EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Update on therapeutics and vaccine for COVID-19

18 NOVEMBER 2021

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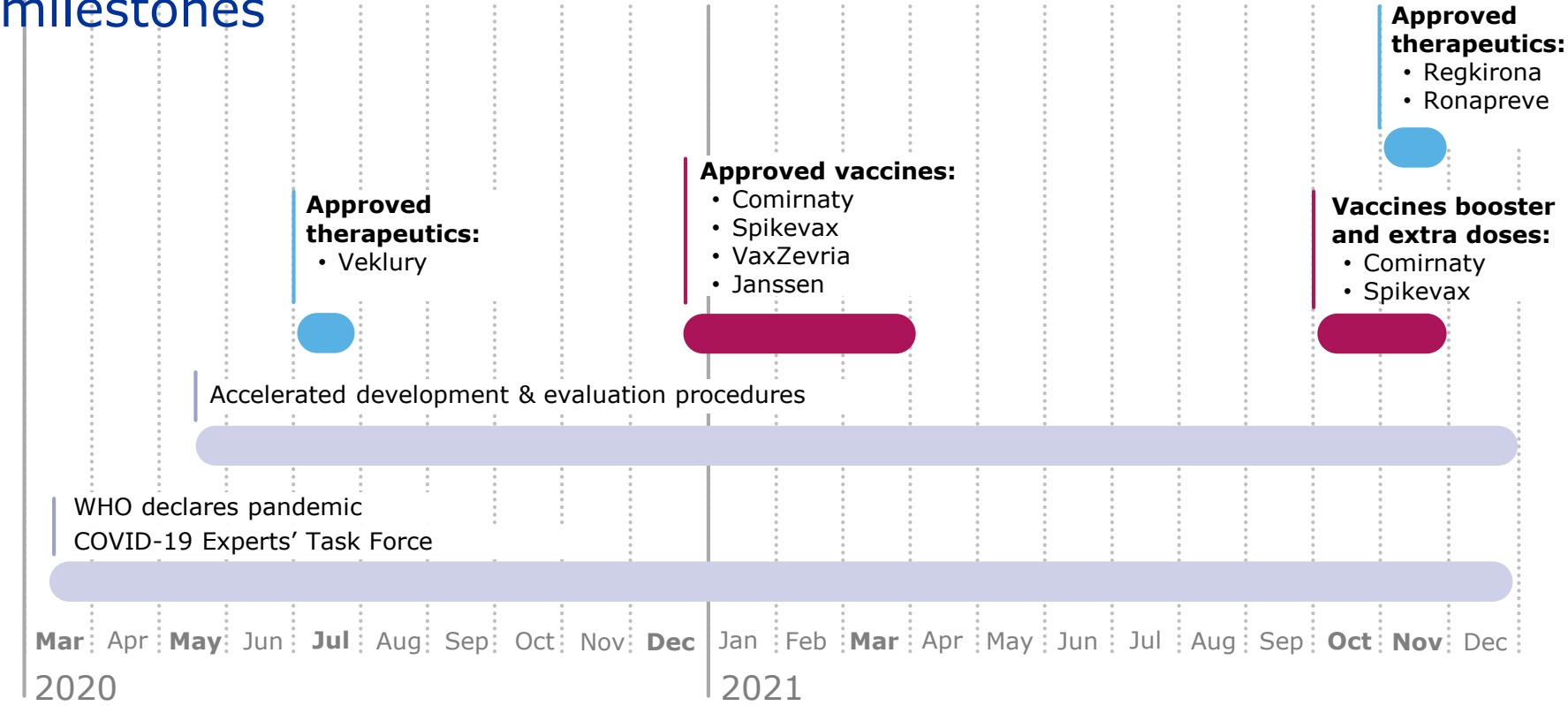
An agency of the European Union

EMA response to COVID-19 pandemic - milestones



COVID-19 therapeutics approved in the EU

3 therapeutics **authorised in the EU**

- **Veklury (remdesivir)** - approved for the **treatment of COVID-19** in people over the age of 12 with pneumonia requiring extra oxygen
- **Regkirona (regdanvimab)** – approved for the **treatment of COVID-19** in adults at increased risk of severe disease
- **Ronapreve (casirivimab / imdevimab)** – approved for the **prevention of COVID-19** in people from 12 years of age, and the **treatment of the disease** in people from 12 years of age at increased risk of severe disease

Ronapreve clinical efficacy data

REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19 (nejm.org)

Table 2. Hierarchical End Points.

Hypothesis-Testing Hierarchy and Comparison*	Treatment Effect	Relative Risk Reduction % (95% CI)	P Value
Patients with ≥1 Covid-19–related hospitalization or death from any cause through day 29 — no./total no. (%)			
2400 mg vs. placebo	18/1355 (1.3) vs. 62/1341 (4.6)	71.3 (51.7–82.9)	<0.001
1200 mg vs. placebo	7/736 (1.0) vs. 24/748 (3.2)	70.4 (31.6–87.1)	0.002
In patients with baseline viral load >10^6 copies/ml, 2400 mg vs. placebo	13/924 (1.4) vs. 55/876 (6.3)	77.6 (59.3–87.7)	<0.001
In patients who were serum antibody–negative at baseline, 2400 mg vs. placebo	12/940 (1.3) vs. 49/930 (5.3)	75.8 (54.7–87.0)	<0.001
In patients with baseline viral load >10^6 copies/ml, 1200 mg vs. placebo	6/482 (1.2) vs. 20/471 (4.2)	70.7 (27.6–88.1)	0.005
In patients who were serum antibody–negative at baseline, 1200 mg vs. placebo	3/500 (0.6) vs. 18/519 (3.5)	82.7 (41.6–94.9)	0.001
Patients with ≥1 Covid-19–related hospitalization or death from any cause, day 4 through day 29 — no./total no. (%)			
2400 mg vs. placebo	5/1351 (0.4) vs. 46/1340 (3.4)	89.2 (73.0–95.7)	<0.001
1200 mg vs. placebo	5/735 (0.7) vs. 18/748 (2.4)	71.7 (24.3–89.4)	0.010
Median time to resolution of Covid-19 symptoms — days			
2400 mg vs. placebo	10 vs. 14; 4-day faster resolution		<0.001
1200 mg vs. placebo	10 vs. 14; 4-day faster resolution		<0.001

* All analyses were conducted in the modified full analysis set, which included all patients who were confirmed by means of quantified reverse-transcriptase–polymerase-chain-reaction testing of nasopharyngeal swabs to be positive for severe acute respiratory syndrome coronavirus 2 at randomization and who had at least one risk factor for severe Covid-19. The placebo group of 1341 patients who underwent randomization concurrently with the group that received 2400 mg of REGEN-COV included the placebo group of 748 patients who underwent randomization concurrently with the group that received 1200 mg of REGEN-COV.

Ronapreve clinical efficacy data - Post-exposure prophylaxis

PCR –

Table 7: Primary analysis of study COV-2069, Cohort A

	casirivimab and imdevimab (single 1 200 mg dose)	**Placebo**
Primary analysis population: seronegative at baseline	n = 753	n = 752
Risk of COVID-19		
Through Day 29 (primary endpoint)		
Unadjusted Risk reduction (Adjusted Odds ratio, p-value)[1]	81% (0.17; p < 0.0001)	
Number of individuals with events	11 (1.5%)	59 (7.8%)

[1] The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

PCR +

Table 8: Primary analysis study COV-2069, Cohort B

	casirivimab and imdevimab (single 1 200 mg dose)	**Placebo**
Primary analysis population: seronegative at baseline	n = 100	n = 104
Risk of COVID-19		
Overall risk reduction through Day 29 (primary endpoint)		
Unadjusted Risk reduction (Adjusted Odds ratio, p-value)[1]	31% (0.54; p = 0.0380)	
Number of individuals with events	29 (29%)	44 (42.3%)

[1] The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

Marketing authorisations under evaluation

	Olumiant (baricitinib)	**Kineret (anakinra)**	**RoActemra (toculizumab)**
Start of evaluation	29 April 2021	19 July 2021	16 August 2021
New/ repurposed	Repurposed	Repurposed	Repurposed
COVID indication	**To treat COVID-19** in hospitalised patients from 10 years of age who require extra oxygen	**To treat COVID-19** in adults with pneumonia at increased risk of developing severe respiratory failure	**To treat COVID-19** in adults who are already receiving corticosteroids and require extra oxygen or mechanical ventilation
Route of administration	**Pill** to be taken by mouth	To be given as an **injection**	To be given as an **injection or infusion (drip) into the vein**

Under rolling review by EMA

	Sotrovimab	**Tixagevimab/cilgavimab**	**Molnupiravir**
Start of rolling review	7 May 2021	14 October 2021	25 October 2021
New/ repurposed	New	New	New
COVID indication	**To treat COVID-19** in people from 12 years of age	**To prevent COVID-19** in adults	**To treat COVID-19** in adults
Route of administration	To be given as an **infusion (drip) into the vein**	To be given as an **injection or infusion (drip) into the vein**	**Pill** to be taken by mouth

Molnupiravir / Paxlovid

- While the more comprehensive rolling review is ongoing, **EMA will provide advice to Member States on the use of molnupiravir** for the treatment of COVID-19 (under Art. 5.3)
- **Member States can then decide on the use** of molnupiravir in their territories (e.g. in emergency settings such as with high infection levels and death rates)
- EMA is reviewing the available data on molnupiravir in the **shortest possible timeframe**
- **The Agency will communicate** on the outcome of this review and that of the rolling review once they conclude
- **Paxlovid currently under development** – EMA discussing potential opinion to Member States on early use for emergency settings, ahead of a rolling review and a marketing authorisation application

SCIENCEINSIDER | HEALTH

A prominent virologist warns COVID-19 pill could unleash dangerous mutants. Others see little cause for alarm

Merck & Co.'s newly approved oral drug works by generating mutations, raising hypothetical fears

7 NOV 2021 • 12:35 PM • BY ROBERT F. SERVICE

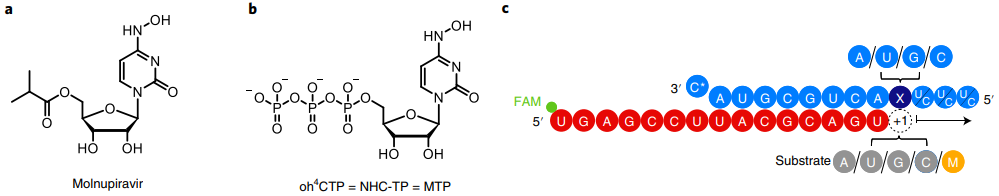
ARTICLES
https://doi.org/10.1038/s41594-021-00651-0
nature structural & molecular biology

Check for updates

OPEN

Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis

Florian Kabinger[1,5], Carina Stiller[2,5], Jana Schmitzová[1,5], Christian Dienemann[1], Goran Kokic[1], Hauke S. Hillen[3,4], Claudia Höbartner[2]✉ and Patrick Cramer[1]✉



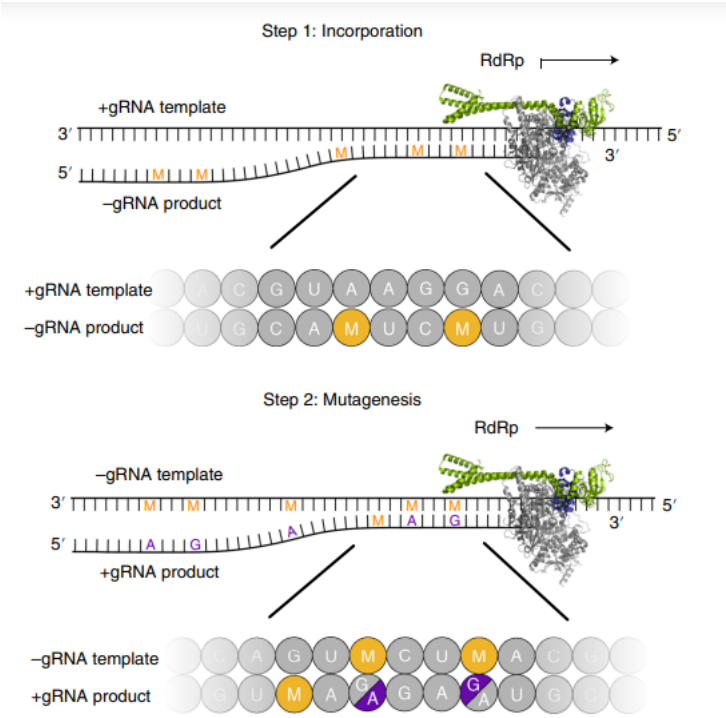


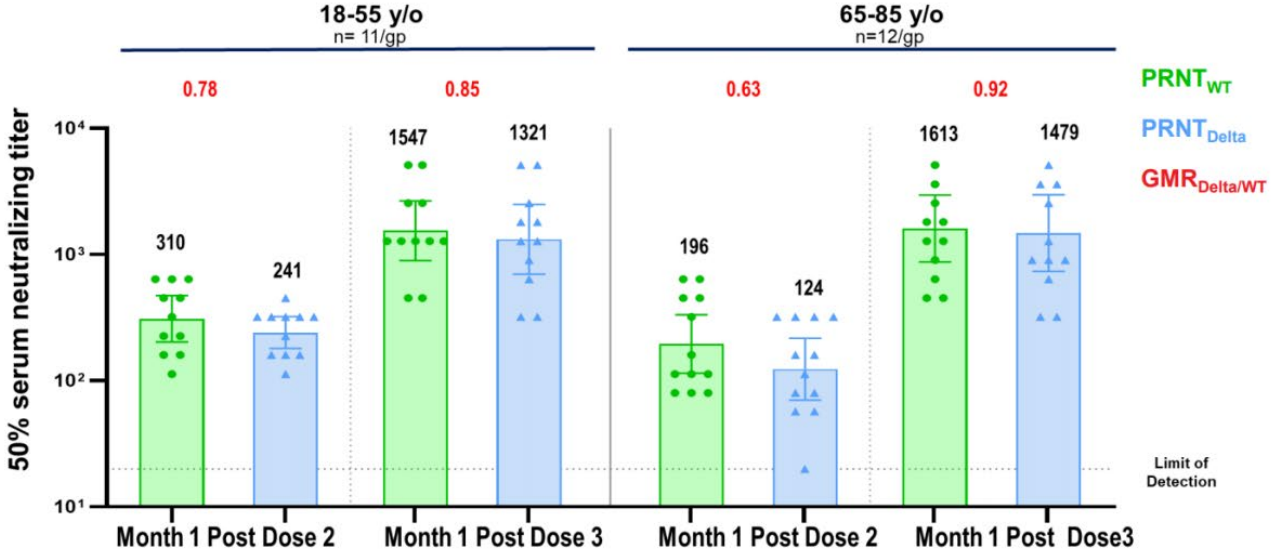
Fig. 5 | Two-step model of molnupiravir-induced RNA mutagenesis. In the presence of NTPs and MTP, M nucleotides can be incorporated by SARS-CoV-2 RdRp instead of C or U into the negative-strand genomic (−gRNA) or subgenomic RNA (−sgRNA) during copying of the positive-strand genomic RNA template (+gRNA). The obtained M-containing negative-strand RNAs can then be used as a template for the production of mutagenized +gRNA and positive-strand subgenomic mRNA (+sgmRNA). These RNA products are predicted to be mutated and not to support formation of functional viruses. RNA of random sequence is shown, with M and mutated residues indicated as orange and violet letters, respectively.

ONES TO WATCH: VACCINE MAKERS WITH PROTEIN JABS IN LATE-STAGE CLINICAL TRIALS

Company	Location	Vaccine type	Cell manufacturing system
Biological E	Hyderabad, India	Soluble protein	Microbial cells (yeast)
Clover Biopharmaceuticals	Chengdu, China	Soluble protein	Mammalian cells (hamster ovary)
Medicago	Quebec City, Canada	Virus-like particle	Plant cells (tobacco-like *Nicotiana benthamiana*)
Novavax	Gaithersburg, Maryland	Protein nanoparticle	Insect cells (fall armyworm)
Sanofi/GlaxoSmithKline	Paris/Brentford, UK	Soluble protein	Insect cells (fall armyworm)
SK bioscience	Seongnam, South Korea	Protein nanoparticle	Mammalian cells (human)

[How protein-based COVID vaccines could change the pandemic (nature.com)]

COVID-19 Vaccine: 3rd Dose Strongly Boosts Neutralizing Titers Against Delta Strain[1,2]



Post dose 3 titers vs. the Delta variant are **>5-fold post dose 2 titers** in 18-55 y/o & **>11-fold post dose 2 titers** in 65-85 y/o

1. Initial data; 2. Samples were tested against each variant separately; PRNT: Plaque Reduction Neutralizing Test; Wt: Wild Type; GMR: Geometric Mean Ratio

Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study (thelancet.com)

	Total	PCR positive	PCR negative	SAR (95% CI)	p value
Contacts					
All	231	53	178	23 (18–29)	NA
Fully vaccinated	140	31	109	22 (16–30)	0·16
Unvaccinated	44	15	29	34 (22–49)	..
Partially vaccinated	47	7	40	15 (7–28)	NA
Household contacts					
All	205	53	152	26 (20–32)	NA
Fully vaccinated	126	31	95	25 (18–33)	0·17
Unvaccinated	40	15	25	38 (24–53)	..
Partially vaccinated	39	7	32	18 (9–33)	NA

χ^2 test was performed to calculate p values for differences in SAR between fully vaccinated and unvaccinated cases. One PCR-negative contact who withdrew from the study without vaccination status information was excluded. NA=not applicable. SAR=secondary attack rate.

Table 1: SAR in contacts of delta-exposed index cases recruited to the ATACCC2 study

	VL growth rate (95% CrI), $\log_{10}$ units per day	Posterior probability estimate is less than pre-alpha	Posterior probability estimate is less than alpha	Posterior probability estimate is less than delta (unvaccinated)	Posterior probability estimate is less than delta (fully vaccinated)
Pre-alpha (n=49)	3·24 (1·78–6·14)	..	0·44	0·27	0·21
Alpha (n=39)	3·13 (1·76–5·94)	0·56	..	0·32	0·25
Delta, unvaccinated (n=16)	2·81 (1·47–5·47)	0·73	0·68	..	0·44
Delta, fully vaccinated (n=29)	2·69 (1·51–5·17)	0·79	0·75	0·56	..

VL growth rates are shown as within-sample posterior mean estimates. Remaining columns show population (group-level) posterior probabilities that the estimate on that row is less than an estimate for a different group. Posterior probabilities are derived from 20 000 posterior samples and have sampling errors of <0·01. VL=viral load. CrI=credible interval.

Table 3: Estimates of VL growth rates for pre-alpha, alpha, and delta (unvaccinated and fully vaccinated) cases, derived from ORF1ab cycle threshold data

	VL decline rate (95% CrI), $\log_{10}$ units per day	Posterior probability estimate is larger than pre-alpha	Posterior probability estimate is larger than alpha	Posterior probability estimate is larger than delta (unvaccinated)	Posterior probability estimate is larger than delta (fully vaccinated)
Pre-alpha (n=49)	0·69 (0·58–0·81)	..	0·07	0·21	0·01
Alpha (n=39)	0·82 (0·67–1·01)	0·93	..	0·60	0·16
Delta, unvaccinated (n=16)	0·79 (0·59–1·04)	0·79	0·40	..	0·15
Delta, fully vaccinated (n=29)	0·95 (0·76–1·18)	0·99	0·84	0·85	..

VL decline rates are shown as within-sample posterior mean estimates. Remaining columns show population (group-level) posterior probabilities that the estimate on that row is less than an estimate for a different group. Posterior probabilities are derived from 20 000 posterior samples and have sampling errors of <0·01. VL=viral load. CrI=credible interval.

Table 4: Estimates of VL decline rates for pre-alpha, alpha, and delta (unvaccinated and fully vaccinated) cases, derived from ORF1ab cycle threshold data

Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: A nationwide cohort study | Elsevier Enhanced Reader

Table 2
Vaccine effectiveness of different vaccine schedules against symptomatic Covid-19 infection during follow-up

Vaccine schedule	Incident symptomatic Covid-19 infection (N)		Mean date of infection	Follow-up (days)		Incidence rate/ 100,000 person-days		Adjusted for age	Fully adjusted model*	Fully adjusted vaccine effectiveness (95% CI)*
	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	HR (95% CI)	HR (95% CI)	
ChAdOx1 nCoV-19 / BNT162b2	170	259	21 July, 2021	85.9	60.1	2.1	7.2	0.32 (0.26-0.39)	0.33 (0.27-0.41)	67% (59-73)
ChAdOx1 nCoV-19 / mRNA-1273	17	47	22 July, 2021	86.5	61.3	1.2	7.0	0.21 (0.12-0.37)	0.21 (0.12-0.38)	79% (62-88)
ChAdOx1 nCoV-19 / ChAdOx1 nCoV-19	446	323	19 July, 2021	73.0	61.8	1.4	4.8	0.48 (0.41-0.56)	0.50 (0.42-0.59)	50% (41-58)
BNT162b2 / BNT162b2	5,113	10,188	9 May, 2021	101.7	67.2	2.4	16.6	0.16 (0.16-0.17)	0.22 (0.21-0.22)	78% (78-79)
mRNA-1273 / mRNA-1273	312	889	26 May, 2021	99.1	63.7	1.3	13.5	0.12 (0.10-0.13)	0.13 (0.12-0.16)	87% (84-88)

* Adjusted for age, sex, baseline date for vaccination, home maker service, place of birth, education, and diagnoses according to Table 1.

[Immunogenicity and efficacy of heterologous ChadOx1/BNT162b2 vaccination (nature.com)]

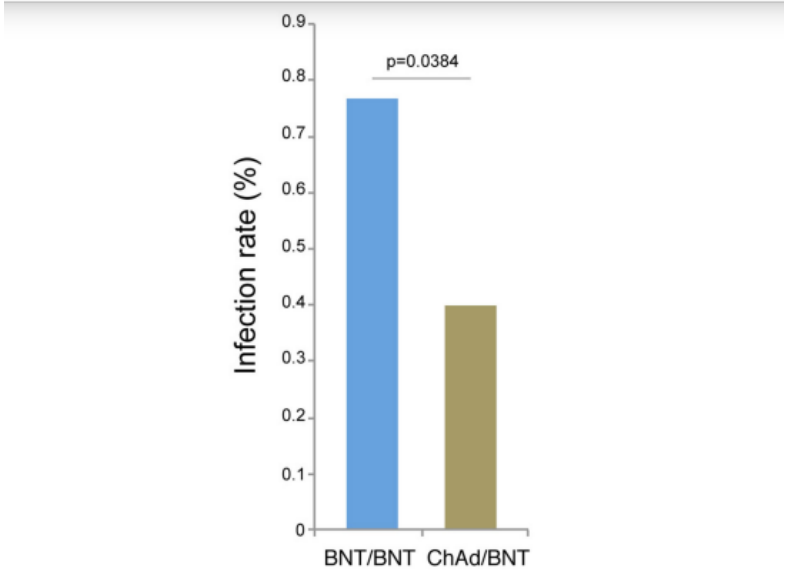


Fig. 1 | Incidence of SARS-CoV-2 infection after different vaccination regimens. Histograms show the infection rate (as documented by positive SARS-CoV-2 RT-PCR) among groups of healthcare workers who were vaccinated with the homologous BNT/BNT combination (n=81/10609) within the recommended 4-week timeframe between the two doses, or with the BNT boost after receiving the first ChAd dose (n=10/2512) approximately 12 weeks before, as recorded by the service of occupational medicine, Hospices Civils de Lyon. Data show the infection that occurred after the 14-days post-boost period, up to the end of recording (08/15/2021). Statistical significance was calculated using a logistic regression model adjusted for age; the exact p-value is shown. Demographic data and other statistics are available in Table 1.

Heterologous SARS-CoV-2 Booster Vaccinations – NIH Preliminary Report

Table 2. SARS-CoV-2 IgG Binding and Neutralizing Antibody Assays

Group	1	2	3	4	5	6	7	8	9
Primary EUA Immunization	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech	Janssen	Moderna	Pfizer/BioNTech
Vaccine	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2	Ad26.COV2-S	mRNA-1273	BNT162b2
	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg	$5x10^{10}$ vp	100-mcg	30-mcg
Booster	Moderna mRNA-1273 100-mcg			Janssen Ad26.COV2-S $5x10^{10}$ vp			Pfizer/BioNTech BNT162b2 30-mcg		
Neutralizing Antibody Titer (International Unit (IU)/mL)									
D614G ‡									
Day 1 GMT (95% CI)	8.9 (6.2-12.8)	88.7 (67.7-115.9)	24.8 (18.0-34.2)	7.6 (4.9-11.8)	61.7 (45.0-84.6)	18.6 (13.4-25.7)	9.4 (6.4-13.6)	57.6 (45.0-73.7)	21.4 (15.3-30.0)
Day 15 GMT (95% CI)	676.1 (517.5-883.3)	901.8 (727.5-1117.8)	785.8 (596.4-1035.2)	31.42 (22.3-44.3)	382.1 (290.5-502.5)	216.4 (157.8-296.9)	341.3 (239.6-486.3)	677.9 (559.4-821.3)	446.7 (340.3-586.3)
Day 29 GMT (95% CI)	431.7 (322.6-577.6)	700.0 (568.6-861.8)	495.7 (370.4-663.4)	In process	In process	In process	In process	In process	In process
Percentage with four-fold rise at Day 15 (95% CI)	100.0% (93.2%-100.0%)	86.0% (73.3%-94.2%)	100.0% (92.9%-100.0%)	50.0% (35.5-64.5%)	61.2% (46.2-74.8%)	82.0% (68.6-91.4%)	98.0% (89.0-99.9%)	93.8% (82.8-98.7%)	97.9% (88.9-99.9%)
Day 15 geometric mean fold rise (95% CI)	75.9 (55.0-104.8)	10.2 (8.0-12.8)	31.7 (23.8-42.2)	4.2 (3.0-5.8)	6.2 (4.5-8.5)	12.5 (8.7-17.9)	35.1 (23.9-51.6)	11.5 (9.0-14.8)	20.0 (14.6-27.4)

Effectiveness of BNT162b2 Vaccine against Delta Variant in Adolescents (nejm.org)

Table 1. Effectiveness of BNT162b2 Vaccine among Adolescents.*

Time Period	Documented SARS-CoV-2 Infection				Symptomatic Covid-19			
	Unvaccinated Group	Vaccinated Group	Vaccine Effectiveness (95% CI)	Risk Difference (95% CI)	Unvaccinated Group	Vaccinated Group	Vaccine Effectiveness (95% CI)	Risk Difference (95% CI)
	events (no. at risk)		%	*no. of events/ 100,000 persons*	*events (no. at risk)*		%	*no. of events/ 100,000 persons*
Days 14–20 after first dose	463 (69,408)	192 (69,609)	59 (52–65)	436.5 (363.1–510.2)	95 (70,203)	41 (70,227)	57 (39–71)	86.1 (49.0–123.7)
Days 21–27 after first dose	400 (56,997)	137 (57,358)	66 (59–72)	514.7 (423.1–590.6)	84 (57,803)	15 (57,878)	82 (73–91)	133.0 (101.1–169.4)
Days 7–21 after second dose	818 (46,384)	79 (46,815)	90 (88–92)	2032.7 (1866.3–2184.6)	151 (47,194)	11 (47,303)	93 (88–97)	379.6 (317.0–451.3)

* Data are for adolescents between the ages of 12 and 18 years who were members of Clalit Health Services from June 8 to September 14, 2021. The study population included 94,354 adolescents in both the unvaccinated and vaccinated groups.

TABLE 3. Vaccine effectiveness* against COVID-19 among hospitalized patients aged 12–18 years, by vaccination status† — 19 pediatric hospitals, 16 states,§ July–September 2021

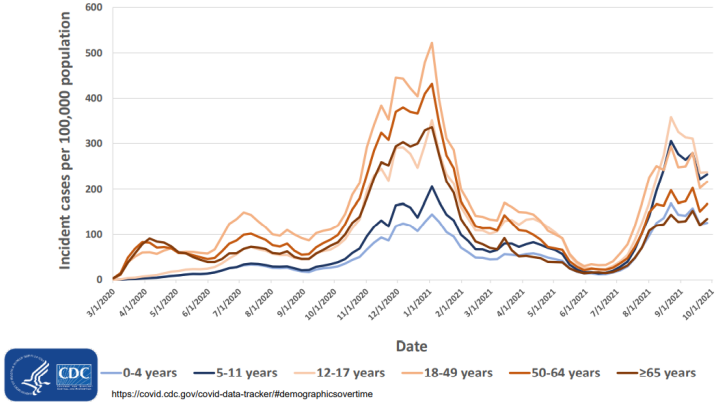
Age group, yrs	No. vaccinated/Total (%)		Vaccine effectiveness, % (95% CI)
	Case-patients	Controls	
All	**6/179 (3.4)**	**93/285 (32.6)**	**93 (83–97)**
12–15	4/106 (3.8)	53/179 (29.6)	91 (74–97)
16–18	2/73 (2.7)	40/106 (37.7)	94 (78–99)

[Effectiveness of Pfizer-BioNTech mRNA Vaccination Against COVID-19 Hospitalization Among Persons Aged 12–18 Years — United States, June–September 2021 (cdc.gov)]

73% cases with co-morbidities including obesity

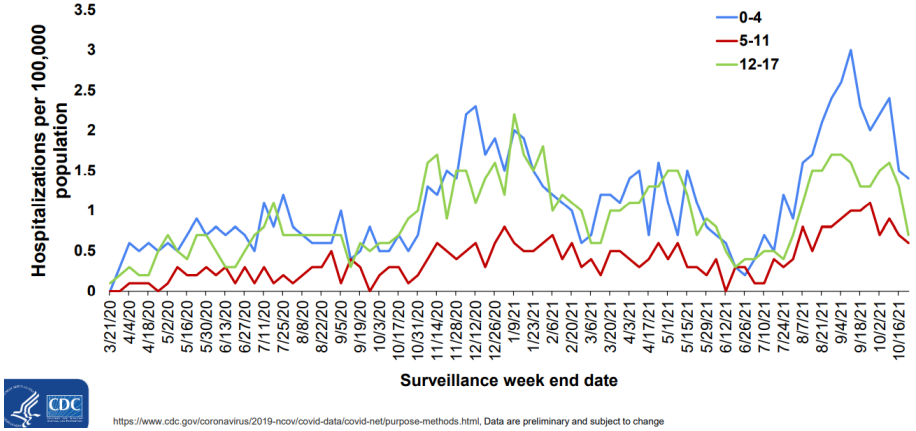
US paediatric COVID-19

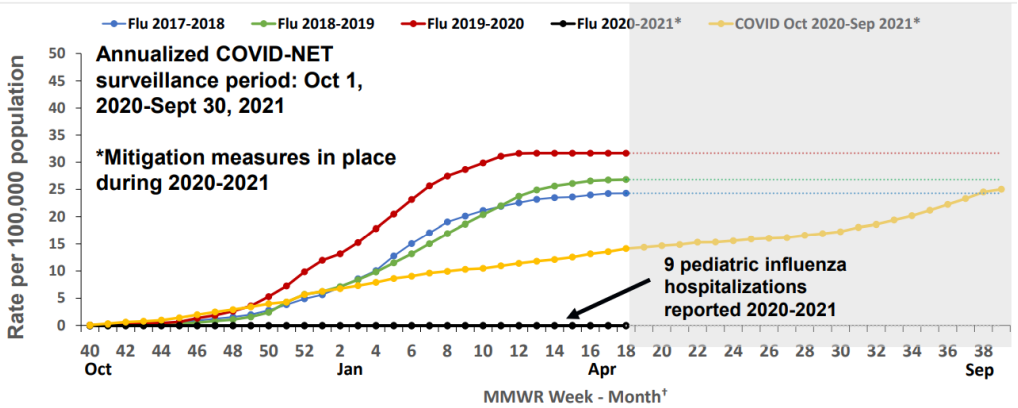
COVID-19 Weekly Cases per 100,000 Population by Age — United States, March 1, 2020–October 10, 2021



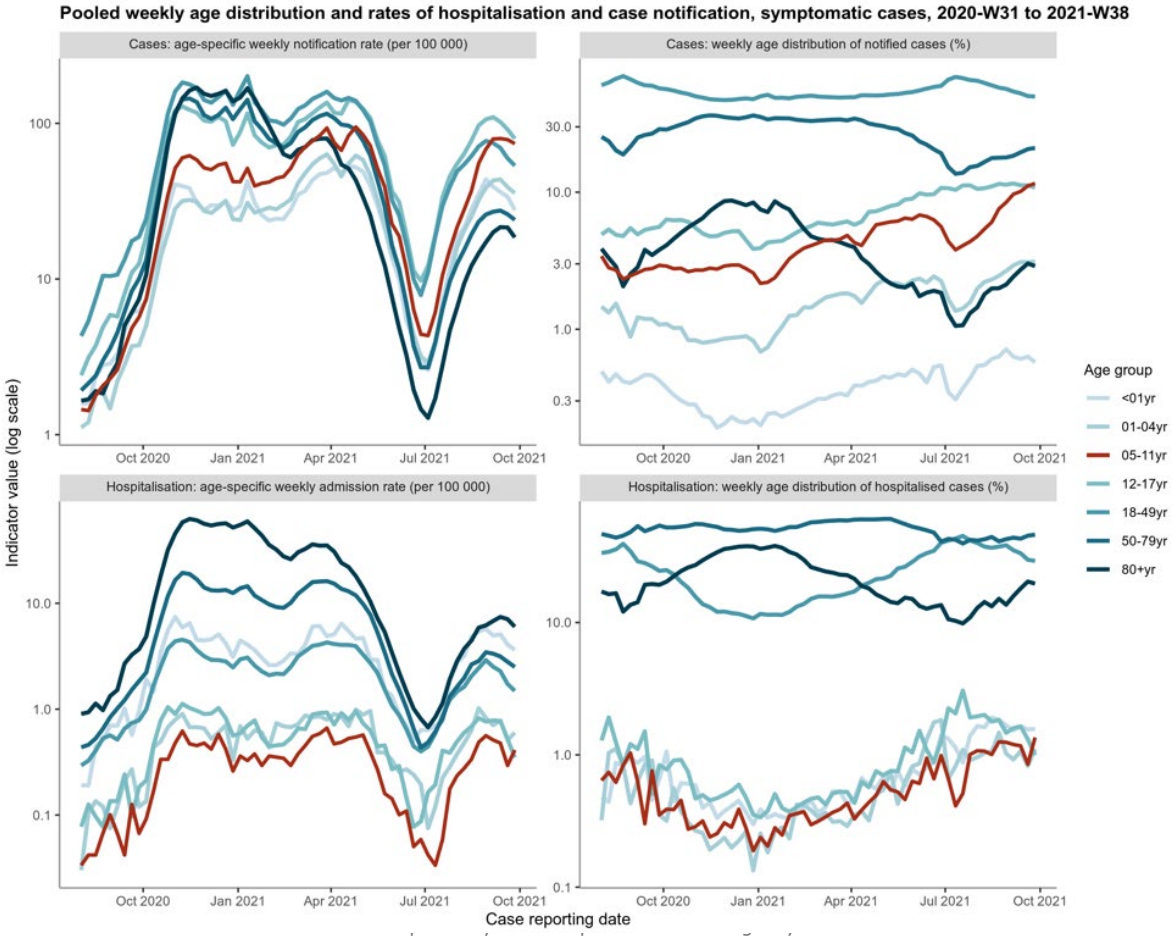
>1.9 million cases among children 5-11 years of age

COVID-19-Associated Weekly Hospitalizations per 100,000 — COVID-NET by Age Group, March 21, 2020–October 23, 2021





ECDC data from the EU/EAA



EUROPEAN MEDICINES
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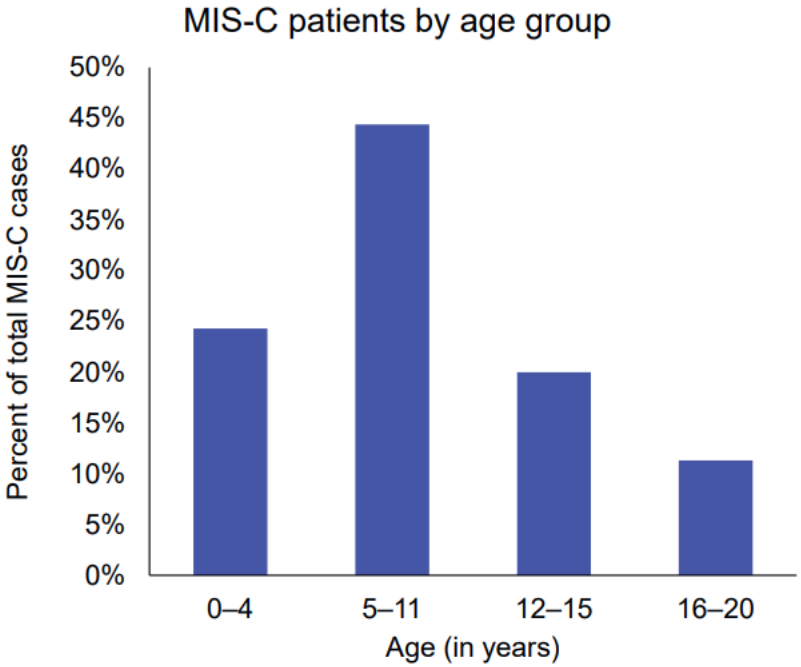
MIS-C in Children

- 5,217 MIS-C cases reported to national surveillance with date of onset between February 19, 2020–September 23, 2021
  - Median age of **9** years
  - **2,316** (**44%**) of these cases occurred in children aged 5–11 years
- **61%** occurred in children who are Hispanic/Latino or Black, Non-Hispanic
- Among children aged 5–11 years, 9 died (**20%** of MIS-C deaths)



Bowen, et al. Demographic and Clinical Factors Associated With Death Among Persons <21 Years Old With Multisystem Inflammatory Syndrome in Children—United States, February 2020–March 2021, *Open Forum Infectious Diseases*, Volume 8, Issue 8, August 2021,, https://doi.org/10.1093/ofid/ofab388
https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance

Latest updates on EMA's corporate website:

COVID-19 pandemic

ema.europa.eu

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European Medicines Agency

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