CDC Centers for Disease Control and Prevention

COVID-19

COVID-19 Vaccines for Moderately or Severely Immunocompromised People

Updated Jan. 7, 2022

DEFINITION

Immunocompromised

Having a weakened immune system can make you more likely to get severely ill from COVID-19. Many conditions and treatments can cause a person to be immunocompromised or have a weakened immune system. Primary immunodeficiency is caused by genetic defects that can be inherited. Prolonged use of corticosteroids or other immune weakening medicines can lead to secondary or acquired immunodeficiency.

Primary Series Shots

People who are immunocompromised are especially vulnerable to COVID-19. Everyone, including immunocompromised people, should receive a COVID-19 vaccine primary series if they are 5 years and older as soon as possible.

Additional Primary Shot and Booster Shot for Some Immunocompromised People

After completing the primary series, **some** moderately or severely immunocompromised people should get an additional primary shot.

Everyone 12 years and older, including immunocompromised people, should get a booster shot. If you are eligible for an additional primary shot, you should get this dose first before you get a booster shot.

Eligible For	IF YOU RECEIVED Pfizer-BioNTech	IF YOU RECEIVED Moderna	IF YOU RECEIVED Johnson & Johnson's Janssen
Additional Primary Shot	People **age 5+** who are moderately or severely immunocompromised **should** get an additional primary shot of Pfizer-BioNTech COVID-19 vaccine Given 28 days after 2nd shot	People age 18+ who are moderately or severely immunocompromised **should** get an additional primary shot of Moderna COVID-19 vaccine Given 28 days after 2nd shot	No additional primary shot is recommended at this time

Booster Shot	• Teens **ages 12–17** should only get a Pfizer-BioNTech COVID-19 vaccine booster shot • People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 2 months after 1st shot

Who Is Moderately or Severely Immunocompromised?

People are considered to be moderately or severely immunocompromised if they have:

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking medicine to suppress the immune system
- Received a stem cell transplant within the last 2 years or are taking medicine to suppress the immune system
- Moderate or severe primary immunodeficiency (such as DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids or other drugs that may suppress your immune response

People should talk to their healthcare provider about their medical condition, and whether getting an additional primary shot is appropriate for them.

Scheduling Your Additional Primary Shot

If you need help scheduling your additional primary shot, contact the location that set up your previous appointment. If you need to get your additional primary dose in a location different from where you received your previous shot, there are several ways you can find a vaccine provider.

What to Expect during and after Your Additional Primary Shot Appointment

- Bring your CDC COVID-19 Vaccination Record card to your additional primary shot appointment so your provider can fill in the information about your additional primary dose. If you did not receive a card at your first appointment, contact the vaccination site where you got your first shot or your state health department to find out how you can get a card.
- You may experience side effects after getting a COVID-19 vaccine. These are normal signs that your body is building protection against COVID-19.
- Use v-safe to tell CDC about any side effects. If you enter your additional primary shot in your v-safe account, the system will send you daily health check-ins.

Frequently Asked Questions

Can you mix and match the vaccines for your additional primary shot?

No, the vaccine used for the additional primary shot should be same as the vaccine used for the primary vaccine series. If the mRNA vaccine product given for the first two doses is not available or is unknown, either mRNA COVID-19 vaccine product may be administered.

What are the benefits of an additional primary shot for people who are immunocompromised who received an mRNA COVID-19 primary vaccine series?

An additional primary shot may prevent serious and possibly life-threatening COVID-19 in people who may not have responded to their two-dose mRNA COVID-19 vaccine primary series. The mRNA COVID-19 vaccines (Pfizer-BioNTech or Moderna) have been shown to prevent COVID-19 following the two-dose series. Limited information suggests that immunocompromised people who have low or no protection after two shots of mRNA vaccines may have an improved immune (antibody) response after an additional primary dose of the same vaccine.

What are the risks of vaccinating individuals with an additional primary shot?

There is limited information about the risks of receiving an additional primary shot of mRNA COVID-19 vaccine. The safety, efficacy, and benefit of the additional primary dose in immunocompromised people continues to be evaluated. So far, reactions reported after the additional primary shot of mRNA COVID-19 vaccine are similar to that of the two-dose primary series: fatigue and pain at the injection site were the most commonly reported side effects, and overall, most symptoms were mild to moderate.

As with the two-dose primary series, serious side effects are rare, but may occur.

What is the difference between an additional primary shot and a booster shot?

An additional primary dose is administered to people with moderately or severely compromised immune systems. The additional primary dose of an mRNA COVID-19 vaccine is intended to improve immunocompromised people's response to their vaccine primary series. A booster shot is administered when a person has completed their vaccine primary series to enhance or restore protection against COVID-19 which may have decreased over time.

For Healthcare and Public Health

- Talking with Patients Who Are Immunocompromised
- Use of COVID-19 Vaccines Currently Authorized in the United States

Last Updated Jan. 7, 2022

Ministerio
de Salud Pública

DIRECCIÓN GENERAL DE LA SALUD
DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.
Fecha: 9/2/2022
Temas a tratar:
Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).
Nombre: Natalia Cristoforone
Departamento de Medicina Familiar y Comunitaria. Facultad de Medicina UdelaR

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

Firma:

Natalia Cristoforone

Ministerio de Salud Pública

DIRECCIÓN GENERAL DE LA SALUD
DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: *9 Febrero 2022*

Temas a tratar: *1) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes*

2) Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo

Nombre: *Jose A. Chabalgoity*

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

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DIRECCIÓN GENERAL DE LA SALUD
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Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 09/02/22

Temas a tratar:

- Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
- Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo

Nombre: Leonardo Oliva

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		x
Honorarios como conferencista financiados por empresas vinculadas		x
Honorarios por consultoría de las empresas vinculadas a		x
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		x
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

Tel. int. 1934 4050/4051

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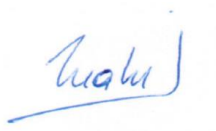
DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 09 de Febrero de 2022
Temas a tratar: Dosis de refuerzo de vacuna contra COVID-19 en adolescentes, y pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo.
Nombre: María Moreno

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		x
Honorarios como conferencista financiados por empresas vinculadas		x
Honorarios por consultoría de las empresas vinculadas a		x
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		x
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.



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DIRECCIÓN GENERAL DE LA SALUD
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Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9 de febrero 2022

Temas a tratar:

1) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
2) - Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).

Nombre: Miguel Alegretti

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

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DIRECCIÓN GENERAL DE LA SALUD
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Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha:

Temas a tratar:

Nombre:

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		
Honorarios como conferencista financiados por empresas vinculadas		
Honorarios por consultoría de las empresas vinculadas a		
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora

Nombre: Adriana Alfonso

	SI (marcar si corresponde)	**NO (marcar si corresponde)**
Listado de actividades relacionadas con empresas		

Participación en estudios clínicos financiados por empresas vinculadas a
No

Honorarios como conferencista financiados por empresas vinculadas

No

Honorarios por consultoría de las empresas vinculadas a

No

Asistencia a congresos, etc. Financiados por las empresas vinculadas a

No

Otros: No soy funcionaria de ningún laboratorio ni empresa farmacéutica / No tengo familiares funcionarios de laboratorio ni empresa farmacéutica

Firma: Dra. Adriana Alfonso

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ÁREA DE VIGILANCIA EN SALUD DE LA POBLACIÓN
DIVISIÓN EPIDEMIOLOGÍA
UNIDAD DE INMUNIZACIONES

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones

Fecha: 14 02 2022

Temas a tratar:

Vacunación COVID dosis refuerzo

Nombre: Alicia M Fernández
Institución/Departamento que representa: Área Programática de Niñez MSP

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas al tema a tratar		X
Honorarios como conferencista financiados porempresas vinculadas		X
Honorarios por consultoría delas empresas vinculadas al tema a tratar		X
Asistencia a congresos, etc. Financiados por las empresasvinculadas al tema a tratar		X

Se recuerda que aquellos miembros de la Comisión que presenten algún **conflicto de interés tendrán voz pero no voto** en esta instancia.

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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora

Nombre		
Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**

Participación en estudios clínicos financiados por empresas vinculadas a
No

Honorarios como conferencista financiados por empresas vinculadas

No

Honorarios por consultoría de las empresas vinculadas a

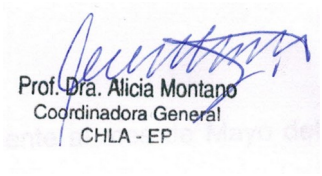
No

Asistencia a congresos, etc. Financiados por las empresas vinculadas a

No

Otros: No soy funcionaria de ningún laboratorio ni empresa farmacéutica / No tengo familiares funcionarios de laboratorio ni empresa farmacéutica

Firma


Prof. Dra. Alicia Montano
Coordinadora General
CHLA - EP

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DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9/2/2022

Temas a tratar:
1) - Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
2) - Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer)

Nombre:
Daniel Strozzi Scala

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones

Fecha: 16/2/2022

Temas a tratar:

APLICACIÓN DE DOSIS DE REFUERZO EN POBLACIÓN VACUNADA CON ESQUEMA DE 3 DOSIS

Nombre: ADRIANA DELFRARO

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas al tema a tratar:		**X**
Honorarios como conferencista financiados por empresas vinculadas:		**X**
Honorarios por consultoría de las empresas vinculadas al tema a tratar:		**X**
Asistencia a congresos, etc. Financiados por las empresas vinculadas al tema a tratar:		**X**
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia**.**

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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 8/2/2022

Temas a tratar:

1) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
2) Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).

Nombre: María Inés Fariello

Listado de actividades relacionadas con empresas	**SI (marcar si correspond e)**	**NO (marcar si correspond e)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9 de febrero de 2022

Temas a tratar: Dosis de refuerzo vacuna Covid 19 en adolescentes y pertinencia de cuarta dosis en grupos de riesgo referidos en el asunto de la convocatoria
Nombre: GABRIEL PELUFFO

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		x
Honorarios como conferencista financiados por empresas vinculadas		x
Honorarios por consultoría de las empresas vinculadas a		x
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		x
Otros:		

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Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9 de febrero 2022

Temas a tratar: 1) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes

2) - Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).

Nombre: ~~Gualberto González~~

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		x
Honorarios como conferencista financiados por empresas vinculadas		x
Honorarios por consultoría de las empresas vinculadas a		x

Asistencia a congresos, etc. Financiados por las empresas vinculadas a		x
Otros:		

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Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9/2/2022

Temas a tratar:
) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).

Nombre: Gustavo Alberto Giachetto Larraz

Depto. de Pediatría, Facultad de Medicina, Udelar

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

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de interés tendrán voz pero no voto en esta instancia.

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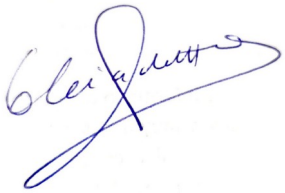

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DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 09/02/2022

Temas a tratar: Dosis de refuerzo de vacuna contra COVID-19 en adolescentes; Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo

Nombre: Javier Diaz

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

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DIRECCIÓN GENERAL DE LA SALUD
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Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 16/2/22

Temas a tratar:Continuación de temas planteados para reunión CNAV del 9/2/22

Nombre: Juan E. GIL YACOBAZZO

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

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Ministerio de Salud Pública

DIRECCIÓN GENERAL DE LA SALUD
DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9 de febrero de 2022

Temas a tratar: 1) - Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
2) - Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer)

Nombre: Julio Medina

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a *		X

Otros *: La Cátedra de Enfermedades Infecciosas (de la cual soy el Prof. Director) en los últimos 5 años ha recibido apoyo de los siguientes laboratorios:

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GP-PHARM
JANSSEN
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PFIZER
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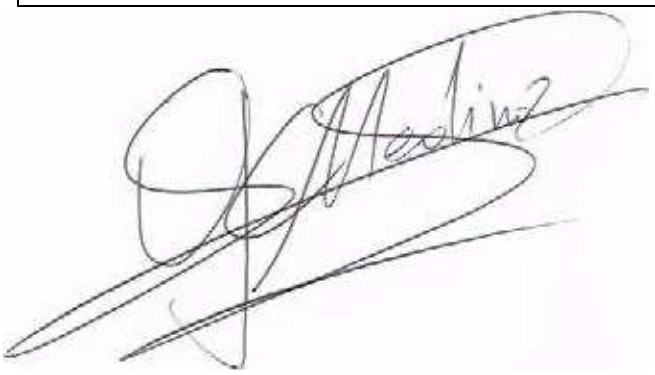
ROEMMERS
TRESUL
URUFARMA

Ese apoyo está destinado a sostener la página web, actividades de educación médica contínua, compra de libros y licencias de ZOOM etc. También para asistir a congresos nacionales e internacionales, los cuales son distribuidos equitativamente entre docentes, residentes y postgrados. La mayor parte de los apoyos se efectivizan a través de la Fundación Manuel Quintela. Ningún apoyo a congreso llega a título personal de ningún docente-sino a la Cátedra como tal que luego por consenso es distribuido internamente.



Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

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Nombre: Marianela Barcia

Listado de actividades relacionadas con empresas	SI (marcar si corresponde)	NO (marcar si corresponde)
Participación en estudios clínicos financiados por empresas vinculadas a		x
Honorarios como conferencista financiados por empresas vinculadas		x
Honorarios por consultoría de las empresas vinculadas a		x

Asistencia a congresos, etc. Financiados por las empresas vinculadas a		x
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto de interés tendrán voz pero no voto en esta instancia.

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Ministerio de Salud Pública

DIRECCIÓN GENERAL DE LA SALUD
DIVISIÓN EPIDEMIOLOGÍA
Unidad de Inmunizaciones

Declaración de potenciales conflictos de interés para la reunión de la Comisión Nacional Asesora de Vacunaciones.

Fecha: 9/2/2022

Temas a tratar:
) Dosis de refuerzo de vacuna contra COVID-19 en adolescentes
Pertinencia de cuarta dosis de vacuna contra COVID-19 en grupos de riesgo (adultos mayores con esquema primario con SNV, inmunodeprimidos que recibieron Pfizer, refuerzo en inmunodeprimidos que recibieron SNV+SNV+Pfizer+Pfizer).

Nombre: Mónica Pujadas Ferrer

SUP – Comisión ad hoc

Listado de actividades relacionadas con empresas	**SI (marcar si corresponde)**	**NO (marcar si corresponde)**
Participación en estudios clínicos financiados por empresas vinculadas a		X
Honorarios como conferencista financiados por empresas vinculadas		X
Honorarios por consultoría de las empresas vinculadas a		X
Asistencia a congresos, etc. Financiados por las empresas vinculadas a		X
Otros:		

Se recuerda que aquellos miembros de la Comisión que presenten algún conflicto

de interés tendrán voz pero no voto en esta instancia.

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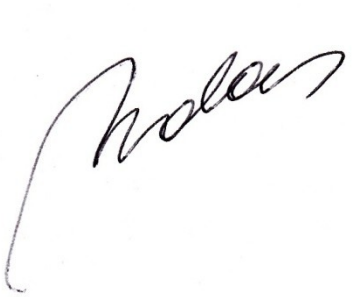

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa

TO THE EDITOR: In early November 2021, the B.1.1.529 (omicron) variant was first identified in South Africa and has rapidly become the dominant variant in Gauteng province, where a third wave of coronavirus disease 2019 (Covid-19) driven by the B.1.617.2 (delta) variant had largely subsided. As of November 15, the omicron variant was being detected in more than 75% of Covid-19–positive tests that were sequenced in South Africa[1] (Figs. S1 and S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). On November 26, the World Health Organization declared omicron a variant of concern. In a study of live-virus neutralization assays, omicron was shown to escape antibody neutralization by the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech).[2] Thus, data were needed regarding the effectiveness of the current vaccines against the omicron variant in preventing hospitalization for Covid-19.

Using data from Discovery Health, a South African managed care organization, we estimated the vaccine effectiveness of two doses of the BNT162b2 vaccine (i.e., full vaccination) against hospitalization for Covid-19 caused by the omicron variant by analyzing data sets that included the results of polymerase-chain-reaction (PCR) assays, preauthorization admission data, a full history of members' medical records, registrations regarding chronic diseases, and data regarding body-mass index to obtain the number of Covid-19 risk factors per patient, according to the guidelines of the Centers for Disease Control and Prevention (CDC).[3] Vaccination status was determined from claims data in the private sector, and patients who had been vaccinated in the public sector were listed in a vaccine category called "other vaccine type" (Table S4). Among fully vaccinated members, we compared the vaccine effectiveness against Covid-19 hospitalization associated with the omicron variant during the period from November 15 to December 7 in South Africa, which we dubbed a proxy for dominance of the omicron variant (omicron proxy period), against estimates of vaccine effectiveness between September 1 and October 30, when the delta variant was dominant (comparator period).

In our study, we used a test-negative design and data-exclusion rules to obtain estimates of vaccine effectiveness[4] (Table S1), according to the following formula: 1 − odds ratio for Covid-19 hospitalization in the vaccinated population, where the odds ratio was calculated with the use of logistic regression after adjustment for confounders of age, sex, previous Covid-19 infection, surveillance week, geographic location, and the number of CDC risk factors. In this analysis, Covid-19 hospitalization was a dependent variable, and vaccination status was included as an independent variable.

We then performed three sensitivity analyses on different subsets of data during the omicron proxy period. First, we performed PCR tests showing S-gene target failure as an indication of omicron infection. Second, we included only PCR results obtained from patients in Gauteng province, given the geographic concentration of the omicron variant during the study period. Third, we limited PCR test results to those obtained from patients who had been hospitalized (e.g., respiratory medical admissions), with the latter used as a proxy for identifying tests among a symptomatic population (Table S4).

We analyzed 133,437 PCR test results that had been obtained during the comparator period, of which 38,155 (28.6%) had been obtained at least 14 days after the patient had received the second dose of vaccine. For the proxy omicron period, we analyzed 78,173 PCR test results, of which 32,325 (41.4%) had been obtained at least 14 days after

Table 1. Hospitalization for Covid-19 and Test Positivity before and during the Proxy Omicron Period in Gauteng Province (September–December 2021).

Vaccination Status	Comparator Period (September 1–October 31)			Proxy Omicron Period (November 15–December 7)		
	Tests Administered (N=133,437)	Positive Test Results (N=8,569)	Covid-19 Admissions (N=925)	Tests Administered (N=78,173)	Positive Test Results (N=19,070)	Covid-19 Admissions (N=429)
	number (percent)					
Not vaccinated	53,371 (40.0)	5,231 (61.0)	684 (73.9)	26,331 (33.7)	7,889 (41.4)	220 (51.3)
BNT162b2 vaccine						
One dose	16,918 (12.7)	1,279 (14.9)	71 (7.7)	6,185 (7.9)	1,481 (7.8)	34 (7.9)
<14 days after second dose	5,200 (3.9)	185 (2.2)	13 (1.4)	653 (0.8)	114 (0.6)	0
≥14 days after second dose	38,155 (28.6)	706 (8.2)	77 (8.3)	32,325 (41.4)	6,290 (33.0)	121 (28.2)
Other vaccine type*	19,793 (14.8)	1,168 (13.6)	80 (8.6)	12,679 (16.2)	3,296 (17.3)	54 (12.6)

* Data are based on a match with the national Electronic Vaccination Data System as of August 25, 2021, since such data were not available from the Department of Health regarding vaccine type and vaccinations administered in the public sector since that date. Thus, estimates of vaccine effectiveness should be viewed as conservative since unvaccinated controls may have inadvertently been included among vaccinated persons. On the basis of the number of Discovery Health patients who had been vaccinated in public-sector sites before August 25, 2021, the rate of misclassification of unvaccinated controls was estimated to be no more than 10%.

Table 2. Effectiveness of Two Doses of BNT162b2 Vaccine before and during Proxy Omicron Period.*

Variable	Vaccine Effectiveness (95% CI)	
	Comparator Period	Proxy Omicron Period
	%	
Overall estimate	93 (90–94)	70 (62–76)
Sensitivity analyses of PCR results		
Patients with S-gene target failure	—	69 (48–81)
Patients in Gauteng province	—	70 (59–78)
Patients with Covid-19 symptoms	—	50 (35–62)

* The overall estimates of vaccine effectiveness were calculated according to a test-negative design after adjustment for confounders. The three sensitivity analyses included the results of polymerase-chain-reaction (PCR) tests showing S-gene target failure (as an indication of omicron infection), PCR results obtained only from patients in Gauteng province, and PCR results obtained only from patients who had been hospitalized (i.e., symptomatic population).

the second dose (Table 1). The overall test positivity was 6.4% during the comparator period and 24.4% during the proxy omicron period, whereas the Covid-19 admission rate was 10.8% and 2.2%, respectively, as a percentage of positive PCR test results. Patients with positive cases were younger during the proxy omicron period than during the comparator period (Table S3).

During the proxy omicron period, we found a vaccine effectiveness of 70% (95% confidence interval [CI], 62 to 76), a finding that was supported by the results of all sensitivity tests. This measure of vaccine effectiveness was significantly different from that during the comparator period, when the rate was 93% (95% CI, 90 to 94) against hospitalization for Covid-19 (Table 2).

Thus, during the proxy omicron period, we saw a maintenance of effectiveness of the BNT162b2 vaccine (albeit at a reduced level) against hospital admission for Covid-19 that was presumed to have been caused by the omicron variant as compared with the rate associated with the delta variant earlier in the year. The addition of a booster dose of vaccine may mitigate this reduction in vaccine effectiveness.[5]

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

This letter was published on December 29, 2021, at NEJM.org.

1. Network for Genomic Surveillance in South Africa. SARS-CoV-2 sequencing update. December 3, 2021 (https://www.nicd.ac.za/wp-content/uploads/2021/12/Update-of-SA-sequencing-data-from-GISAID-3-Dec-21-Final.pdf).
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Montevideo, 18 de marzo de 2022

Pedido de informe 1/538/2022

Respecto al pedido de informe de Libertad Sanitaria se presenta:

1) Acta de la reunión de la Comisión Nacional Asesora de Vacunas y el grupo ad-hoc la cual se encuentra publicada en la página web del Ministerio. Se adjunta enlace: https://www.gub.uy/ministerio-salud-publica/comunicacion/publicaciones/actas-reuniones-comision-nacional-asesora-vacunaciones

2) Integración de la CNAV, del grupo ad hoc y detalle de otros asesores participantes de la reunión. Se aclara que la reunión del 9 de fenrero se continuó el día de 16 febrero por lo tanto se presentan los participantes en ambas reuniones

Participan los siguientes miembros:

- Dirección de Epidemiología: Dra. Adriana Alfonso Departamento de Vigilancia en Salud: Dr. Miguel Alegretti (presente el 9/2/2022)

- Unidad de Inmunizaciones: Ex. Prof. Agdo Dr. Gabriel Peluffo, Ex. Prof. Adj. Dra. Graciela Pérez Sartori, Prof. Agda. Dra. Patricia Barrios, Asistente Dr. Steven Tapia Villacís.

- Unidad de Farmacovigilancia: Dra. Salomé Fernandez, Dra. Susana Rodríguez (presentes el 9/2/2022)

- Cátedra de Enfermedades Infecciosas: Prof. Adj Victoria Frantchez.

- Unidad Académica de Bioética: Prof. Agda. Dra. Marianela Barcia.

- Depto. Clínico de Medicina: Asistente Dr. Leonardo Oliva

- Área Economía de la Salud: Javier Díaz.

- Comisión Honoraria de la lucha antituberculosa: Ex. Prof. Dra. Alicia Montano

- Programa de Salud de la Niñez: Ex. Prof. Adj. Dra. Alicia Fernández.

- Depto. de Medicina Familiar y Comunitaria: Prof. Adj. Dra. Natalia Cristoforone.

- Instituto de Pediatría: Prof. Gustavo Giachetto (presente en reunión del 9/2/2022)

- Depto. Desarrollo Biotecnológico: Prof. Alejandro Chabalgoity.

- Por el grupo ad hoc participan: Cátedra de Enfermedades Infecciosas (Ex GACH): Prof. Dr. Julio Medina Cátedra de Inmunología, Facultad de Química, UdelaR: Prof. Gualberto González, Depto.

Desarrollo Biotecnológico UdeLaR: Prof. Agda. Dra. Maria Moreno Depto. Métodos Cuantitativos. Facultad de Medicina (Ex GACH): Prof. Agdo. Dr. Juan Gil. Fac de Ingeniería UdelaR C. Naturales y Exactas/Matemàticas (Ex GACH): Prof. Adj. Dra. Maria Inés Fariello. Sección Virología de la Fac. Ciencias: Prof. Agda. Dra. Adriana Delfraro Cátedra de Inmunobiología, Facultad de Medicina. UdelaR: (Ex GACH) Prof. Dr. Otto Pristch (presente en reunión del 9/2/2022) Diplomatura de Infectología Pediátrica Facultad de Medicina. UdelaR (Ex GACH): Pediatra Epidemióloga Infectóloga Pediatra Prof Agda. Dra. Mónica Pujadas. Departamento de Medicina: Prof. Gabriela Ormachea (presente en reunión 16/2/2022)

- Participantes con voz sin voto: Ministro de Salud Pública: Dr. Daniel Salinas

3) Declaración de conflicto de interés de cada participante. Se adjuntan los conflicto de interés de los miembros principales con voz y voto.

4) La evidencia actual disponible que estuvo a consideración. Se adjuntan los documentos analizados.

Unidad de Inmunizaciones

WHO SAGE ROADMAP FOR PRIORITIZING USE OF COVID-19 VACCINES

An approach to optimize the global impact of COVID-19 vaccines, based on public health goals, global and national equity, and vaccine access and coverage scenarios

First issued 20 October 2020

Updated: 13 November 2020

Updated: 16 July 2021

Latest update: 21 January 2022

World Health Organization

Preamble

This interim guidance constitutes a major revision of the *WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines*, first issued October 2020, and updated in November 2020 and July 2021. It is based on work conducted by the SAGE Working Group on COVID-19 Vaccines and SAGE members, from October 2021 to January 2022, including consultation with RITAG[1] chairs, and dedicated discussions at extraordinary meetings of the Strategic Advisory Group of Experts (SAGE) on Immunization on 7 December 2021 and 19 January 2022 *(1)*.

This revised Roadmap takes into account increasing vaccine availability, vaccine coverage rates, and the evolving epidemiological situation including COVID-19 variants of concern. Scenarios in which vaccination coverage exceeds 50% of the population are considered, as are topics such as vaccine use in children and adolescents and prioritization of additional and booster doses in relation to vaccination coverage rates. To assist countries in developing recommendations for optimized use of vaccines against COVID-19, priority-use groups for vaccination (both primary series and booster doses) are identified based on epidemiological scenarios, public health goals, and vaccine coverage scenarios (in accordance with *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination (2)*).

This Roadmap is complementary to the *Strategy to achieve global Covid-19 vaccination by mid-2022 (3)* issued in September 2021, which was developed by WHO in collaboration with its COVAX partners and key regional and national stakeholders, and which specifies national vaccine coverage categories. The Roadmap emphasizes the importance of prioritizing the distribution of increasingly available vaccine supply to optimize impact on health, socioeconomic conditions, and equity, and focuses on in-country vaccine policies.

Declarations of interests were collected from all external contributors and assessed for any conflicts of interest. Summaries of the reported interests can be found on the SAGE meeting webpage and SAGE Working Group webpage.

[1] RITAG: Regional Immunization Technical Advisory Group

Executive summary

By the end of December 2021, about 12 months after the first COVID-19 vaccine received WHO Emergency Use Listing (EUL), more than 9 billion COVID-19 vaccine doses had been administered globally and 48% of the global population had received the primary vaccination series. However, profound inequities in vaccine access and coverage remain worldwide, with some countries reporting vaccination coverage rates below 5%, and others above 80%. Because millions of people in many countries have been left behind in completing a primary vaccination series, globally-coordinated efforts and funding must be strengthened to achieve equitable distribution to, and uptake of, vaccines in all countries. In 2022, more vaccine doses will become available, enabling many countries to achieve high vaccination coverage by mid-2022. Achieving high vaccine access and coverage rates depends not only on vaccine supplies, but also vaccine acceptance and a country's capacity to roll out available supply.

This Roadmap builds on WHO's *Strategy to achieve global Covid-19 vaccination by mid-2022 (3)* which highlights four objectives for vaccination programmes to achieve the overall goal of full recovery from the COVID-19 pandemic to: i) minimize deaths, severe disease and overall disease burden; ii) curtail the health system impact; iii) fully resume socioeconomic activity; and iv) reduce the risk of new variants. These four objectives are interdependent, and each is important. Currently available COVID-19 vaccines have a modest impact on reducing transmission in the context of SARS-CoV-2 Variants of Concern (VoCs), particularly Omicron. Therefore, averting severe disease and deaths, and protecting health systems remain the primary objectives of vaccine use in the context of the global COVID-19 response, while also reducing morbidity including post COVID conditions. This Roadmap also considers vaccine use in resuming socioeconomic recovery, particularly the priority of maintaining uninterrupted education to keep children connected and learning.

Countries are in different stages of the pandemic and vaccine roll-out, and have different population age structures. To guide country decision-making on how to optimize the public health and social impact of available vaccine supplies and absorptive capacity to administer primary vaccination series and booster doses while attending to equity considerations, the Roadmap identifies priority-use groups and accounts for vaccination coverage rates of the primary series and time since the start of the vaccination programme, in accordance with the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination (2)*.

In most countries, groups at higher risk of severe disease and death were first to receive the primary vaccine series; these groups are therefore among the first to show evidence of declining vaccine effectiveness over time. Emerging evidence indicates that vaccine effectiveness against SARS-CoV-2 infection and any symptomatic COVID-19 declines significantly over a period of six months after completion of the primary series, likely resulting from waning protective vaccine-induced immunity, compounded by lower vaccine-induced neutralizing antibody activity against VoCs, including the Delta and Omicron variants. By contrast, vaccine-induced protection against severe COVID-19 outcomes remains relatively better maintained for at least six months after completion of the primary vaccination series, with some declines from maximum protection after completion depending on vaccine platform and VoC. In the short-term, a third dose (booster dose) may fully or partially restore vaccine effectiveness. Variant-adapted COVID-19 vaccines, while in development, are not yet available, hence their potential use is not considered in this Roadmap.

Given that achieving high rates of primary series coverage among the groups at higher risk of severe disease and death remains a critical priority to optimize the impact of available COVID-19 vaccine supply, this Roadmap is built upon two key findings derived from modelling and vaccine effectiveness data:

1. ***Within a priority-use group*, increasing the primary vaccination series coverage rate has a greater impact on reducing hospitalizations and deaths per dose than use of equivalent vaccine supply to increase the booster dose coverage rate**.

2. ***Across priority-use groups*, increasing the booster dose coverage rate for higher priority-use groups will usually[†] yields greater reductions in severe disease and death than use of equivalent vaccine supply to increase the primary vaccination series coverage rates of lower priority-use groups.**

[†]In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and rollout timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

WHO recommends for low, moderate, and high primary series coverage rates in higher priority-use groups (see also **Table 1** below) that:

1. ***Countries with low rates of primary series coverage* should first achieve high primary series coverage rates among the higher priority-use groups before offering vaccine doses to lower priority-use groups.**[†]

Note: As older adults comprise a large fraction of the highest priority-use group, settings unable to access or deliver vaccines to older adults should consider prioritizing new delivery systems specifically to achieve high coverage rates in this subgroup.

[†]As more vaccine becomes available, lower priority-use groups should be offered vaccine, taking into account national epidemiological data and other relevant considerations. Lower priority-use groups should not be offered primary series doses before higher priority-use groups have been offered primary series doses, unless vaccine programmes encounter significant vaccine delivery or acceptability obstacles to uptake in higher priority-use groups that would result in vaccine wastage. In such cases, community engagement and social mobilization efforts to reach higher priority-use groups should be prioritized.

2. ***Countries with moderate-to-high rates of primary series coverage* in higher priority-use groups should usually[‡] prioritize available resources to first achieve high booster dose coverage rates in higher priority-use groups before offering vaccine doses to lower priority-use groups.**

[‡] In some circumstances, there may be a relatively close trade-off in optimizing the impact of vaccine use between offering booster doses to older adults to avert more hospitalizations and deaths versus offering primary series doses to the remaining adults, adolescents, and children, that depend on country conditions, including supply and rollout timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection.

Table 1: Prioritized use of primary series and booster doses by vaccine coverage rates in higher priority-use (I & II) groups

Priority-use groups†	Vaccine coverage rates of *higher priority-use* (I & II) groups
	Low → Moderate → High → Very high
I. *Highest priority-use* Older adults; Health workers; Immunocompromised persons	Primary series + Additional dose* / Booster**
II. *High priority-use* Adults with comorbidities; Pregnant persons; Teachers and other essential workers; Disadvantaged sociodemographic subpopulations at higher risk of severe COVID-19	Primary series + Booster
III. *Medium priority-use* Remaining adults; Children and adolescents with comorbidities	Primary series + Booster
IV. *Lowest priority-use* Healthy children and adolescents	Primary series + Booster (booster doses in children below the age of 12 years have not yet been assessed)

†*Priority-use groups*: The extent of risk of severe disease and death is the main determinant for assignment of a subgroup (or subpopulation) to a priority-use group. This criterion aligns with a specification of the human well-being principle in the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccines*. In addition, other specifications of that principle, including reducing societal and economic disruption and protecting essential health services, as well as of the national equity and reciprocity principles, are also used to justify assignment of some of the subgroups to a priority-use group.

**Additional dose:* Persons with moderate to severe immunocompromising conditions should receive an *expanded primary vaccination series* through an additional dose about 1–3 months after completion of the primary series (see *Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons (4)*. Such persons are also a high priority-use group for a subsequent (booster) dose.

***Booster dose:* The optimal interval between completion of a primary series and administration of a booster dose has yet to be determined, and depends on epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation of specific variants of concern. As a general principle, dependent on vaccine product, an interval of 4–6 months since completion of the primary series could be considered for countries experiencing significant loss of vaccine effectiveness against severe disease in the context of an impending or ongoing major surge of cases, while a longer interval could be considered for those countries currently not experiencing, or at low risk of, an increasing incidence of cases.

Healthy children and adolescents belong to the lowest priority-use group because of their relatively low risk of severe disease, hospitalization, and death. Vaccinating this age group is less urgent than vaccinating adults, particularly older adults. However, there are benefits of vaccinating children and adolescents that go beyond the direct health benefits, such as minimizing school disruptions. The decision to vaccinate healthy children and adolescents must account for prioritization to first fully protect higher priority-use groups (e.g., older adults and health workers) through primary vaccination series, and, as vaccine effectiveness declines with time, through booster doses. As such, before considering implementing a primary vaccination series in adolescents and

children, using the vaccine supply to attain high coverage rates of primary series – and booster doses as needed based on evidence of waning and optimizing vaccination impact – in higher priority-use groups, such as older adults, must be considered.

Homologous schedules (both for primary series and booster doses) are considered standard practice based on substantial safety, immunogenicity, and efficacy data available for each WHO EUL COVID-19 vaccine. Nonetheless, increasing evidence shows that, for some vaccines, heterologous schedules may offer superior immunogenicity. WHO supports a flexible approach to use of either homologous or heterologous vaccination schedules, and considers a heterologous schedule using any EUL COVID-19 vaccines as sufficient for completion of a primary vaccination series. Heterologous vaccination schedules should be implemented only after careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

The need for and optimal timing of the primary vaccination series and booster dose may be different in an individual who has had a prior SARS-CoV-2 infection or who has experienced a breakthrough infection after initiation of the primary series when compared to a previously uninfected individual. On a population level, the number of doses and interdose interval, as well as the need for booster doses, may differ in settings with high seroprevalence from infection-induced immunity. However, seroprevalence rates observed in population-based studies may not be representative of the entire population or certain subpopulations and age groups, and may also differ by population density. While there may be some benefit to account for the variations in population seropositivity rates in different priority-use groups and the degree of infection-induced protective immunity within countries or communities that may already have experienced high levels of community transmission, basing national vaccination policies on seroprevalence rates or individual pre-vaccination screening is currently not recommended. When more evidence is available, advice on if and how infection-induced immunity should be considered in national vaccination policies will be updated accordingly.

As there is modest impact of vaccines on transmission, and substantially less impact for the newly emerged Omicron variant, public health and social measures must continue, including use of effective face masks, physical distancing, handwashing, and other measures based on the epidemiology of SARS-CoV-2 and vaccine coverage rates. This advice will be updated as information on the impact of vaccination on virus transmission and indirect protection in the community accrues. Countries' strategies related to COVID-19 control should be designed to facilitate participation of children and adolescents in education and other aspects of social life.

Introduction

To support countries in implementing their respective vaccination programmes against coronavirus disease (COVID-19), the Strategic Advisory Group of Experts (SAGE) on Immunization of the World Health Organization (WHO) developed a three-step process to provide guidance for overall programme optimization, as well as vaccine-specific recommendations.

Step 1: A values framework. The *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination (2)*, issued on 14 September 2020, outlines the general principles, objectives, and target groups for prioritizing the use of COVID-19 vaccine supplies.

Step 2: A roadmap for optimizing uses of COVID-19 vaccines based on priority-use groups (Prioritization Roadmap). This Prioritization Roadmap remains fully aligned with the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination (2)*. To support countries in planning vaccination programmes, this Roadmap suggests public health strategies and identifies target groups for optimization of COVID-19 vaccine use (referred to as "priority-use groups") in the context of different epidemiological settings, public health goals, and levels of vaccine access and coverage. The initial Roadmap, entitled *WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply* (first published on 7 October 2020 and updated on 13 November 2020 and 16 July 2021), considered priority uses of vaccines at a time when vaccine supply was limited and deployment of the primary vaccination series was the only consideration. The focus of this current Roadmap is the optimization of vaccine use, including as a booster dose, and vaccination of adolescents and children. This update also reflects additional data from pre- and post-authorization studies, as well as lessons learned from COVID-19 vaccine programme implementation. The Roadmap will be updated, as necessary, to accommodate the dynamic nature of the pandemic, greater availability of vaccines, and evolving evidence about vaccine use and impact.

Step 3: Evidence to vaccine-specific recommendations. Specific recommendations for the use of EUL and WHO prequalified vaccines will be issued based on SAGE's *Evidence to recommendations for COVID-19: evidence framework (5)*. Currently, eight vaccines have been recommended by WHO for emergency use, and vaccine-specific interim recommendations on the use of these EUL vaccines have been issued (see: COVID-19 vaccines technical documents: Product specific documentation). These recommendations are updated as additional evidence on effectiveness, safety, and other needs (e.g., use of additional and booster doses) becomes available, and as epidemiological and other contextual conditions evolve.

Definitions

Throughout this Roadmap, "optimization" refers to policy considerations and decisions that aim to make the most effective and efficient use of COVID-19 vaccine supplies in specific epidemiological settings to achieve global and local public health goals.

The following definitions and terminology for additional doses and booster doses are used by WHO throughout its policy recommendations on COVID-19 vaccination.

- *Additional doses* of a vaccine may be needed as part of an *extended primary vaccination series* for target populations where the immune response rate following the standard primary series is deemed insufficient. The objective of an additional dose in the primary series is to optimize or enhance the immune response to establish a sufficient level of effectiveness against disease. In particular, immunocompromised individuals often fail to mount a protective immune response after a standard primary series. In addition, older adults may also respond poorly to a standard primary series with some vaccines.
- *Booster doses* are administered to a population that has completed a *primary vaccination series* (including additional doses in an extended primary series). The objective of a booster dose is to restore vaccine effectiveness when, with time, the

immunity and clinical protection of a primary vaccination series has fallen below a rate deemed sufficient in that population.

Epidemiological setting scenarios

The epidemiological settings used in this Roadmap take into consideration the relative benefits and potential risks of COVID-19 vaccine use (i.e., both primary vaccination series and booster dose). The public health strategy for optimizing vaccine use depends on the burden of disease and the local epidemiology, including transmission patterns, seroprevalence from infection-induced immunity in the target population, circulation of specific variants of concern (VoCs), and the incidence rate of infection in the specific setting at the time vaccination is being contemplated.

Transmission patterns

WHO uses seven categories[2] to describe transmission patterns at national and subnational levels to guide decisions for preparedness, readiness and response activities (see: WHO's *Critical preparedness, readiness and response actions for COVID-19*). Although countries are in different epidemiological phases with different transmission patterns, essentially all are experiencing at least one of the four community transmission levels, which share common COVID-19 response aims: to slow transmission; to reduce case numbers; and to end community outbreaks. Hence, this Roadmap considers a single epidemiological scenario, community transmission.

Infection-induced immunity

Immunity derived from SARS-CoV-2 infection may provide variable protection against re-infection and severe disease. Infection-induced protective immunity may wane over time and be lower against new VoCs. Uncertainty remains as to the relative protection afforded by infection-induced, versus vaccine-induced, immunity, although initial evidence suggests that some COVID-19 vaccines provide higher levels of protective immunity than does infection, and that vaccination increases protective immunity in those with a prior infection. Preliminary evidence suggests that infection/vaccination-induced hybrid immunity from three exposures to Spike protein (i.e., one or more exposures from vaccination and one or more from SARS-CoV-2 infection, the latter either before or after vaccination) may provide superior neutralization capacity against VoCs, including Omicron, compared with two doses of vaccination, or previous natural SARS-CoV-2 infection without vaccination *(6)*.

As such, the need for, and optimal timing of, the primary vaccination series and booster dose may be different in an individual who had prior SARS-CoV-2 infection(s), or who experienced a breakthrough infection after initiation of the primary series, when compared to a previously uninfected individual. On a population level, the number of doses and interdose interval, as well as the need for booster doses, may differ in settings with high seroprevalence from infection-induced immunity. Furthermore, seroprevalence is likely to help to inform future strategies and may be considered as part of comprehensive surveillance. However, under current conditions of limited serological testing capacity in many settings, pre-vaccination screening for past infection will increase logistical complexity and hamper the programmatic roll-out of vaccines and may not be cost–effective.

[2] The seven transmission categories defined by WHO are: 1. No (active) cases; 2. Imported/Sporadic cases; 3. Clusters of cases; 4. Community transmission (CT)1: Low incidence of locally acquired widely dispersed cases detected in the past 14 days; 5. CT2: Moderate incidence of locally acquired widely dispersed cases detected in the past 14 days; 6. CT3: High incidence of locally acquired widely dispersed cases in the past 14 days; 7. CT4: Very high incidence of locally acquired widely dispersed cases in the past 14 days.

In addition, seroprevalence rates observed in population-based studies may not be representative of the entire population or certain subpopulations and age groups, and may also differ by population density (e.g., higher rates in urban settings than in rural settings). While there may be some benefit to account for the variations in population seropositivity rates in different priority-use groups and the degree of infection-induced protective immunity within countries or communities that may have already experienced high levels of community transmission, basing national vaccination policies on seroprevalence rates or individual pre-vaccination screening is currently not recommended. When more evidence is available, advice will be updated accordingly on if and how infection-induced immunity should be considered in national vaccination policies.

Variants of concern

The level of initial protective immunity achieved and the degree of waning of vaccine effectiveness, and hence the need for a booster dose, may differ depending on the circulating SARS-CoV-2 viruses, particularly VoCs, in the population. The protection conferred by vaccination also depends on the severity of the clinical outcome. While evidence shows that vaccine effectiveness against symptomatic SARS-CoV-2 infections wanes significantly during the six months following vaccination, vaccine effectiveness against hospitalizations and death wanes only modestly during the same period. This extent of waning is variant-dependent and may further depend upon the vaccine product(s) in use, and the priority-use group(s) (e.g., older adults, immunocompromised persons, those at high risk of exposure).

The Omicron variant which emerged in November 2021 is highly transmissible; it rapidly becomes the dominant variant where it circulates, and is spreading globally. Evolving evidence suggests that the Omicron variant is associated with less severe clinical disease compared with previous VoCs. Currently available COVID-19 vaccines continue to protect against severe disease, hospitalizations and death due to Omicron, albeit less so compared with other variants. Vaccine effectiveness following a primary vaccine series is low for mild infections due to Omicron. A booster dose enhances vaccine effectiveness against severe disease and hospitalizations *(6)* but vaccine impact on preventing mild disease, asymptomatic infections and viral shedding is modest and short-lived even with a booster dose. The emergence of Omicron re-emphasizes the urgent need to achieve very high vaccination coverage rates in the higher priority-use groups. It remains unknown to what extent Omicron cross-protects against other circulating VoCs, and those that will potentially newly emerge. The extent to which infection-induced immunity will contribute to high rates of protection against severe disease, hospitalization, and deaths in populations with lower vaccine coverage rates may be an important consideration in setting vaccine coverage targets for those populations. Variant-adapted COVID-19 vaccines, while in development, are not yet available, hence their potential use is not considered in this Roadmap. This Roadmap will be updated when more data accumulate.

Vaccine access and coverage

Vaccine supply has increased exponentially since January 2021. By the end of December 2021, 9 billion doses had been administered, and >48% of the global population fully vaccinated with a primary series. However, vaccine distribution remains grossly inequitable: some low-income countries have achieved less than 5% vaccine coverage, and only 9% of people in low-income countries have received at least one dose. As long as there is inequitable vaccine distribution with associated low coverage rates in some countries, the burden of mortality will remain inequitably distributed, and the risk of emergence and spread of new VoCs will likely remain high. Globally-coordinated efforts, and funding to fully enable COVAX, need to be strengthened to achieve equitable vaccine distribution to, and uptake in, all countries.

Vaccine coverage rates are determined not only by vaccine supply, but also by community vaccine acceptance, and the absorptive capacity by countries to implement vaccination programmes and other logistical constraints. WHO's *Strategy to achieve global*

Covid-19 vaccination by mid-2022 (3) describes the following stratified vaccination coverage rates: low (<10%); medium (10–40%); high (41–70%); and very high (>70%).

Public health goals scenarios

The *Strategy to achieve global Covid-19 vaccination by mid-2022 (3)* highlights four objectives for vaccination programmes to achieve the overall goal of full recovery from the COVID-19 pandemic: i) to minimize deaths, severe disease and overall disease burden; ii) to curtail the health system impact; iii) to fully resume socioeconomic activity; and iv) to reduce the risk of new variants. These four objectives are interdependent and each is important. However, currently available COVID-19 vaccines have modest impact on reducing transmission in the context of VoCs. Therefore, the emphasis on averting severe disease and deaths, and protecting health systems continues in the context of the global COVID-19 response. Hence, older adults, immunocompromised persons and health workers are the highest priority. Using vaccine to minimize the overall disease burden (including post COVID conditions), as well as other strategic uses of vaccine, also contributes to the objective of fully resuming socioeconomic activity, including ensuring stability of education for children and adolescents.

Priority-use groups

This Roadmap identifies four priority-use groupings, from highest to lowest priority-use, based largely on risk of severe disease, hospitalizations, and death. This health risk criterion aligns with a specification of the human well-being principle in the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccines.* In addition, other specifications of that principle, including reducing societal and economic disruption and protecting essential health services, as well as of the national equity and reciprocity principles, are also used to justify categorization of some priority-use groupings. For example, teachers and other school staff are highlighted as a priority-use subgroup of particular importance to advancing the well-being of children, and societal functioning. Similarly, as regards to equity, this Roadmap also identifies, for special consideration, adults from disadvantaged communities experiencing higher rates of poor health and inadequate health care, as well as higher risks of SARS-CoV-2 infection from living and work conditions. The Values Framework goals and principles which underpin the placement of priority-use subgroups in each of the priority-use groupings can be found in Annex 1; the explanation of the four priority-use groupings in Annex 2; and the risk stratification for health workers in Annex 3.

A major lesson learned from vaccine roll-out during this pandemic is that overly complicated or prescriptive prioritization schema are difficult to implement and thus have limited use. For example, some countries use an age-descending approach only. In this Roadmap, the four priority-use groupings are populated by a limited number of commonly identified subgroups (Annex 2).

Optimized use of COVID-19 vaccines

Primary vaccination series

Achieving high primary series coverage among the priority-use subgroups at higher risk of severe disease and death remains a critical priority to optimize the impact of available COVID-19 vaccine supply.

Countries with low coverage rates of the primary vaccination series should first achieve high rates among the subgroups at higher risk of severe disease and death (i.e., most subgroups in the highest and high priority-use groups). As more vaccine becomes available, additional priority-use groups should be vaccinated, taking into account national epidemiological data and other relevant considerations. Primary series doses should not be offered to lower priority-use groups without first being offered to higher priority-

use groups unless there is adequate justification to do so. Justification may include significant vaccine delivery or acceptability obstacles to uptake in higher priority-use groups that would result in vaccine wastage; in such cases, social mobilization efforts to reach higher priority-use groups should be prioritized. The programmatic need in geographically isolated or hard to reach locations to provide vaccine at the same time to lower priority-use groups as well as higher priority use groups may also be adequate justification.

As older adults comprise a large fraction of the highest priority-use group, settings unable to access or deliver vaccines to older adults should consider prioritizing new delivery systems specifically to achieve high coverage rates in this subgroup. WHO has published tools, guidance, national deployment and vaccination plans and training resources (*7–9)*.

Booster doses

With many countries having implemented a primary vaccination series more than 6 months ago, waning of clinical vaccine effectiveness over time has been demonstrated, further compounded by lower vaccine effectiveness in the context of Delta and Omicron VoCs due to immune escape mechanisms of these variants and likely other virological factors (e.g., tropism, incubation period, force of infection). Current evidence underpins that waning vaccine effectiveness is moderate for severe disease, hospitalizations and death, but more significant for asymptomatic and mildly symptomatic SARS-CoV-2 infections. It is particularly important to monitor for loss of sufficient vaccine effectiveness among those at highest risk of severe disease or death. Because these higher risk groups may have been vaccinated first, they may be among the first groups to show evidence of loss of sufficient vaccine effectiveness due to the longer elapsed time since completion of their primary series.

Booster doses should be offered based on evidence that doing so would optimize impact against severe disease, hospitalization, and death, and to protect health systems. The order of implementing booster doses should follow that for primary vaccination series – i.e., booster doses should be prioritized first to the higher priority-use groups before extending to lower priority-use groups, unless there is adequate justification not to do so. Such justification may include significant vaccine delivery or acceptability obstacles to uptake in higher priority-use groups that would result in vaccine wastage. In such cases, strategies should be prioritized to improve vaccine delivery, community engagement, and social mobilization efforts to reach higher priority-use groups.

Within a given priority-use group, primary series vaccination will have greater impact per dose than booster doses. Across priority-use groups, the benefits of booster doses for higher priority-use groups versus primary series doses for lower priority-use groups may be a relatively close trade-off that depends on country conditions, including supply and roll-out timelines, past epidemic dynamics and infection-induced immunity, vaccine product, vaccine effectiveness, and waning of protection. When high primary series coverage rates have been achieved among subgroups at higher risk of severe disease and death (e.g., older adults), booster doses for these subgroups may yield greater reductions in severe disease and death than use of equivalent vaccine supply for primary series vaccination of lower priority-use groups.

The optimal interval between completion of a primary series and administration of a booster dose has yet to be determined, and depends on epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation and frequency of specific VoCs. As a general principle, an interval of 4–6 months since completion of the primary series could be considered for countries experiencing loss of vaccine effectiveness against severe disease in the context of an impending or ongoing major surge of cases, especially in the context of Omicron, while a longer interval could be considered for settings currently not experiencing, or are at low risk of, an increasing incidence of cases.

Some countries are implementing a 2nd booster dose for their highest risk populations 3–4 months after an initial booster dose. More data on the waning of protective immunity and vaccine effectiveness against severe disease and hospitalization after an initial booster dose is required before a recommendation may be made on additional booster doses.

Table 1: Prioritized use of primary series and booster doses by vaccine coverage rates in higher priority-use (I & II) groups

Priority-use groups†	Vaccine coverage rates of *higher priority-use* (I & II) groups
	Low → Moderate → High → Very high
I. *Highest priority-use* Older adults; Health workers; Immunocompromised persons	Primary series + Additional dose* / Booster**
II. *High priority-use* Adults with comorbidities; Pregnant persons; Teachers and other essential workers; Disadvantaged sociodemographic subpopulations at higher risk of severe COVID-19	Primary series + Booster
III. *Medium priority-use* Remaining adults; Children and adolescents with comorbidities	Primary series + Booster
IV. *Lowest priority-use* Healthy children and adolescents	Primary series + Booster (booster doses in children below the age of 12 years have not yet been assessed)

†*Priority-use groups*: The extent of risk of severe disease and death is the main determinant for assignment of a subgroup (or subpopulation) to a priority-use group. This criterion aligns with a specification of the human well-being principle in the *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccines*. In addition, other specifications of that principle, including reducing societal and economic disruption and protecting essential health services, as well as of the national equity and reciprocity principles, are also used to justify assignment of some of the subgroups to a priority-use group.

**Additional dose:* Persons with moderate to severe immunocompromising conditions should receive an *expanded primary vaccination series* through an additional dose about 1–3 months after the completion of the primary series (see *Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons (4)*. Such persons are also a high priority-use group for a subsequent (booster) dose.

***Booster dose:* The optimal interval between completion of a primary series and administration of a booster dose has yet to be determined, and depends on epidemiological setting, vaccine product, targeted age groups, background seroprevalence, and circulation of specific variants of concern. As a general principle, dependent on vaccine product, an interval of 4–6 months since completion of the primary series could be considered for countries experiencing significant loss of vaccine effectiveness against severe disease in the context of an impending or ongoing major surge of cases, while a longer interval could be considered for those countries currently not experiencing, or at low risk of, an increasing incidence of cases.

Heterologous primary vaccination series and booster doses

Homologous schedules are considered standard practice based on substantial safety, immunogenicity, and efficacy data available for each WHO EUL COVID-19 vaccine. However, WHO supports a flexible approach to use of either homologous or heterologous vaccination schedules, and considers two heterologous doses of any EUL COVID-19 vaccine to be a complete primary series. Heterologous vaccination should only be implemented with careful consideration of current vaccine supply, vaccine supply projections, and other access considerations, alongside the potential benefits and risks of the specific products being used.

Rapidly achieving high vaccination coverage with a primary vaccine series in higher priority-use groups should continue to be the focus while vaccine supply remains constrained. Either homologous or heterologous schedules should be used. The process of vaccination should not be delayed over considerations regarding the potential benefits of heterologous versus homologous schedules.

For countries considering heterologous schedules, WHO makes the following recommendations on the basis of equivalent or favourable immunogenicity or effectiveness for heterologous versus homologous schedules *(7)*:

- Depending on product availability, countries implementing WHO EUL inactivated vaccines for initial doses may consider using WHO EUL vectored or mRNA vaccines for subsequent doses.
- Depending on product availability, countries implementing WHO EUL vectored vaccines for initial doses may consider using WHO EUL mRNA vaccines for subsequent doses.
- Depending on product availability, countries implementing WHO EUL mRNA vaccines for initial doses may consider using WHO EUL vectored vaccines for subsequent doses.

Recommendations as to the relative risks and benefits of homologous versus heterologous primary and booster doses will be reviewed as additional data become available.

Community engagement, effective communication, and legitimacy

Community engagement and effective communication are essential to the success of COVID-19 vaccine programmes. These elements are grounded in the legitimacy principle of the Values Framework. This principle requires that prioritization decisions are made through transparent processes based on shared values, best available scientific evidence, and appropriate representation and input by affected parties. Adhering to the legitimacy principle is a way to promote public trust and acceptance of a COVID-19 vaccine.

When applied in practice, countries may embrace the legitimacy principle through practical strategies that improve the public's perception and understanding of vaccine development and prioritization processes. Examples of such strategies include i) culturally and linguistically accessible communications made freely available regarding COVID-19 vaccination; ii) engagement of community leaders and trusted community representatives to contribute to communications; and iii) inclusion of diverse and affected stakeholder groups in decision-making and planning processes. Community engagement and effective communication are especially important in subpopulations that may be unfamiliar with or distrustful of health-care systems. To complement this work, the routine gathering of local data on the behavioural and social drivers of vaccination will offer valuable insights to guide the implementation of effective strategies to achieve high confidence and uptake.

As outlined in the Values Framework, personal, financial, or political conflicts of interest or corruption should not be tolerated in the prioritization of groups for COVID-19 vaccination. In all cases, decision-makers must be able to publicly defend their decisions and actions with reasons that even those who disagree can view as reasonable, and not arbitrary or self-serving. Countries should ensure that individuals are not able to use their social, financial, or political privilege to bypass country-level prioritization.

Annex 1. Values Framework

Table A1. Values Framework: goals and principles*

Goal Statement	COVID-19 vaccines must be a global public good. The overarching goal is for COVID-19 vaccines to contribute significantly to the equitable protection and promotion of human well-being among all people of the world.
Principles	**Objectives**
Human Well-being	Reduce deaths and disease burden from the COVID-19 pandemic;
	Reduce societal and economic disruption by containing transmission, reducing severe disease and death, or a combination of these strategies;
	Protect the continuing functioning of essential services, including health services.
Equal Respect	Treat the interests of all individuals and groups with equal consideration as allocation and priority-setting decisions are being taken and implemented;
	Offer a meaningful opportunity to be vaccinated to all individuals and groups who qualify under prioritization criteria.
Global Equity	Ensure that vaccine allocation takes into account the special epidemic risks and needs of all countries; particularly low-and middle-income countries;
	Ensure that all countries commit to meeting the needs of people living in countries that cannot secure vaccine for their populations on their own, particularly low- and middle-income countries.
National Equity	Ensure that vaccine prioritization within countries takes into account the vulnerabilities, risks and needs of groups who, because of underlying societal, geographic or biomedical factors, are at risk of experiencing greater burdens from the COVID-19 pandemic;
	Develop the immunization delivery systems and infrastructure required to ensure COVID-19 vaccines access to priority populations and take proactive action to ensure equal access to everyone who qualifies under a priority group, particularly socially disadvantaged populations.
Reciprocity	Protect those who bear significant additional risks and burdens of COVID-19 to safeguard the welfare of others, including health and other essential workers.
Legitimacy	Engage all countries in a transparent consultation process for determining what scientific, public health, and values criteria should be used to make decisions about vaccine allocation between countries;
	Employ best available scientific evidence, expertise, and significant engagement with relevant stakeholders for vaccine prioritization between various groups within each country, using transparent, accountable, unbiased processes, to engender deserved trust in prioritization decisions.

* Extracted from: *WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination*.

Annex 2. Priority-use groups

Highest priority-use groups

Older adults

Older age is associated with a steep rise in risk for more severe disease, hospitalizations, and death. The risk of death related to COVID-19 is extremely high in older adults compared with that in younger adults. For example, in the United States of America, the mortality risk is estimated to be 90 times higher among adults aged 65–74 years than among those aged 18–29 years. A similar pattern of significantly higher mortality in older adults has been observed in other countries. The evidence to date from modelling analyses suggests that using years of lives lost[3] instead of deaths would not substantially alter the priority-use ranking of older adults relative to younger persons when age is the only dimension considered.

Population age structures differ from country to country. In some countries, older adults, particularly those aged 60 years and older, constitute more than 20% of the populations; in other countries less than 5%. WHO recommends that very high vaccination coverage rates should be achieved for all older adults. The threshold for the definition of "older adults" may vary from country to country but is typically adults older than 60 years of age.

Health workers

Health workers are all people engaged in work actions whose primary intent is to improve human health. This includes health service providers, such as doctors, nurses, midwives, public health professionals, laboratory technicians, health technicians, medical and non-medical technicians, personal care workers, community health workers, healers and practitioners of traditional medicine. It also includes health management and support workers, such as cleaners, drivers, hospital administrators, district health managers and social workers, and other occupational groups in health-related activities. The International Labour Organization (ILO), together with WHO, published a risk stratification for exposure to SARS-CoV-2 (see: *Preventing and mitigating COVID-19 at work*). Linked to the Values Framework, health workers at high and very high risk of exposure (see Annex 3 and *COVID-19: Occupational health and safety for health workers: interim guidance*) are in the highest priority-use group for vaccination. The reasons for prioritizing health workers for vaccination are first, that protecting these workers protects the availability of critical essential services; second, evidence suggests that health workers are at high risk of acquiring infection and possibly of severe morbidity and mortality (health workers were among the first victims of the pandemic). There is also a risk of onward transmission to people and patients who are at higher risk of serious COVID-19 outcomes; and third, that prioritization is supported by the principle of reciprocity: health workers play critical roles in the COVID-19 response, putting not only themselves but also potentially their household members at higher risk for the sake of others.

Moderately and severely immunocompromised persons[4]

[3] "Years of life lost" is a measure thought by many to integrate a commitment to maximizing health benefit with a commitment to promoting equity, where equity is understood to include an obligation to ensure that younger people have a fair chance to reach later stages of life.

[4] Persons are considered moderately or severely immunocompromised if they:

- **are receiving active cancer treatment**: Active immunosuppressive treatment for solid tumour or hematologic malignancy (including leukemia, lymphoma, and myeloma), or within 12 months of ending such treatment.
- **have received a transplant**: Receipt of solid organ transplant and taking immunosuppressive therapy; receipt of stem cell transplant (within 2 years of transplantation, or taking immunosuppressive therapy).
- **have an immunodeficiency condition**: Severe primary immunodeficiency; chronic dialysis.
- **have an HIV infection *with a current CD4 count of <200 cells/µl and/or lack viral suppression***

Moderately and severely immunocompromised persons (ICPs) are at higher risk of severe COVID-19, regardless of age, although increasing age remains an important co-factor. For purposes of this Roadmap, moderately and severely ICPs include those with active cancer, immunodeficiency, transplant recipients, and those actively receiving treatment with immunosuppressives. This category also includes people living with HIV with a current CD4 cell count of <200 cells/µl; those with evidence of an opportunistic infection; and those not on HIV treatment, and/or with a detectable viral load (i.e., advanced HIV disease). (For further details, see: *Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons (4)*.)

Available data for WHO EUL COVID-19 vaccine products suggest that vaccine effectiveness and immunogenicity are lower in ICPs compared to persons without immunocompromising condition. Emerging evidence suggests that an additional vaccine dose included in an extended primary series enhances immune responses in some ICPs. Reactogenicity data of an additional (third) dose given to ICPs, where reported, have generally been similar to those observed for the standard primary series of the vaccine being administered. Given the significant risk of severe COVID-19 for ICPs, if infected, WHO considers that the benefits of an additional (third) dose in an extended primary series outweigh the risks based on available data, although additional safety monitoring is required.

Available evidence suggests that an additional (third) dose should be given 1–3 months after the completion of the standard primary series in order to increase protection as quickly as possible in ICPs. The most appropriate timing for the additional dose may vary depending on the epidemiological setting and the extent and timing of immune suppressive therapy and course of the disease, and should be discussed with the treating physician. Additional booster doses may be necessary for ICPs. Information and, where possible, counselling about the limitations around the data on administration of an additional dose to ICPs should be provided to inform individual benefit–risk assessment.

Given that protection may remain inadequate in a portion of ICPs even after the administration of an additional dose, WHO further recommends that close contacts (particularly caregivers) of such individuals should be vaccinated if eligible. Additional public health and social measures at the household level to protect ICPs are also warranted depending on the local epidemic circumstances.

High priority-use groups

Adults with comorbidities

Several comorbidities such as diabetes, hypertension, chronic cardiac, lung and kidney diseases, neurodegenerative diseases, and conditions associated with immunosuppression are associated with a higher risk of severe disease, independent of age, but often further compounded by increasing age.

Pregnant women

Pregnant women with COVID-19 are at higher risk of developing severe disease, with increased risk of intensive care unit admission and invasive ventilation, compared to non-pregnant women of reproductive age. COVID-19 in pregnancy is also associated with an increased risk of preterm birth and of neonates requiring neonatal intensive care. It may also be associated with an increased risk of maternal mortality. Pregnant women who are aged 35 years or older, or have a high body mass index, or an existing comorbidity, such as diabetes or hypertension, are at particular risk of serious outcomes from COVID-19.

- **are receiving immunosuppressive treatment**: Active treatment causing significant immunosuppression (including high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumour-necrosis factor (TNF) blockers, and other drugs that are significantly immunosuppressive; or have received immunosuppressive chemotherapy or radiotherapy in the previous 6 months.

Developmental and reproductive toxicology (DART) studies in pregnant animals have been conducted for all eight WHO EUL vaccines to date, and no harmful effects have been reported. Based on the severity of the risks of COVID-19 disease in pregnancy, WHO has concluded that the benefits of vaccination for pregnant women generally outweigh the risks. When considering use of a COVID-19 vaccine during pregnancy, a detailed discussion on the use of each specific WHO EUL COVID-19 vaccine product in pregnancy can be found in the section on pregnant women in the vaccine-specific interim recommendation documents (see: *COVID-19 vaccines technical documents: Product specific documentation*).

Teachers and other essential workers in sectors outside of health

Teachers, school staff and other essential workers are also included as high priority-use groups because of the role these subgroups play in helping to maintain societal functioning and well-being, including for children, and because their occupations generally put them at a higher risk of SARS-CoV-2 exposure.

Disadvantaged sociodemographic subpopulations at higher risk of severe COVID-19 disease

Which disadvantaged sociodemographic subgroups are at higher risk of severe disease or death will vary from country to country but by and large these subgroups are characterized by limited economic and political power and often reduced social standing. In many contexts, the evidence of elevated risk of severe COVID-19 and death will be lacking or less clear than for risk factors such as age or medically diagnosed comorbidities. Policymakers may have to decide which disadvantaged groups are likely to be sufficiently burdened by COVID-19. While broader efforts must be made to reach out and identify risks among disadvantaged subgroups, these decisions may have to be based on reasonable assumptions about differential impact inferred from other relevant contexts, including past public health emergencies. Some individuals in socioeconomically disadvantaged subgroups would likely qualify for prioritization of vaccine use if their comorbidities were known or ascertainable, if they had better access to health care. In many contexts, disadvantaged subgroups are more likely to experience a higher burden of infection and consequent COVID-19 because of crowded work or living conditions over which they have no effective control, as well as a higher prevalence of background states of poor health that increase their risk of severe COVID-19.

Medium priority-use group

All remaining adults

This priority-use group includes all adults in neither the highest nor high priority-use groups.

Children and adolescents with comorbidities

Comorbidities such as diabetes, cardiac, lung and kidney diseases in children and adolescents are associated with a higher risk of severe COVID-19, but generally, this risk is still lower compared to adults with the same comorbidities, as increasing age is an independent risk factor for severe disease. All children and adolescents with moderate and severe immunocompromising conditions belong to the highest priority-use group *(4)*. Down Syndrome and other neurodevelopmental diseases put children at higher risk of severe COVID-19; some countries may consider place such children and adolescents in the highest priority-use grouping

Lowest priority-use group

Children and adolescents

Children (i.e., those younger than 18 years of age) warrant special consideration for at least three reasons: i) children are dependent on adults and the wider society for their well-being; ii) although severe COVID-19 is rare in otherwise healthy children, it is occasionally observed; and iii) setbacks in well-being and education during childhood can have severe and lifelong negative effects.

A recent *WHO Interim statement on COVID-19 vaccination for children and adolescents* reviewed the burden of disease in children and adolescents; the role of children and adolescents in transmission of SARS-CoV-2; the socioeconomic impact of the COVID-19 pandemic and pandemic response on children and adolescents; and the rationale for vaccinating adolescents and children. The statement concluded that countries should consider the individual and population benefits of vaccinating children and adolescents in their specific epidemiological and social context when developing their COVID-19 immunization policies and programmes. As children and adolescents tend to have milder disease compared to adults, unless they are in a subgroup at higher risk of severe COVID-19, it is less urgent to vaccinate this lowest priority-use group than older adults, those with chronic health conditions, and health workers.

Indirect protection of at-risk adults through vaccinating high-transmitting younger age subgroups against SARS-CoV-2 was an approach used for influenza. However, while the effectiveness of COVID-19 vaccines against asymptomatic infection (a proxy for transmission) was high for ancestral virus and the Alpha variant, it was reduced by around 20% against Delta *(8)* and is thought to be further reduced by Omicron *(9)*. As vaccine effectiveness against infection and transmission wanes over time (while against severe disease it is relatively well maintained), potential use of COVID-19 vaccines for indirect impacts of vaccine strategies is limited.

Nonetheless, there may be benefits of vaccination that go beyond the direct health benefits to children and adolescents. Vaccination may minimize disruptions to education for children, and maintenance of their overall well-being, health and safety are important considerations. Countries' strategies related to COVID-19 control should facilitate children's participation in education and other aspects of social life, and minimize school closures, even without vaccinating children and adolescents. UNICEF and WHO have developed guidance on how to minimize transmission in schools and keep schools open, regardless of vaccination of school-aged children *(10)*.

The decision to vaccinate adolescents and children must account for prioritization to first fully protect the higher priority-use groups through primary vaccination series, and, as vaccine effectiveness declines with time since completion of the primary vaccination series, through booster doses. As such, before considering implementing primary vaccination series in adolescents and children, attaining high coverage of primary series – and booster doses as needed based on evidence of waning and optimizing vaccination impact – in higher priority-use groups, particularly older adults, must be considered.

WHO recommends that countries that have achieved high vaccination coverage rates in the higher priority-use groups prioritize global sharing of COVID-19 vaccines (preferentially through the COVAX facility or alternative arrangements) before proceeding to vaccination of healthy children and adolescents who are at lowest risk for severe disease (see Table A2).

Table A2. Subpopulations in the four priority-use groups based on the extent of risk of severe disease, hospitalization and death, or disruption to health systems, education, or other essential services[5]

Priority-use groups	Subpopulations
Highest	• Older adults defined on the basis of age-based risk specific to country/region; specific age cut-off to be decided at the country level. • Health workers.† • Moderately and severely immunocompromised persons.*
High	• Adults with comorbidities or health states (such as pregnancy) that put them at increased risk of severe disease. • Teachers and school staff. • Other essential workers outside health and education sectors (examples include police officers, municipal service workers, child-care providers, agriculture and food workers, transportation workers, seafarers and air crews, government workers essential to the critical functioning of the state and not covered by other categories). • Disadvantaged sociodemographic subpopulations at increased risk of severe disease and death because of higher burden of poor health, inadequate access to health services, underdiagnosis of comorbidities, and/or crowded living and working conditions. Efforts should be made to ensure that these groups are equitably included in this high priority-use category.
Medium	• All remaining adults in neither high nor highest priority-use groups. • Children and adolescents with underlying medical conditions that put them at increased risk of severe COVID-19.
Lowest	• Healthy adolescents and children.

† COVID-19: Occupational health and safety for health workers: interim guidance. 2 February 2021. International Labour Organization and World Health Organization; 2021 (see: www.who.int/publications/i/item/WHO-2019-nCoV-HCW_advice-2021.1).
* Interim recommendations for an extended primary series with an additional vaccine dose for COVID-19 vaccination in immunocompromised persons: interim guidance. 26 October 2021. Geneva: World Health Organization; 2021 (see: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-immunocompromised-persons).
Note: there is no intent of order within the priority-use groupings

5

Annex 3. Definition and risk stratification of health workers

Health workers are all people engaged in work actions whose primary intent is to improve human health. This includes health service providers, such as doctors, nurses, midwives, public health professionals, laboratory technicians, health technicians, medical and non-medical technicians, personal care workers, community health workers, healers and practitioners of traditional medicine. It also includes health management and support workers, such as cleaners, drivers, hospital administrators, district health managers and social workers, and other occupational groups in health-related activities. Health workers include not only those who work in acute care facilities but also those employed in long-term care, public health, community-based care, social care and home care and other occupations in the health and social work sectors (as defined by the International Standard Industrial Classification of All Economic Activities (ISIC), revision 4, section Q: Human health and social work activities).

According to the Prioritization table above, all health workers are currently allocated to the highest priority-use group for ease of vaccine roll-out. However, countries may find the following levels useful in assessing the risk of occupational exposure to SARS-CoV-2 for jobs or tasks of health workers, prior to introducing mitigation measures (see *COVID-19: Occupational health and safety for health workers: interim guidance, 2 February 2021*).

a) **Low risk**. Jobs or work without frequent, close contact with the public or others, that do not require contact with people known to be, or suspected of being, actively infected with the virus responsible for COVID-19. Workers in this group have minimal occupational contact with the public and other co-workers, for example performing administrative duties in non-public areas of health-care facilities away from other staff members, or telehealth services in individual offices.

b) **Medium risk**. Jobs or tasks with close, frequent contact with the general public or others, but that do not require contact with people known to be, or suspected of being, actively infected with the virus responsible for COVID-19. In areas where COVID-19 cases continue to be reported, this risk level may apply to workers who have frequent and close contact with people in busy staff work areas within a health-care facility and work activities where safe physical distance may be difficult to maintain, or tasks that require close and frequent contact between co-workers. In areas without community transmission of COVID-19, this scenario may include frequent contact with people returning from areas with known higher levels of community transmission. Examples include, providing care to the general public who are not known, or suspected of having, COVID-19; or working in busy staff work areas within a health-care facility.

c) **High risk**. Jobs or tasks with high potential for close contact with people who are known, or suspected of having, COVID-19, as well as contact with objects and surfaces possibly contaminated with the virus, for example, direct patient care, domestic services or home care for people for people with COVID-19. Jobs and tasks that may fall under this category may include: entering the room of a known or suspected COVID-19 patient; providing care for a known or suspected COVID-19 patient not involving aerosol-generating procedures; transportation of people known or suspected to have COVID-19 without separation between the driver and the passenger.

d) **Very high risk**. Jobs or tasks with risk of exposure to aerosols containing SARS-CoV-2, in settings where aerosol-generating procedures are performed on patients with COVID-19, such as tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, sputum induction, bronchoscopy, spirometry, and autopsy procedures; and working with COVID-19 patients in crowded, enclosed places without adequate ventilation.

Annex 4. Summary of major updates

Update 19 January 2022

Section	Rational for update
Title	Shortening of title: from *WHO SAGE Roadmap For Prioritizing Uses Of Covid-19 Vaccines In The Context Of Limited Supply* To *WHO SAGE Roadmap For Prioritizing Use Of Covid-19 Vaccines.* Change of subtitle: from *An approach to inform planning and subsequent recommendations based upon epidemiologic setting and vaccine supply scenarios* to *An approach to optimize the global impact of COVID-19 vaccines, based on public health goals, global and national equity, and vaccine access and coverage scenarios.* These changes are made to reflect the increasing vaccine supply globally.
Preamble/Introduction	This revised Roadmap takes into account increasing vaccine availability and vaccine coverage rates. Scenarios in which vaccination coverage exceeds 50% of the population are considered. It further considers additional topics such as vaccine use in children and adolescents and the administration of booster doses.
Definitions	Definitions to guide the user were added (e.g. additional doses, booster doses).
Epidemiological setting scenarios, including - variants of concern and - infection-induced immunity	The scenarios were revisited in light of the current epidemiology, transmission patterns, variants of concern and their impact on vaccine performance, as we as the increasing population-level immunity from infection.
Public health goals scenarios	The *Strategy to achieve global Covid-19 vaccination by mid-2022* was added and referred to.
Optimized use of COVID-19 vaccines	A major overhaul of this section was conducted. The priority-use groups for COVID-19 vaccination were revisited and are reflected in Table 1. Further information on priority use groups was added in the respective sections on page 9 and in Annex 2. Primary as well as booster dose schedules were considered.
Heterologous primary vaccination series and booster doses	The section was added and current WHO guidance was referenced.

Update 16 July 2021

Section	Rationale for update
Rationale	The new version states that while vaccines are now licensed and available, the supply remains limited and unreliable in many settings. It further states that, while all currently recommended COVID-19 vaccines have similar broad indications for use, countries may decide to consider specific product attributes when prioritizing populations. The updated Prioritization Roadmap does not propose coverage targets for countries. The 2020 version of the Prioritization Roadmap worked with an initial target of 20% population coverage, based on the expected supply of vaccines. The updated Prioritization Roadmap provides guidance up to a population coverage level of 50%
Process of Prioritization Roadmap development	The update reflects the methods and processes used to develop this version of the Prioritization Roadmap.
Key assumptions	A key assumption in 2020 was that COVID-19 vaccines would probably have an impact on transmission. There is now some evidence that supports this statement
Key assumptions	Post-COVID-19 condition was noted, but as evidence is still emerging, the impact of vaccines on long-term sequelae from SARS-CoV-2 infection have not been included.
Pregnant women, breastfeeding women and children	Substantive changes have been made to these sections to reflect the recent evidence.
Epidemiological settings	The need to keep a vaccine reserve has been removed. Pregnant women have been moved to stage II. Seafarers and air crews have been added to stage II. Settings and geographical locations of high transmission have been removed.

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WHO secretariat: Annelies Wilder-Smith, Joachim Hombach, Melanie Marti, Shalini Desai, Katherine O`Brien.

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WHO continues to monitor the situation closely for any changes that may affect this interim guidance. Should any factors change, WHO will issue a further update. Otherwise, this interim guidance document will expire 2 years after the date of publication.

WHO reference number: WHO/2019-nCoV/Vaccines/SAGE/Prioritization/2022.1

CUARTA DOSIS DE VACUNA CONTRA SARS-COV-2:
PERSONAS INMUNOCOMPROMETIDAS

División de Prevención y Control de Enfermedades
Departamento de Inmunizaciones
Subsecretaría de Salud Pública

06 de enero 2022

Ministerio de Salud
Gobierno de Chile

PLAN DE ACCIÓN CORONAVIRUS COVID-19

VACUNACIÓN DE PACIENTES INMUNOCOMPROMETIDOS EN CHILE

A partir de febrero 2021 se inició la vacunación de la población general comenzando con los mayores de 85 años. En el mes de marzo comenzó la vacunación de la población con comorbilidades que incluyó a pacientes inmunocomprometidos cuyo riesgo de evolución grave era mayor al de otras poblaciones de la misma edad sin comorbilidades como las descritas a continuación:

- Pacientes en diálisis (hemo o peritoneo).
- Pacientes con trasplante de órgano sólido: corazón, pulmones, riñón, hígado, páncreas.
- Pacientes con trasplante de precursores hematopoyéticos.
- Pacientes con cáncer en tratamiento (radioterapia, quimioterapia o terapia hormonal).
- Pacientes con enfermedades autoinmunes que reciben tratamientos biológicos o de pequeñas moléculas.

El 19 de julio[1], se publicó el documento del Departamento de Inmunizaciones *"Dosis de refuerzo en los pacientes inmunocomprometidos"* basado en la evidencia surgida en relación con la duración de la protección de las vacunas contra SARS-CoV-2 en las personas que tienen un sistema inmune comprometido, ya sea por una patología definida o por un tratamiento específico.

En ese momento se recomendó la administración de una dosis de refuerzo o tercera dosis de vacuna contra COVID-19 en estos grupos específicos desde los 12 años en adelante. La vacuna utilizada fue BNT162b2 del laboratorio Pfizer-BioNTech y se recomendó un intervalo mínimo entre la segunda y tercera dosis de 2 meses (8 semanas). La vacuna se podía solicitar a través de vacunas especiales, y a partir de la semana del 11 de agosto se incorporó al calendario[2] a este grupo de pacientes.

ANTECEDENTES INTERNACIONALES DE VACUNACIÓN DE INMUNOCOMPROMETIDOS

La Organización Mundial de la Salud (OMS) define que el objetivo de la dosis de refuerzo es restaurar la eficacia de la vacuna que, posterior al esquema de vacunación primario, la inmunidad y protección clínica han caído por debajo de una tasa considerada suficiente en esa población. En ocasiones, los inmunocomprometidos, no logran generar una respuesta inmunitaria protectora después del esquema de vacunación primario estándar en algunas vacunas, por lo que se debe administrar una dosis adicional como parte de una serie primaria extendida[3].

Hasta la fecha, la evidencia indica una reducción mínima a modesta de la protección de la vacuna contra la enfermedad grave durante los 6 meses posteriores a la serie primaria. La disminución de la eficacia contra todas las enfermedades e infecciones clínicas es más pronunciada. Actualmente, es insuficiente la información para evaluar si la variante Omicron afecta la eficacia de la vacuna, particularmente contra la enfermedad grave.

1 Departamento de Inmunizaciones-Ministerio de Salud. Dosis de refuerzo de vacuna contra SARS-COV-2 en pacientes inmunocomprometidos [Internet]. 19 de julio 2021. Disponible en: https://www.minsal.cl/wp-content/uploads/2021/07/Dosis-de-refuerzo-de-vacuna-contra-SARS-CoV-2-en-pacientes-inmunocomprometidos.pdf

2 Departamento de Inmunizaciones-Ministerio de Salud. Dosis de refuerzo en la campaña de vacunación contra SARS-CvO2 en Chile [Internet]. 16 de agosto 2021. Disponible en: https://www.minsal.cl/wp-content/uploads/2021/08/Dosis-de-refuerzo-en-la-campan%CC%83a-de-vacunacio%CC%81n-contra-SARS-CoV-2-en-Chile.pdf

3 World Health Organization. Interim statement on booster doses for COVID-19 vaccination [Internet]. 22 diciembre 2021. Disponible en: https://www.who.int/news/item/22-12-2021-interim-statement-on-booster-doses-for-covid-19-vaccination---update-22-december-2021

Se requieren más datos para entender el impacto potencial de la vacunación de refuerzo sobre la duración de la protección contra la enfermedad grave, pero también contra la enfermedad leve, la infección y la transmisión, particularmente contra variantes emergentes. A medida que los programas de vacunación protegen a la población contra las enfermedades graves y la muerte, la protección contra enfermedades más leves y la reducción de la transmisión se convierten en consideraciones adicionales importantes.

El 15 de agosto la Administración de Alimentos y Medicamentos de los EE. UU. (FDA, por sus siglas en inglés)[4], enmendó las autorizaciones de uso de emergencia de la vacuna Pfizer-BioNTech y de Moderna para permitir el uso de una dosis adicional en ciertos individuos inmunocomprometidos con la finalidad de aumentar la protección en esta población, específicamente, para aquellas personas receptores de trasplantes de órganos sólidos o a quienes se les haya diagnosticado afecciones de salud que se consideran tener un nivel equivalente de inmunocompromiso.

Los Centros de Control y Prevención de Enfermedades (CDC, por sus siglas en inglés) han propuesto que una vez que completan el esquema de vacunación primario, las personas con compromiso inmunitario moderado a grave deben recibir una dosis principal adicional[5].

Todas las personas de 12 años o más, incluidas las personas inmunocomprometidas, deben recibir una dosis de refuerzo al menos tres o más meses después del esquema primario. Un intervalo más largo entre la serie primaria y la dosis de refuerzo puede resultar en títulos de anticuerpos más altos[6]. Si es elegible para una dosis principal adicional, debe recibir esta dosis antes que la dosis de refuerzo. La dosis adicional se debe administrar de ≥28 días después de completar la serie inicial de 2 dosis[5,7,] .

Respecto a la seguridad de la dosis de refuerzo, en Israel se observó que las tasas de miocarditis/pericarditis después de la dosis de refuerzo de la vacuna COVID-19 de Pfizer-BioNTech (30 µg) (administrada al menos cinco meses después del esquema primario y donde la serie primaria se administró utilizando los intervalos recomendados por el fabricante en los mayores de 12 años) han sido más bajas que las tasas observadas después de la segunda dosis, pero más altas que las tasas observadas después de la primera dosis de esta vacuna en el esquema primario[7].

Aunque lo datos sobre una cuarta dosis de vacuna COVID-19 después del esquema primario recomendado de tres dosis en individuos inmunocomprometidos son limitados actualmente, muchos de estos individuos tienen un mayor riesgo de resultados graves de COVID-19 y también tienen un mayor riesgo de disminuir la protección con el tiempo desde la vacunación. Existe heterogeneidad entre las personas inmunocomprometidas, y los riesgos de COVID-19, así como la probabilidad de una respuesta reducida a las vacunas, variarán según la edad y la condición de inmunocompromiso.

El 21 de diciembre el comité asesor del ministerio de salud de Israel señaló que se administrará una cuarta dosis de refuerzo para las personas de 60 años o más, inmunocomprometidos y trabajadores del sistema de salud. El intervalo entre la cuarta y tercera dosis es de 4 meses[8].

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ELECCIÓN DE LA VACUNA DE REFUERZO A NIVEL INTERNACIONAL

Los estudios clínicos disponibles respecto al uso de dosis de refuerzo, en su mayoría han sido con vacunas contra SARS-CoV-2 de plataforma ARNm, debido a que se han observado efectos secundarios extremadamente raro pero graves asociados a la vacuna contra SARS-CoV-2 de AstraZeneca (plataforma adenoviral no replicante), incluso varios países detuvieron parcial o completamente su uso, lo que originó que aquellas personas que ya habían recibido una dosis de dicha vacuna debieron recibir como segunda dosis una vacuna distinta, esta mezcla de plataformas de vacunas diferentes se ha denominado esquema heterólogo[9].

Hasta la fecha, los estudios de esquemas de vacunación heterólogos muestran que, al administrar una vacuna de ARNm posterior a la vacuna ChAdOx1-S de AstraZeneca, los niveles de anticuerpos fueron más altos y hubo una mayor respuesta inmune mediada por células T en comparación con el esquema homólogo de AstraZeneca[10].

Para el caso de dosis de refuerzo en personas con esquema de virus inactivado, en Turquía se realizó un estudio en que midieron los niveles de anticuerpos posterior a una dosis de refuerzo con vacuna contra SARS-CoV-2 del laboratorio Pfizer-BioNTech administrada 6 meses después de un esquema primario con vacuna CoronaVac del laboratorio Sinovac. Se observó un mayor aumento de IgG anti-spike (proteína clave del SARS-CoV-2) con la vacuna de Pfizer-BioNTech en comparación con el refuerzo con CoronaVac. En relación con los efectos adversos, más participantes del grupo BNT162b2 (Pfizer-BioNTech) informaron dolor e hinchazón en el lugar de la inyección, así como fatiga y dolor muscular que los que recibieron CoronaVac como tercera dosis[11].

Según los CDC de Estados Unidos, se debe preferir la vacuna contra SARS-CoV-2 de ARNm como dosis de refuerzo incluso para aquellas personas que recibieron la vacuna de plataforma Adenoviral no replicante aprobada en Chile (Janssen). Sin embargo, si no se puede administrar una vacuna de ARNm, es preferible ofrecer la vacuna de Janssen como refuerzo a no proporcionar ningún refuerzo de la vacuna COVID-19[12].

Al 25 de octubre de 2021, más de 13 millones de personas en los Estados Unidos recibieron una dosis adicional o de refuerzo de una vacuna contra SARS-CoV-2 (predominantemente con Pfizer-BioNTech), y no se han observado eventos adversos distintos a los descritos para cada vacuna[13].

9 Nature. Mix-and-match COVID vaccines ace the effectiveness test [Internet]. 2021. Disponible en: https://www.nature.com/articles/d41586-021-02853-4

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IMPLEMENTACIÓN DE CUARTA DOSIS DE VACUNA CONTRA SARS-COV-2 EN INMUNOCOMPROMETIDOS

Debido a los antecedentes anteriormente descritos, se recomienda una dosis de refuerzo con vacuna contra SARS-CoV-2 de Pfizer-BioNTech en las personas inmunocomprometidas, según la siguiente tabla:

TABLA N°1: INDICACIÓN PARA INMUNOCOMPROMETIDOS.

Vacuna de Pfizer-BioNTech	Población elegible
Dosis de refuerzo (3ª dosis)	Las personas inmunocomprometidas de 12 años o más deben recibir una dosis adicional para completar el esquema de vacunación primario (3ª dosis). Se administra desde las 8 semanas después de la 2°dosis.
Segunda dosis de refuerzo (4ª dosis)	Las personas inmunocomprometidas de 12 años o más deben recibir una dosis de refuerzo del esquema de vacunación primario (4ª dosis). Se administra desde las 16 semanas después de la 3°dosis.


Ministerio de Salud
Gobierno de Chile


PLAN DE ACCIÓN
CORONAVIRUS
COVID-19

Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study

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Summary

Introduction The inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac, Sinovac) has been widely used in a two-dose schedule. We assessed whether a third dose of the homologous or a different vaccine could boost immune responses.

Methods RHH-001 is a phase 4, participant masked, two centre, safety and immunogenicity study of Brazilian adults (18 years and older) in São Paulo or Salvador who had received two doses of CoronaVac 6 months previously. The third heterologous dose was of either a recombinant adenoviral vectored vaccine (Ad26.COV2-S, Janssen), an mRNA vaccine (BNT162b2, Pfizer–BioNTech), or a recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca), compared with a third homologous dose of CoronaVac. Participants were randomly assigned (5:6:5:5) by a RedCAP computer randomisation system stratified by site, age group (18–60 years or 61 years and over), and day of randomisation, with a block size of 42. The primary outcome was non-inferiority of anti-spike IgG antibodies 28 days after the booster dose in the heterologous boost groups compared with homologous regimen, using a non-inferiority margin for the geometric mean ratio (heterologous *vs* homologous) of 0·67. Secondary outcomes included neutralising antibody titres at day 28, local and systemic reactogenicity profiles, adverse events, and serious adverse events. This study was registered with Registro Brasileiro de Ensaios Clínicos, number RBR–9nn3scw.

Findings Between Aug 16, and Sept 1, 2021, 1240 participants were randomly assigned to one of the four groups, of whom 1239 were vaccinated and 1205 were eligible for inclusion in the primary analysis. Antibody concentrations were low before administration of a booster dose with detectable neutralising antibodies of 20·4% (95% CI 12·8–30·1) in adults aged 18–60 years and 8·9% (4·2–16·2) in adults 61 years or older. From baseline to day 28 after the booster vaccine, all groups had a substantial rise in IgG antibody concentrations: the geometric fold-rise was 77 (95% CI 67–88) for Ad26.COV2-S, 152 (134–173) for BNT162b2, 90 (77–104) for ChAdOx1 nCoV-19, and 12 (11–14) for CoronaVac. All heterologous regimens had anti-spike IgG responses at day 28 that were superior to homologous booster responses: geometric mean ratios (heterologous *vs* homologous) were 6·7 (95% CI 5·8–7·7) for Ad26.COV2-S, 13·4 (11·6–15·3) for BNT162b2, and 7·0 (6·1–8·1) for ChAdOx1 nCoV-19. All heterologous boost regimens induced high concentrations of pseudovirus neutralising antibodies. At day 28, all groups except for the homologous boost in the older adults reached 100% seropositivity: geometric mean ratios (heterologous vs homologous) were 8·7 (95% CI 5·9–12·9) for Ad26.COV2-S vaccine, 21·5 (14·5–31·9) for BNT162b2, and 10·6 (7·2–15·6) for ChAdOx1 nCoV-19. Live virus neutralising antibodies were also boosted against delta (B.1.617.2) and omicron variants (B.1.1.529). There were five serious adverse events. Three of which were considered possibly related to the vaccine received: one in the BNT162b2 group and two in the Ad26.COV2-S group. All participants recovered and were discharged home.

Interpretation Antibody concentrations were low at 6 months after previous immunisation with two doses of CoronaVac. However, all four vaccines administered as a third dose induced a significant increase in binding and neutralising antibodies, which could improve protection against infection. Heterologous boosting resulted in more robust immune responses than homologous boosting and might enhance protection.

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Research in context

Evidence before this study

By Jan 17, 2022, 9·7 billion doses of COVID-19 vaccines had been deployed worldwide to reduce severe disease and death caused by the SARS-CoV-2. The most widely used vaccines were mRNA, viral vector, and inactivated vaccines, with widespread two-dose priming undertaken in low-income and middle-income countries with the inactivated vaccines from Sinovac and Sinopharm. As a result of waning immunity after two doses of COVID-19 vaccines and some evidence of reduced effectiveness, many countries are now considering offering third or booster doses. We searched PubMed for studies in English from Jan 1 to Dec 31, 2021 on booster doses of vaccines for individuals who had received two priming doses of the inactivated vaccine, CoronaVac. We found that heterologous boosting of CoronaVac with recombinant adenovirus type-5 COVID-19 vaccine produced greater neutralising antibody titres than did homologous boosting in a randomised trial in China. Similar findings are included in a preprint from Thailand comparing heterologous boosting with ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer–BioNTech), or BBIBP-CorV (Sinopharm), 3–4 months after CoronaVac.

Added value of this study

We report a comprehensive analysis of the immunogenicity and safety of homologous and heterologous boosting of the inactivated vaccine CoronaVac. We show that there are low concentrations of antibody present at 6 months after two doses of CoronaVac and largely undetectable neutralising antibodies. A third dose of CoronaVac boosts these responses and boosts are stronger with two different viral vector vaccines tested; the highest antibody concentrations are observed after an mRNA boost. We also show that heterologous boosting increases live virus neutralisation titres against both delta and omicron variants.

Implications of all the available evidence

Heterologous boosting of the inactivated vaccine, CoronaVac, results in more robust immune responses than homologous boosting and could enhance protection.

Introduction

The inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac; Sinovac Life Sciences, China and Instituto Butantan, Brazil) has been widely used in large-scale vaccination programmes in many countries.

In phase 3 randomised trials, two doses of CoronaVac showed varying levels of short-term efficacy against symptomatic COVID-19 (<6 months since vaccination), with efficacy and effectiveness estimates of 83·5% in Turkey,[1] 50·7% in Brazil,[2] and 65·9% in Chile.[3] Efficacy against COVID-19 hospitalisation was higher with 83·7% (95% CI 58·0–93·7) efficacy in Brazil[2]and 87·5% (86·7 to 88·2) in Chile.[3] In real-world use, a test-negative case control study in Brazil showed 46·8% (38·7–53·8) effectiveness against symptomatic infection and 55·5% (46·5–62·9) effectiveness against hospital admission during spread of the gamma (P.1) variant.[4]

Waning of immune responses has been observed after immunisation with COVID-19 vaccines, with reduced protection against infection and some loss of protection against hospitalisation and death, particularly among older adults. A third dose of CoronaVac (homologous boost) has been shown to be immunogenic.[5,6] However, boosting with a heterologous vaccine might provide greater immunity and protection against variants of concern. Heterologous boosting of CoronaVac with recombinant adenovirus type-5 COVID-19 vaccine produced greater neutralising antibody titres than did homologous boosting in a randomised trial in China.[7] Similar findings have been observed in Thailand in a preprint comparing heterologous boosting with ChAdOx1 nCoV-19 (AstraZeneca), BNT162b2 (Pfizer–BioNTech), or BBIBP-CorV (Sinopharm), 3–4 months after CoronaVac.[8] In mouse models, heterologous boosting of CoronaVac with one of three different vaccines resulted in better outcomes than did homologous boosting.[9,10]

In this study, we compared the safety and immunogenicity of a third heterologous booster dose of one of three different vaccines, with a homologous boost in adults in Brazil who previously received two doses of CoronaVac.

Methods

Study design and participants

In RHH-001, we conducted a phase 4, randomised, participant blind, safety and immunogenicity study of a third heterologous booster dose of either the recombinant adenoviral vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca, in combination with Fiocruz), mRNA vaccine (BNT162b2, Pfizer/BioNTech), or recombinant adenoviral vectored vaccine (Ad26.COV2-S, Janssen), compared with a third homologous boost with inactivated whole virion COVID-19 vaccine CoronaVac. The two study sites were in Brazil (Hospital São Rafael, Salvador, and CRIE UNIFESP, São Paulo).

Participants were eligible if they were 18 years or older; had received their second doses of CoronaVac 182 days (plus or minus 30 days) before enrolment; female participants were not pregnant, puerperal, or nursing; and all participants had given written informed consent. Participant exclusion criteria were history of laboratory-confirmed COVID-19 (or with fever or acute disease within 3 days before randomisation); serious vaccine-related adverse reactions; known bleeding disorders, neurological disorders, or history of Guillain-Barré syndrome; people with autoimmune disease

(excluding people with Hashimoto's thyroiditis, vitiligo, psoriasis, lupus discords, HIV positive, or on HIV treatment); people on immunosuppressive medications within 15 days of vaccine; receipt of other investigational products, other vaccines within 14 days of enrolment or plans to receive vaccine within 28 days of vaccination, monoclonals within 9 months of day 1 or planned during the study, intravenous immunoglobulin, or other blood products; and any condition that could interfere with the primary objectives or represent additional risk to participants. Ethical approval was given by the National Ethical Review Committee, Comissão Nacional de Ética em Pesquisa.

Randomisation and masking

Participants were randomly assigned to receive one of four different booster vaccines of either heterologous dosing with ChAdOx1 nCoV-19, BNT162b2, or Ad26.COV2-S, or homologous dosing with CoronaVac in a 5:6:5:5 ratio. The computer randomisation was conducted using RedCAP, stratified by site, age group (18–60 years or 61 years and older), and day of randomisation, with a block size of 42. Participants were enrolled from both age groups in equal numbers. The randomisation ratio was chosen to minimise vaccine wastage as the vaccines were supplied in five, six, or ten dose vials; therefore, 42 participants could be enrolled and vaccinated in a block with no wastage (appendix p 1). Participants were masked to the vaccine that they had received until the second visit, 28 days after vaccination. Blood samples for immunogenicity were taken before vaccination and at day 28 after vaccination. Study staff were aware of vaccine allocations, but laboratory staff remained masked.

See Online for appendix

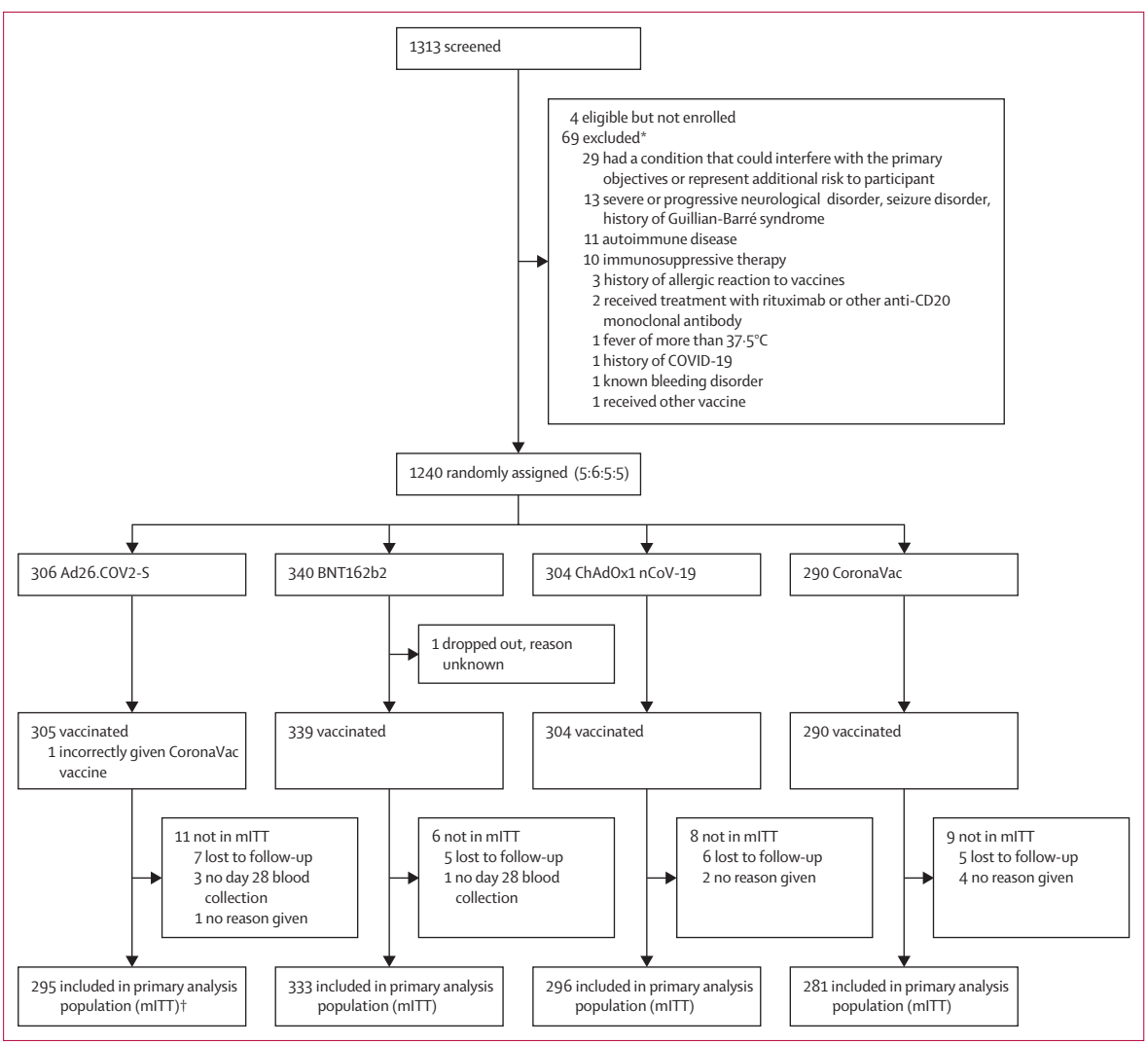

Figure 1: **Trial profile**

mITT=modified intention to treat population. *It is possible to have more than one reason for exclusion per person; therefore, the number of people excluded is less than the sum of the reasons for exclusion. †The one person incorrectly given CoronaVac was included in the mITT.

Procedures

CoronaVac is an inactivated COVID-19 vaccine; a 0·5 mL dose contains 600 SU of inactivated SARS-CoV-2 virus. ChAdOx1 nCoV-19 is a recombinant chimpanzee adenovirus that encodes full length spike SARS-CoV-2 glycoprotein; a 0·5 mL dose contains 5×10^{10} viral particles. BNT162b2 is a mRNA vaccine incorporated into lipid nanoparticles; a 0·3 mL dose contains 30 µg of SARS-CoV-2 spike protein messenger RNA. Ad26.COV2-S is a recombinant adenovirus type 26 that encodes SARS-CoV-2 spike glycoprotein used as a dose of 0·5 mL containing 5×10^{10} viral particles. All vaccines were administered intramuscularly.

A validated multiplexed immunoassay (3-plex ECL based assay on the MSD platform, PPD Vaccines, Richmond, VA, USA) was used to measure anti-spike, receptor binding domain, and nucleocapsid responses. The upper limit of the assay was 2 million arbitrary units per mililitre (AU/mL) and the lower limit was 1 AU/mL.

	Overall (n=1205)	Ad26.COV2-S (n=295)	BNT162b2 (n=333)	ChAdOx1 nCoV-19 (n=296)	CoronaVac (n=281)
Sex					
Male	476 (39·5%)	114 (38·6%)	129 (38·7%)	117 (39·5%)	116 (41·3%)
Female	729 (60·5%)	181 (61·4%)	204 (61·3%)	179 (60·5%)	165 (58·7%)
Age					
18–60 years	616 (51·1%)	153 (51·9%)	165 (49·5%)	150 (50·7%)	148 (52·7%)
Over 61 years	589 (48·9%)	142 (48·1%)	168 (50·5%)	146 (49·3%)	133 (47·3%)
Median (range)	60 (21–98)	59 (22–98)	61 (21–95)	60 (21–96)	58 (21–95)
Race					
White	814 (67·6%)	203 (68·8%)	230 (69·1%)	200 (67·6%)	181 (64·4%)
Black	57 (4·7%)	14 (4·7%)	17 (5·1%)	13 (4·4%)	13 (4·6%)
Mixed	275 (22·8%)	65 (22·0%)	68 (20·4%)	70 (23·6%)	72 (25·6%)
Asian	57 (4·7%)	13 (4·4%)	17 (5·1%)	12 (4·1%)	15 (5·3%)
Not given	2 (0·2%)	0 (0%)	1 (0·3%)	1 (0·3%)	0 (0%)
Medical history					
Type 2 diabetes	127 (10·5%)	34 (11·5%)	21 (6·3%)	39 (13·2%)	33 (11·7%)
Heart failure	9 (0·7%)	3 (1·0%)	1 (0·3%)	2 (0·7%)	3 (1·1%)
COPD	9 (0·7%)	1 (0·3%)	2 (0·6%)	2 (0·7%)	4 (1·4%)
Hypertension	365 (30·3%)	84 (28·5%)	91 (27·3%)	99 (33·4%)	91 (32·4%)
Cancer	126 (10·5%)	27 (9·2%)	33 (9·9%)	38 (12·8%)	28 (10·0%)
Immunosuppressed	3 (0·2%)	1 (0·3%)	2 (0·6%)	0 (0%)	0 (0%)
Chronic kidney disease	7 (0·6%)	0 (0%)	1 (0·3%)	3 (1%)	3 (1·1%)
Coronary artery disease	61 (5·1%)	7 (2·4%)	18 (5·4%)	17 (5·7%)	19 (6·8%)
Cardiomyopathy	7 (0·6%)	2 (0·7%)	3 (0·9%)	1 (0·3%)	1 (0·4%)
Sickle cell anaemia	1 (0·1%)	0 (0%)	1 (0·3%)	0 (0%)	0 (0%)
Obesity	80 (6·6%)	24 (8·1%)	21 (6·3%)	20 (6·8%)	15 (5·3%)
HIV	2 (0·2%)	0 (0%)	2 (0·6%)	0 (0%)	0 (0%)
Time since second vaccine, days					
Mean (SD)	178·4 (9·9)	178·7 (9·6)	178·6 (10·1)	178·9 (9·7)	177·4 (10·3)

COPD=Chronic obstructive pulmonary disease.

Table 1: **Baseline characteristics of primary analysis population**

Antibody neutralisation titres on a random subset of 200 participants were measured with a lentivirus-based pseudovirus particle expressing the D614 SARS-CoV-2 spike protein (Monogram Biosciences, South San Francisco, CA, USA). Results are presented as inhibitory concentration of serum achieving 50% neutralisation of virus (IC_{50}). The lower limit of the assay was 40 IC_{50}.

A random subset of 80 participants (20 per group, stratified by age) were tested for live virus neutralisation using delta (B.1.617.2) and omicron (B.1.1.529) variants of SARS-CoV-2 virus with results reported as a value of 50% focus reduction neutralisation test ($FRNT_{50}$), which is the reciprocal dilution of serum that neutralises 50% of the input virus. The lower limit was 20 $FRNT_{50}$. For all assays, values above the upper limit were analysed at the upper limit, and values below the lower limit were substituted with half the lower limit. Samples were collected and stored locally before shipping to the centralised laboratories for testing.

Outcomes

The primary outcome was non-inferiority of anti-spike IgG antibodies 28 days after the booster dose in the heterologous boost groups compared with homologous regimen. Secondary outcomes included neutralising antibody titres at day 28, local and systemic reactogenicity profiles self-reported by diary cards, adverse events, and serious adverse events (appendix pp 12–79).

Statistical analysis

Antibody data were log-transformed before the analysis. The study used a non-inferiority design with the main hypothesis being that the anti-spike IgG induced by heterologous vaccine schedules is non-inferior to antibodies induced by the homologous vaccine schedule, using a non-inferiority margin for the geometric mean ratios (GMRs; heterologous *vs* homologous) of 0·67. GMRs were calculated by taking the anti-log of the mean difference between groups. Confidence intervals for the GMR with lower bounds greater than 0·67 were considered evidence of non-inferiority. Superiority comparisons were done where non-inferiority was shown using an unadjusted linear model fitted to log-transformed values with vaccine group as a fixed effect. To test the difference between response in younger and older adults, a linear model was fitted to log-transformed antibody values, adjusting for baseline antibody concentrations and vaccine group. The interaction term for vaccine group by age group was also tested but was not significant and was not included in the final model.

The primary analysis population included people who were randomly assigned, received at least one dose of the study vaccines or comparator, and provided post-vaccination immunogenicity data (ie, the modified intention-to-treat population). Missing data were not imputed. Confidence

intervals for percentages were computed using the Binomial Exact (Clopper-Pearson) method. All analyses were done using R, version 4.1.1

Assuming a standard deviation of 0·4 for anti-spike IgG 28 days after the booster dose, 90% power, and alpha of 0·0167 due to three comparisons of heterologous versus homologous schedules, the study required 124 evaluable people per age group and per study group. Allowing for 20% loss to follow-up or incomplete data and the required randomisation ratio, 1240 people were planned for enrolment.

This study was registered with Registro Brasileiro de Ensaios Clínicos, number RBR – 9nn3scw.

Role of the funding source

The study was funded by the Ministry of Health, Brazil and sponsored by Instituto D'Or de Pesquisa e Ensino. The Oxford investigators were supported by the NIHR Oxford Biomedical Research Centre. The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication.

Results

Between Aug 16, and Sep 1, 2021, 1240 participants were randomly assigned in two age groups (18–60 years and 61 years or older), of whom 1239 were vaccinated. One participant was vaccinated with a vaccine to which they had not been randomly assigned (figure 1). 1205 (97%) returned for their day 28 visit and were eligible for inclusion in the primary analysis.

Participants included in the primary analysis ranged in age from 21 years to 98 years (median 60 years). The median time since receipt of the second dose of CoronaVac was 180 days (range 152–210). Of the 1205 participants, 729 (60·5%) were female and 814 (67·6%) were White. The most common pre-existing comorbidity was hypertension, present in 365 (30·3%) participants. Baseline characteristics were balanced across the four vaccine arms of the trial (table 1).

The most common solicited local vaccine reaction in the first 7 days was injection site pain by 183 (60%) of 305 for Ad26.COV2-S, 256 (76%) 339 for BNT162b2, 192 (63%) of 304 for ChAdOx1 nCoV-19, and 114 (39%) of 291 for CoronaVac. Headaches were common for Ad26.COV2-S (137 [45%] of 305) and ChAdOx1 nCoV-19 recipients (148 [49%] of 304), compared with BNT162b2 (102 [30%] of 339) and CoronaVac (58 [20%] of 291). Myalgia was also commonly reported in 121 (40%) of 305 for Ad26.COV2-S group, in 77 (23%) of 339 for BNT162b2 group, 130 (43%) of 304 for ChAdOx1 nCoV-19, and in 30 (10%) of 291 recipients of CoronaVac. Fever and chills were common for Ad26.COV2-S (35 [11%] and 79 [26%] of 305) and ChAdOx1 nCoV-19 (44 [14%] and 99 [33%] of 304), but not for recipients of BNT162b2 (seven [2%] and 29 [9%] of 339) or CoronaVac (two [1%] and 21 [7%] of 291; figure 2).

There were five serious adverse events recorded. Three serious adverse events were considered possibly related to the vaccine received: in the BNT162b2 group, a woman of 83 years had a pulmonary embolism and deep vein thrombosis 2 days after vaccination; in the Ad26.COV2-S group, a woman of 52 years had a subconjunctival haemorrhage 2 days after vaccination, and a man of 71 years had a pulmonary embolism 28 days after vaccination. Unrelated serious adverse events included one case of bullous erysipelas (ChAdOx1 nCoV-19), and one case of coronary arterial disease requiring stent insertion (Ad26.COV2-S). All participants recovered and were discharged home. There were no COVID-19 cases identified during the study.

At baseline there were no significant differences in anti-spike IgG across the four randomised groups (p=0·26). At day 28 after the booster vaccine all groups had a substantial rise in antibody concentrations (appendix p 3). The geometric fold-rise from baseline to day 28 was 77 (67–88) for Ad26.COV2-S, 152 (134–173) for BNT162b2, 90 (95% CI 77–104) for ChAdOx1

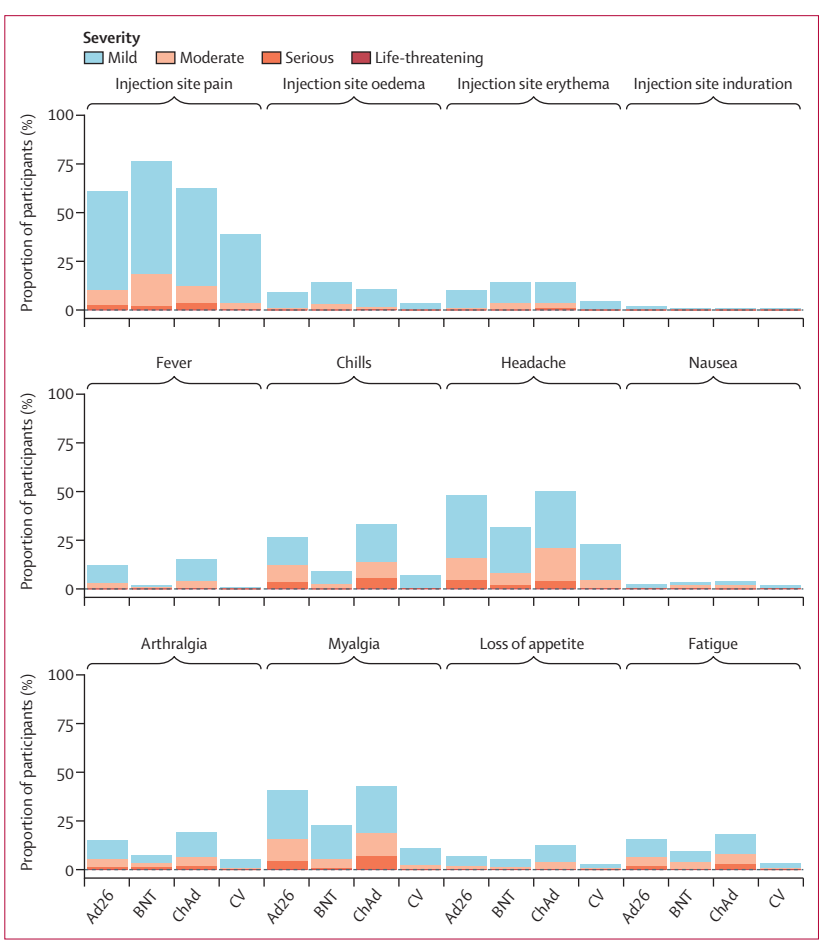

Figure 2: **Local and systemic solicited adverse reactions in the first 7 days after vaccination (safety population)**
Ad26=Ad.26.COV2-S (n=305). BNT=BNT162b2 (n=339). ChAd=ChAdOx1 nCoV-19 (n=304). CV=CoronaVac (n=291).

nCoV-19, and 12 (11–14) for CoronaVac (figure 3; appendix p 3).

All heterologous regimens were non-inferior to CoronaVac. Superiority comparisons were conducted and all heterologous regimens had anti-spike IgG at day 28 that was superior to that induced by the homologous boost (all p<0·0001, table 2). GMRs were 6·7 (95% CI 5·8–7·7) for Ad26.COV2-S, 13·4 (11·6–15·3) for BNT162b2, and 7·0 (6·1–8·1) for ChAdOx1 nCoV-19 (table 2, figure 3). Similar responses were seen with anti-receptor binding domain IgG (appendix p 7–8) but not with anti-nucleocapsid IgG, which was raised in participants receiving the CoronaVac boost containing the inactivated whole virus (appendix p 5–6). Responses in older adults were 19% lower than in younger adults at day 28, across all vaccines when tested in a linear model adjusted for vaccine group and baseline antibody levels (GMR 0·81 [95% CI 0·73–0·89] in 61 years and older *vs* 18–60 years, adjusted for vaccine group and baseline anti-spike IgG). In the older age group, the geometric fold-rise was 78·8 (95% CI 65·1–95·2) for Ad26.COV2-S, 165·4 (138·1–198·1) for BNT162b2, 91·5 (72·6–115·2) for ChadOx1 nCoV-19, and 12·5 (10·3–15·2) for CoronaVac.

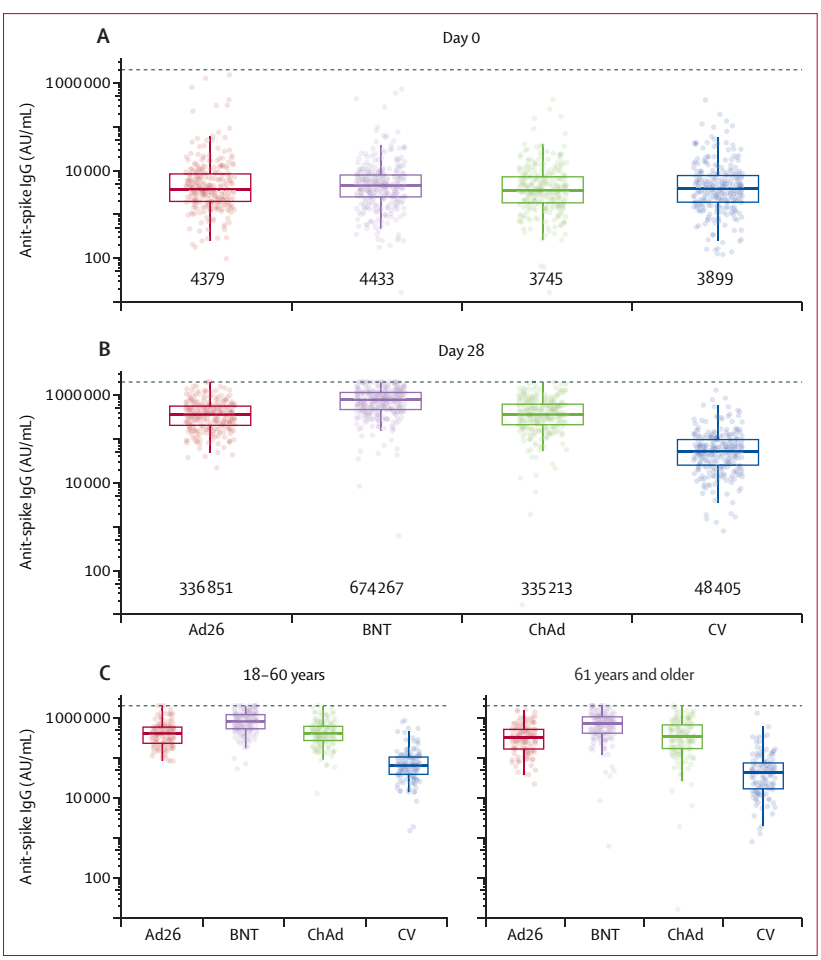

Figure 3: **Anti-spike IgG by multiplex immunoassay by study day and age**
(A) Day 0, (B) day 28, and (C) day 28 responses by age group and booster vaccine allocation. Dotted line shows upper limit of the assay. The midlines of the boxes show medians and the outer bounds of the boxes show IQRs. Error bars extend to the last data point within 1·5 × the IQR above or below the 75th or 25th percentile. Geometric means shown below each group. See table 2 and appendix (p 3) summary statistics and comparisons. Ad26=Ad.26.COV2-S. AU/mL=arbitrary units per millilitre (conversion factor to convert AU/mL units to BAU/mL units using WHO Reference Standard is 0·00645 [95% CI 0·00594–0·00701]). BNT=BNT162b2. ChAd=ChAdOx1 nCoV-19. CV=CoronaVac.

Pseudovirus neutralisation titres were available on a random subset of 200 participants. 6 months after the second dose of CoronaVac and before the booster, 28 (14%) of the 194 participants (95% CI 9·8–20·2) had detectable neutralising antibodies on this assay. This value was lower in older adults (nine [9%] of 101, 95% CI 4·2–16·2) than in adults aged 18–60 years (19 [20%] of 93, 12·8–30·1; p=0·022). All participants in the three heterologous booster groups had neutralisation titres that were above the lower limit of detection 28 days after vaccination compared with 38 (83%) of 46 responders (95% CI 68·6–92·2) in the homologous CoronaVac arm. All heterologous regimens were superior to the homologous boost regimen (all p <0·0001), with GMRs of 8·7 (5·9–12·9) for Ad26.COV2-S, 21·5 (14·5–31·9) for BNT162b2, and 10·6 (7·2–15·6) for ChAdOx1 nCoV-19 (figure 4, table 2; appendix p 9–10).

Neutralising antibody titres measured by a live virus assay were above the lower limit of detection in 75 (94%) of 80 participants tested at day 28 for the delta variant and in 61 (76%) of 80 participants for the omicron variant (figure 5). The geometric mean titres for the four booster vaccines differed significantly at day 28 for both omicron and delta (both p<0·0001), but the ratio of omicron to delta did not differ between groups (p=0·11; appendix p 14).

Discussion

In this study, we have shown that a third dose booster of the four vaccines tested provides a substantial increase in antibody responses after two doses of CoronaVac, when administered about 6 months after the second dose.

Very low neutralising antibody concentrations were detected at 6 months after two doses of the inactivated vaccine, CoronaVac, but both homologous and heterologous COVID-19 booster vaccinations were safe and strongly enhanced the humoral immune responses. The magnitude of the immune boost was greater with the adenoviral vectored vaccines (Ad26.COV2-S and ChAdOx1 nCoV-19) and mRNA vaccine (BNT162b2) than with the homologous regimen, with the highest responses reported after an mRNA boost, similar to recent findings following boosting with these vaccines after two priming doses of either mRNA or viral vector vaccines.[11] In older adults, the difference in neutralising antibody titres was 8–22-fold higher for a heterologous boost than for a homologous boost with CoronaVac. In a preprint by Pan and colleagues,[6] a third dose of CoronaVac given 6 months after the second dose resulted in an approximately 20-fold increase in neutralising antibody titres from a low

baseline, higher than the 7-fold increase reported here for pseudoneutralising titres, or the 12-fold increase seen for anti-spike IgG. Differences in study population and laboratory assays might account for this discrepancy in absolute booster response, but substantial booster responses were observed in both studies. We also found that the booster doses of viral vector and mRNA vaccines substantially increased neutralising capacity of serum samples for both delta and omicron variants (at least 90% seropositive after booster), but lower responses were seen after a CoronaVac boost with just 35% becoming seropositive against omicron. Similarly, one preprint shows a 1·4-fold increase in anti-omicron neutralising capacity after an mRNA boost following two doses of CoronaVac, when compared with the activity of sera after two doses of the mRNA vaccine.[12]

One theoretical advantage of inactivated vaccines is that they contain additional viral proteins, including nucleoprotein, which could potentially broaden protection beyond anti-spike protein responses, and reduce the escape of variants from vaccine immunity. We show a 21-fold increase in anti-N IgG concentrations after the homologous boost but it is not clear whether these antibodies can confer clinical protection. Despite the addition of these anti-N responses, neutralising capacity of these sera is lower than those after a viral vector or mRNA boost, even though the latter responses are limited to anti-spike immunity.

Correlates of protection analysis of trial data from the UK phase 3 ChAdOx1 nCoV-19 vaccine efficacy trial showed that a median anti-spike IgG level of 139 306 AU/mL, and a pseudovirus neutralising antibody titre of 982 IC_{50} (140 IU/mL using the WHO international standard 20/136) was associated with 90% vaccine efficacy.[13] Using the same assays, geometric mean antibody concentrations for the adenoviral-vectored vaccines in this study were 2·4-fold higher than the 90% vaccine efficacy correlate, and the mRNA vaccine had a geometric mean 4·8-times higher than the 90% correlate, suggesting that antibody concentrations in these groups would be associated with very high protection against symptomatic infection with variants circulating before February, 2021. After the booster, the CoronaVac group had a geometric mean titre that corresponded to the 80% vaccine efficacy correlate, using the values from Feng and colleagues.[13]

Immune responses are not always higher with heterologous boosting, highlighting the importance of generating primary data as shown here. Homologous boosting with a second or third dose of BNT162b2 produced higher antibody responses than a heterologous boost with an adenoviral-vectored vaccine (ChAdOx1 nCoV-19 or Ad26.COV2-S), an adjuvanted protein vaccine (NVX-CoV2373, Novavax), or a heterologous mRNA vaccine (CVnCov, CureVac).[11,14]

	Ad26.COV2-S	BNT162b2	ChAdOx1 nCoV-19	CoronaVac	p value*
Anti-spike IgG by multiplex immunoassay					
All participants					
Number of participants	294	333	296	281	..
Geometric mean ratio	6·7 (5·8–7·7)†	13·4 (11·6–15·3)†	7·0 (6·1–8·1)†	ref	<0·0001
18–60 years					
Number of participants	152	165	150	148	..
Geometric mean ratio	6·1 (5·1–7·2)	12·1 (10·3–14·2)	6·4 (5·5–7·6)	ref	..
61 years and over					
Number of participants	142	168	146	133	..
Geometric mean ratio	7·3 (5·8–9·2)	15·0 (12·0–18·6)	7·6 (6·1–9·5)	ref	..
Pseudovirus neutralisation titres					
All participants					
Number of participants	47	49	52	46	..
Geometric mean ratio	8·7 (5·9–12·9)	21·5 (14·5–31·9)	10·6 (7·2–15·6)	ref	<0·0001
18–60 years					
Number of participants	22	23	26	22	..
Geometric mean ratio	7·2 (4·5–11·4)	15·6 (9·8–24·7)	8·2 (5·2–12·9)	ref	..
61 years and over					
Number of participants	25	26	26	24	..
Geometric mean ratio	10·5 (5·6–19·5)	30·7 (16·5–57·1)	14·2 (7·6–26·5)	ref	..

Data are the geometric mean ratio of heterologous versus homologous (95% CI), unless otherwise specified. *p value from ANOVA model comparing log-geometric means across all four groups. †p value <0·0001, values from superiority comparisons comparing heterologous schedules to homologous schedules.

Table 2: **Comparisons of heterologous versus homologous regimens**

WHO has not recommended widespread use of booster doses of COVID-19 vaccines due to continuing inequity in the distribution of first doses of vaccines to many parts of the world.[15] However, in their interim statement on Dec 16, 2021, WHO advises that where countries are considering heterologous schedules, vectored or mRNA vaccines can be considered as third doses in those who received inactivated vaccines for initial doses.[16] Our study shows that either of the four vaccines tested will produce a strong immune boost as a third dose after two doses of CoronaVac; however, heterologous boosting produced a substantially better response in this study. This finding might be especially relevant for the older adult population. It is not yet clear how long immunity will persist after a third dose and follow up at 6 months in this study will provide a comparison of antibody waning across the four vaccines tested.

The lowest reactogenicity was reported after CoronaVac boosting and the greater degree of reactogenicity seen with heterologous boosting in our study reflects similar

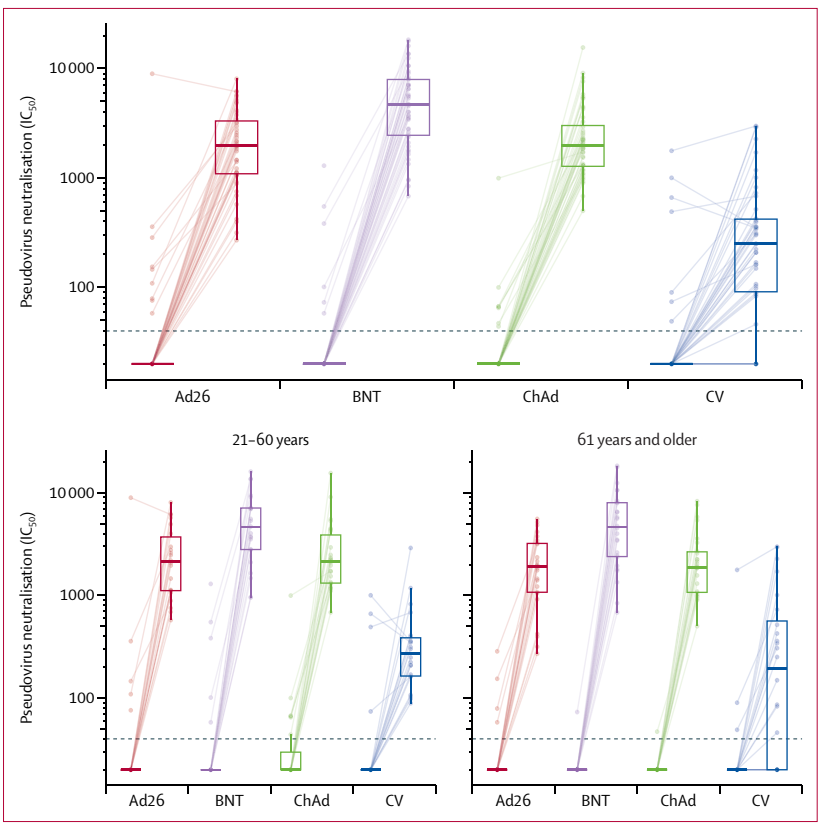

Figure 4: **Pseudovirus neutralisation titres before and 28 days after boost vaccination by vaccine allocation and age group**

Lines connect values from the same participant. Dotted line shows lower limit of the assay. Values below the limit were substituted with a titre of 20. Participants with antibody titres above the lower limit are considered seropositive. The midlines of the boxes show medians and the outer bounds of the boxes show IQRs. Error bars extend to the last data point within 1·5 × the IQR above or below the 75th or 25th percentile. See table 2 and appendix (pp 7–8) for summary statistics. Ad26=Ad.26.COV2-S. BNT=BNT162b2. ChAd=ChAdOx1 nCoV-19. CV=CoronaVac. IC_{50}=inhibitory concentration of serum achieving 50% neutralisation of virus (appendix pp 9–10).

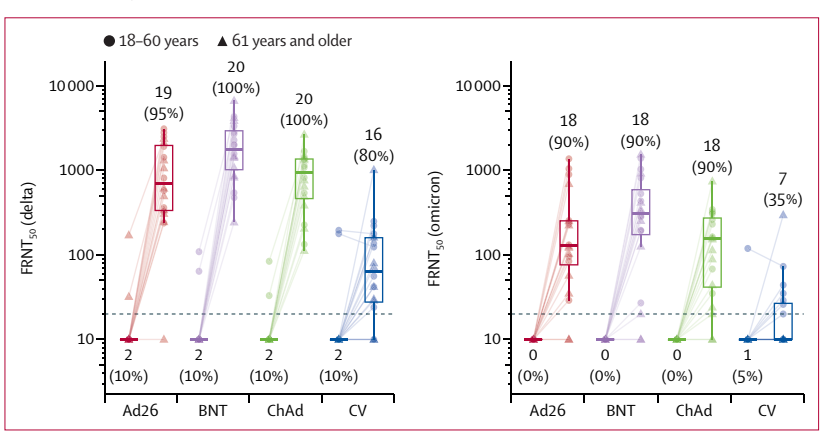

Figure 5: **Live virus neutralisation titres against delta and omicron variant strains, before and 28 days after boost vaccination by booster vaccine groups**

In each group, ten samples were selected from each age group (18–60 years, 61 years and older). Lines connect values from the same participant. Dotted line shows lower limit of the assay. Values below the limit were substituted with a titre of 10. Participants with antibody titres above the lower limit are considered seropositive and are shown as percentages. The midlines of the boxes show medians and the outer bounds of the boxes show IQRs. Error bars extend to the last data point within 1·5 × the IQR above or below the 75th or 25th percentile. See appendix (p 14) for summary statistics. Ad26=Ad.26.COV2-S (n=20). BNT=BNT162b2 (n=20). ChAd=ChAdOx1 nCoV-19 (n=20). CV=CoronaVac (n=20). $FRNT_{50}$=Focus reduction neutralisation test—the reciprocal dilution of serum that neutralises 50% of the input virus (appendix p 11).

findings from other randomised trials such as the Com-COV study, which compared homologous and heterologous boosting with ChAdOx1 nCoV-19 and BNT162b2 and found greater reactogenicity with heterologous schedules.[17] Similarly, the COV-BOOST study of third doses of seven different vaccines showed greater reactogenicity in some heterologous schedules: mRNA-1273 after two doses of ChAdOx1 nCoV-19 or two doses of BNT162b2; and ChAdOx1 nCoV-19 or Ad26.COV2-S after two doses of BNT162b2.[11]

There are some limitations to this study. The study was single-blind for participants until their day 28 visit to ensure recording of vaccine reactions was not influenced by knowledge of the product received, but study staff were aware of vaccine allocations. However, the main outcomes were laboratory measures of antibody values and laboratory staff remained masked. This study was done only in Brazil and so it is not known whether these findings will translate to other populations, although two geographically distinct sites were used in an ethnically diverse population. Although not all available vaccines could be tested, a range of platforms were assessed, including inactivated vaccines, viral vectors, and mRNA, representing the products most widely available in populations where inactivated vaccines have been deployed. We present antibody data only because peripheral blood mononuclear cells, for use in T cell assays, were not collected in this study, and so it is not possible to speculate on the relative merits of the different schedules in inducing cellular immunity. In a previous study, after two doses of ChAdOx1 nCoV-19 or two doses of BNT162b2, T cells responses were induced with heterologous boosting regimens, but an inactivated vaccine (Valneva) did not induce T cell responses when used to boost either mRNA or viral vector vaccines.[11]

In conclusion, this study shows that use of all four vaccines as a third dose is safe and provides a strong immune response that is more robust than when a heterologous vaccine is used.

RHH-001 study team

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Contributors

SACC and AJP conceptualised the study; PA, LW, AVAM, SACC, AJP, TL, and MV provided supervision; ARS, MV, SNFdG, MMdN, MIdMP, IGSG, NS, MMF, RNdAM, ISQO, BSdFS, and MF curated the data; TL and SB did the laboratory work; MV and LC did the statistical analysis; SACC acquired funding; MV wrote the original draft; and SACC, RC, AJP, and TL wrote, reviewed, and edited. All authors critically reviewed and approved the final version. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication

Declaration of interests

AJP is chair of the UK Department of Health and Social Care's Joint Committee on Vaccination and Immunisation, but does not participate in policy advice on coronavirus vaccines, and is a member of the WHO

Strategic Advisory Group of Experts. AJP is an National Institute for Health Research Senior Investigator. TL is named as an inventor on a patent application covering ChAdOx1 nCoV-19. Oxford University has entered into a partnership with AstraZeneca for further development of ChAdOx1 nCoV-19. All other authors declare no competing interests.

Data sharing

Data are provided as a CSV file in supplementary material.

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A DIRECCIÓN GENERAL DE SECRETARÍA

Mediante acceso a la información pública se solicita:

1) Acta de la reunión con fecha 9/2/2022 de la Comisión Nacional Asesora de Vacunas (CNAV) y el grupo ad-hoc.

Se adjunta enlace: https://www.gub.uy/ministerio-salud-publica/comunicacion/publicaciones/actas-reuniones-comisionnacional-asesora-vacunaciones

2) Integración de la CNAV, del grupo ad-hoc y detalle de otros asesores participantes de la reunión.
Surgen de fs. 50 y 51.

3) Declaración de conflicto de interés de cada participante de la reunión.
Se adjuntan fs. 20 a 46.

4) La evidencia actual disponible que estuvo a consideración.
Se adjuntan fs. 17 a 19, 47 a 49, 52 a 80 y 82 a 90.

Se eleva sugiriendo hacer lugar a lo solicitado, proporcionando los documentos a cuyas fojas se referencia en el presente informe.

Ministerio de Salud Pública

Dirección General de Secretaría

VISTO: la solicitud de información pública efectuada al amparo de lo dispuesto por la Ley Nº 18.381, de 17 de octubre de 2008; **RESULTANDO**: que la peticionante hace referencia a la reunión llevada a cabo por la Comisión Nacional Asesora de Vacunas (CNAV) y el grupo ad-hoc, el 9 de febrero de 2022, por lo que solicita acceder al acta correspondiente, integrantes y detalle de otros asesores participantes de la reunión, declaración de conflicto de interés de cada participante y la evidencia actual disponible que estuvo a consideración;

CONSIDERANDO: I) que corresponde hacer lugar a lo peticionado;

II) que de acuerdo a lo dispuesto por el Artículo 16 de la citada disposición legal, el acto que resuelva la petición debe emanar del jerarca máximo del Inciso o quien posea facultades delegadas al efecto;

ATENTO: a lo precedentemente expuesto y a lo establecido por Resolución Ministerial Nº 38/991 de 22 de enero de 1991;

EL DIRECTOR GENERAL DE SECRETARÍA

en ejercicio de las atribuciones delegadas

R E S U E L V E:

1º) Autorízase el acceso a la información, en referencia a la solicitud efectuada al amparo de lo dispuesto por la Ley Nº 18.381, de 17 de octubre de 2008.

2º) Notifíquese a la parte interesada a través de Secretaría de la Dirección General de Secretaría. Pase al Departamento de Comunicaciones para su publicación en la página web institucional. Cumplido, archívese.

Res. N°:
Ref. Nº 001-1-538-2022
VC