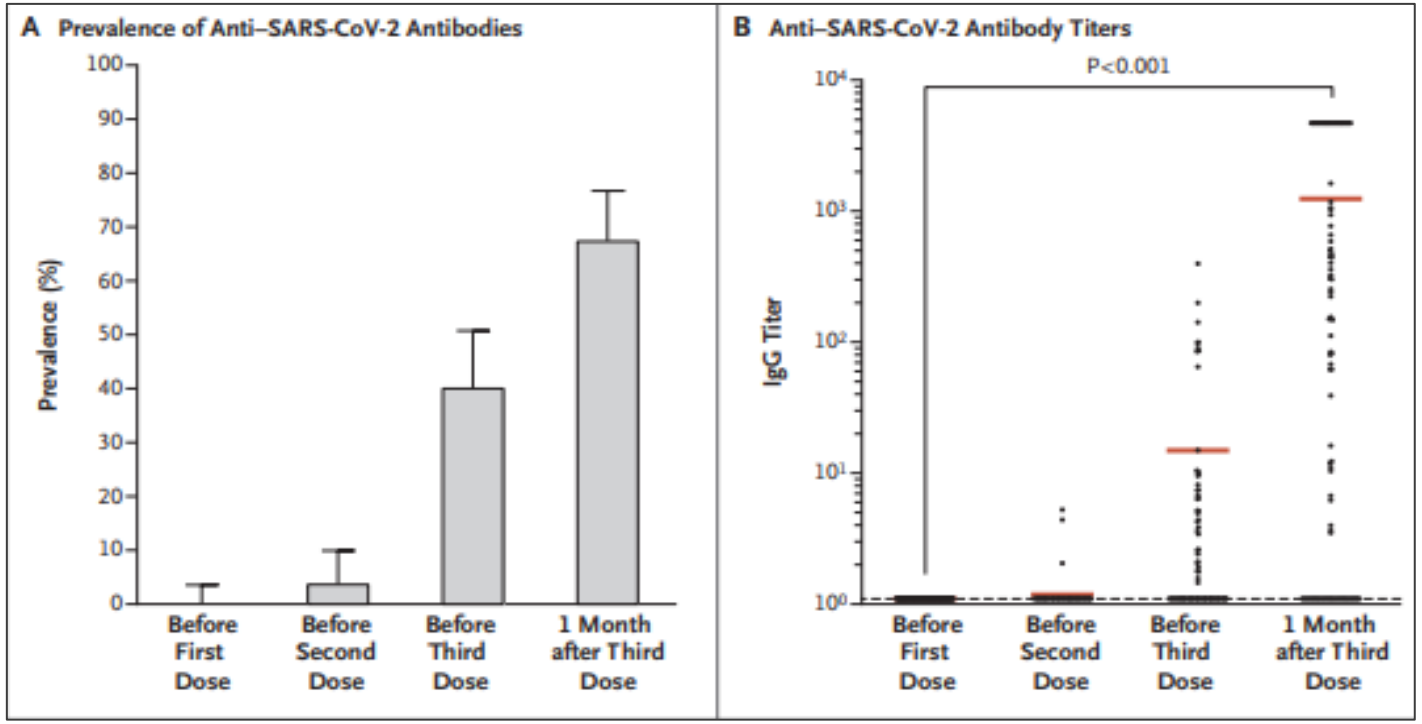
* Recipients received homologous mRNA prime followed by either a single Moderna, Pfizer, or Janssen boost

- Among those who had **no detectable antibody** response to an initial mRNA vaccine series,

33-50% developed an antibody response to an additional dose

See references list at end

Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients

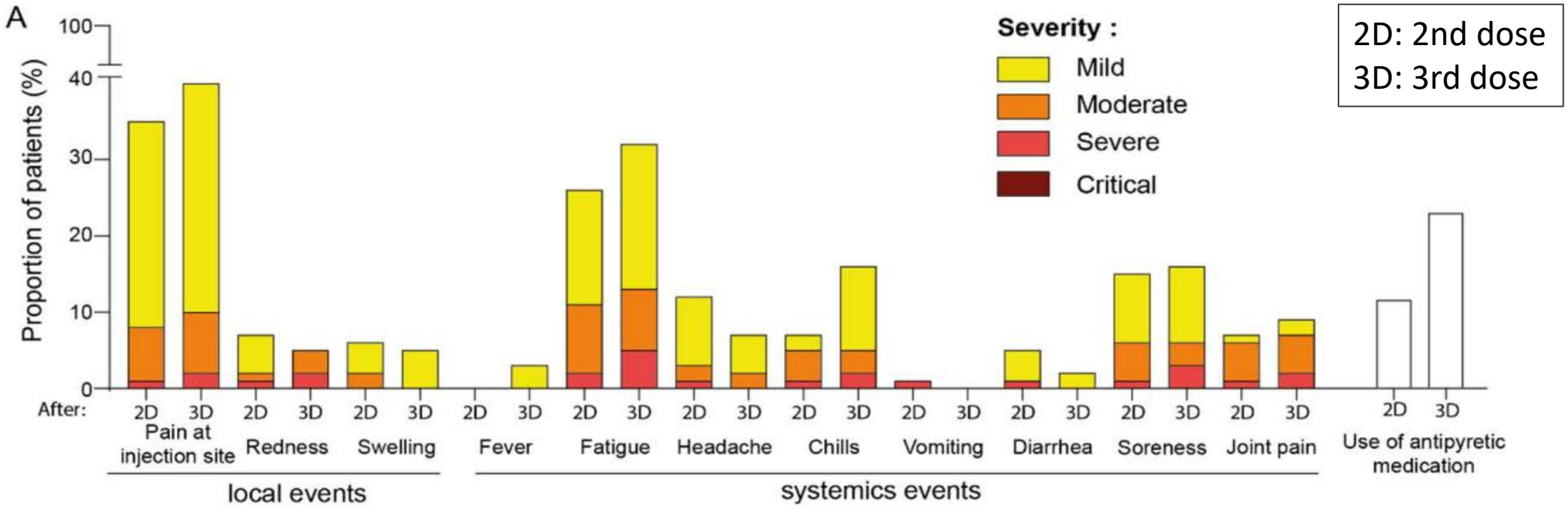


- No serious adverse events were reported after administration of the 3rd dose, and no acute rejection episodes occurred (n=99)

Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)

Reactogenicity of 3rd mRNA vaccine dose in cohort of patients on hemodialysis (n=63*)

- No patients developed critical side effects requiring hospitalization
- Symptoms reported were consistent with previous doses and the intensity of the symptoms was mostly mild or moderate



*Sample included patients who had an optimal and suboptimal antibody response to primary mRNA series and chose to receive a 3rd dose

Maxime et al. (2021) medRxiv doi: https://doi.org/10.1101/2021.07.02.21259913

International policies on additional doses for immunocompromised people

- France[1] (Announced April 11, 2021)
  - 3rd dose 4 weeks after the 2nd dose for patients who are “severely immunocompromised”
  - Could be extended at a later date to include a larger immunocompromised population

- United Kingdom[2] (Announced July 1, 2021)
  - Proposal for an additional dose for immunocompromised people ≥16 years (among others), to be implemented between 6 September and 17 December 2021
  - Decision pending

- Israel[3] (Announced July 11, 2021)
  - People living with organ or stem cell transplants, blood cancer, autoimmune disease and treatment with specific immunosuppressive medications
  - People with breast, lung, or colon cancer do not qualify

1.dgs_urgent_n43_vaccination_modalites_d_administration_des_rappels.pdf (solidarites-sante.gouv.fr), 2. C1327-covid-19-vaccination-autumn-winter-phadvicease-3-planning.pdf
3.https://govextra.gov.il/media/30095/meeting-summary-15122020.pdf

Summary

- Immunocompromised people are at increased risk of poor outcomes from COVID-19
- Studies indicate a reduced antibody response in immunocompromised people following a primary vaccine series, compared to healthy vaccine recipients
- Emerging data suggest that an additional COVID-19 vaccine dose in immunocompromised people enhances antibody response and increases the proportion who respond
- In small studies, the reactogenicity of the 3rd dose of mRNA vaccine was similar to prior doses

Frequently asked questions about vaccination of immunocompromised people

Which immunocompromised groups should be considered for an additional dose as allowed by regulatory mechanisms?

- Conditions and treatments associated with *moderate to severe* immune compromise*
  - Active or recent treatment for solid tumor and hematologic malignancies
  - Receipt of solid-organ or recent hematopoietic stem cell transplant
  - Severe primary immunodeficiency
  - Advanced or untreated HIV infection
  - Treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (e.g., rituximab), and high-dose corticosteroids
- Chronic conditions associated with *varying* degrees of immune deficit, such as asplenia and chronic renal disease*
- Different medical conditions and treatments can result in widely varying degrees of immunosuppression. A patient's clinical team is best able to assess the degree of altered immunocompetence and optimal timing of vaccination

*General Best Practice Guidelines for Immunization and CDC Yellow Book can be consulted for detailed information

Should immunocompromised people undergo antibody testing following COVID-19 vaccination?

- Utility of serologic testing or cellular immune testing to assess immune response to COVID-19 vaccination has not been established
- Exact correlation between antibody level and protection from COVID-19 remains unclear
- Commercial antibody and cellular immune testing may not be consistent across laboratories
- Serologic (antibody) testing or cellular immune testing outside of the context of research studies is **not recommended in the United States at this time**

Are there data to support mixed-dose series in immunocompromised people: for example, Janssen followed by mRNA COVID-19 vaccine?

- Studies from Europe have assessed heterologous primary series (AstraZeneca and Pfizer-BioNTech) in the general adult population and found immunogenicity to be at least equivalent to homologous series [1-5]
  - Large UK trial (Com-COV) found that one dose of AstraZeneca + one dose of Pfizer-BioNTech resulted in superior immunogenicity compared with two doses of AstraZeneca vaccine but lower antibodies than 2 doses of Pfizer-BioNTech; increase in systemic reactogenicity observed with heterologous schedules[5]
- Evidence is needed regarding the safety and immunogenicity of using a mixed-dose approach for Janssen (FDA-authorized adenoviral vector vaccine) + mRNA vaccine in immunocompromised people

1. Borobia et al. Reactogenicity and Immunogenicity of BNT162b2 in Subjects Having Received a First Dose of ChAdOx1s: Initial Results of a Randomized, Adaptive, Phase 2 Trial (CombiVacS). Available at SSRN: https://ssrn.com/abstract=3854768 **2**. Shaw et al. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data, ISSN 0140-6736, https://doi.org/10.1016/S0140-6736(21)01115-6. **3.** Hillus et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunization with ChAdOx1-nCoV19 and BNT162b2: a prospective cohort study. medRxiv; 2021. DOI: 10.1101/2021.05.19.21257334. **4.** Schmidt et al. medRxiv preprint (June 15 2021): https://doi.org/10.1101/2021.06.13.21258859 Click to add text **5.** Liu et al. Lancet preprint (June 25, 2021): http://dx.doi.org/10.2139/ssrn.3874014

Following COVID-19 vaccination, what infection prevention measures should immunocompromised people maintain?

- Immunocompromised people should be counseled about potential for reduced immune responses to COVID-19 vaccination and need to follow prevention measures*
  - Wear a mask
  - Stay 6 feet apart from others they don't live with
  - Avoid crowds and poorly ventilated indoor spaces until advised otherwise by their healthcare provider
- Close contacts of immunocompromised people should be encouraged to be vaccinated against COVID-19

* https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

Is there a role for monoclonal antibody use in immunocompromised people?

- Monoclonal antibodies are currently authorized by FDA for emergency use in persons with SARS-CoV-2 infection who are at high risk for progressing to severe COVID-19 and/or hospitalization

- Monoclonal antibodies are not yet authorized for SARS-CoV-2 infection prevention

https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap#dashboard

What are the implications of the Emergency Use Authorizations (EUAs) for the COVID-19 vaccines, with respect to considerations for an additional dose in immunocompromised persons?

- FDA has authorized mRNA vaccines as a 2-dose series and Janssen COVID-19 vaccine as a single dose
- At this time, we are not aware of data submitted to FDA to support an amendment to the EUA for this population
- CDC/ACIP will closely monitor any updates to data and regulatory mechanisms

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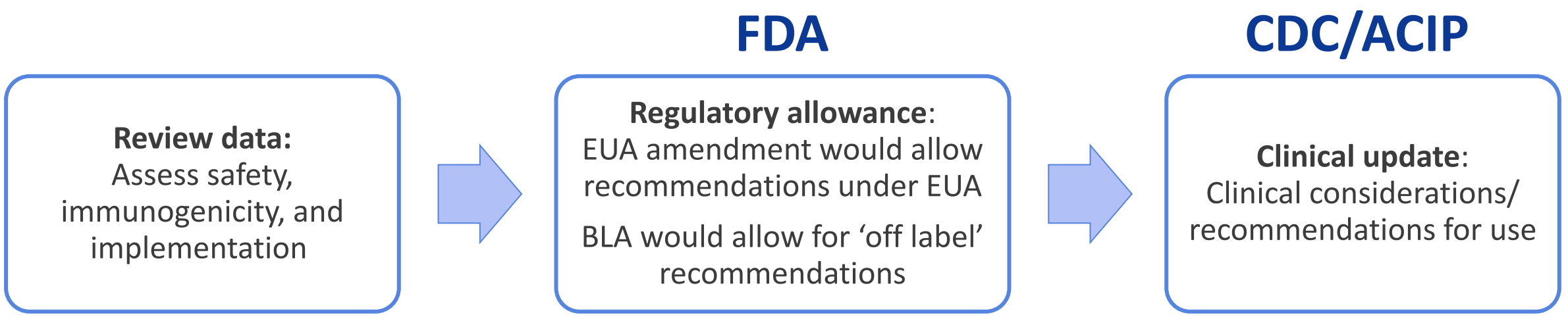
Additional doses in immunocompromised people



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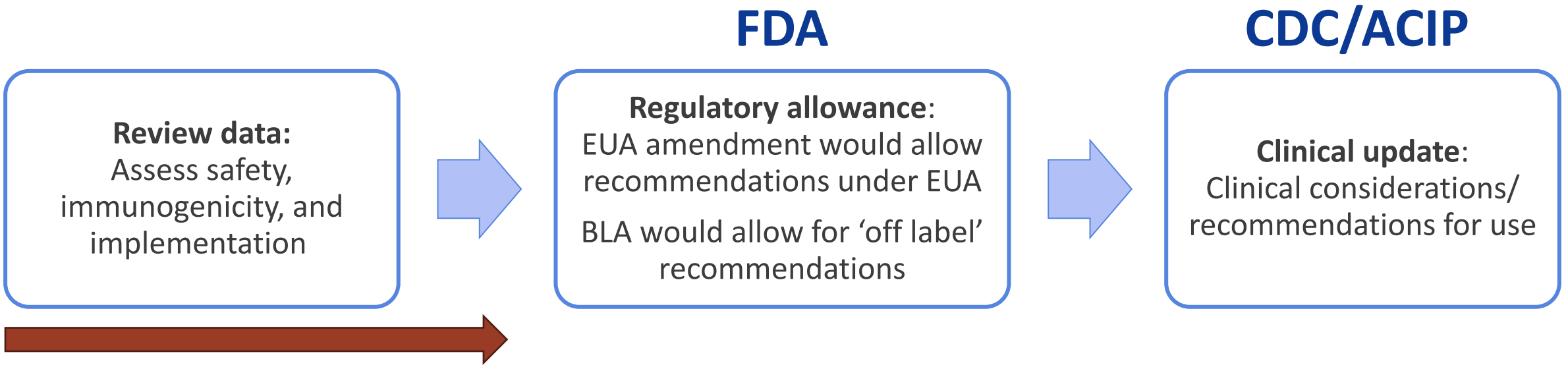
Additional doses in immunocompromised people



Now:

Immunocompromised people should continue to **follow infection prevention measures**:

Wear a mask, stay 6 feet apart from others, avoid crowds and poorly ventilated spaces

Close contacts (≥12 years) of immunocompromised people should be **vaccinated against COVID-19**

Early treatment with **monoclonal antibodies** may be beneficial in this population

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Additional COVID-19 vaccine dose in immunocompromised people: Next steps

- Assess additional studies of safety and immunogenicity of additional dose in immunocompromised people
- Assess additional studies and expert opinion regarding the subpopulations of immunocompromised people who may benefit most from an additional dose
- Determine acceptable intervals and mix and match schedules
- Await regulatory allowance (e.g. FDA amendment of EUA or BLA) for an additional dose of COVID-19 vaccine

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Questions for ACIP

Questions for ACIP

1. What additional data do ACIP need to inform these discussions?

2. Thoughts on the focus of “moderate to severe” immunocompromised populations, once authorized/approved?

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- Vaccine Task Force
- Epi Task Force
- Respiratory Viruses Branch

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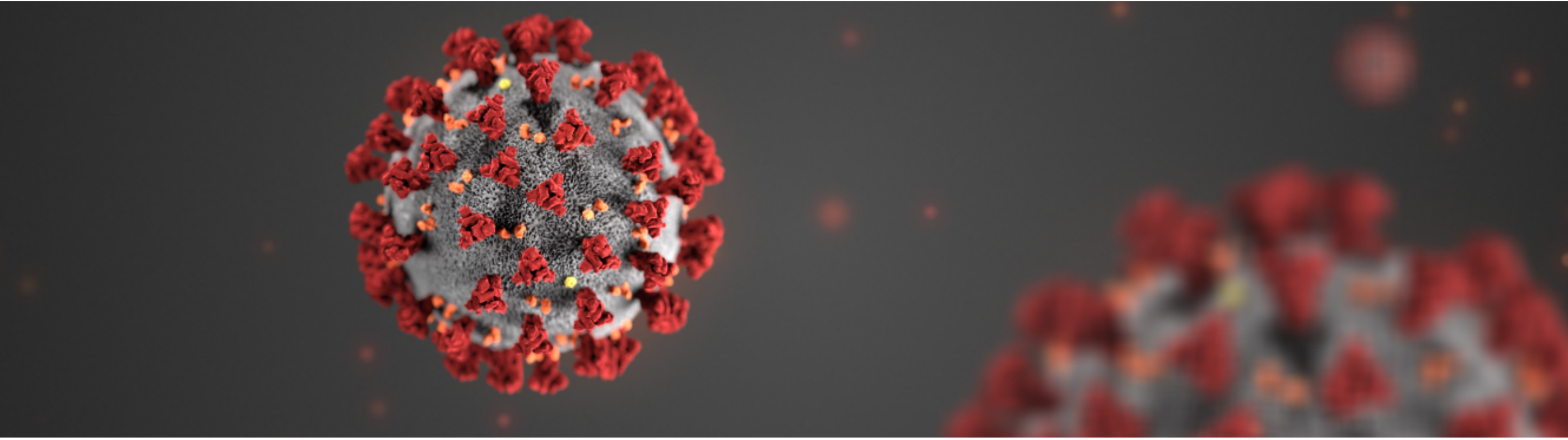

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