The COVID-19 Pandemic

Globally

Reported cases: 526.6 million
Reported deaths: 6,287,117

United States

Reported cases: 84.0 million
Reported deaths: 1,002,070

Sources: WHO; KFF. Data as of 5/31/2022.

Source: CDC. Data as of 5/31/2022.
Daily New Confirmed COVID-19 Cases, United States

7-day rolling average

Jan. 15: 807,815

83,868

Source: Our World in Data
Age-Adjusted Risk of COVID-19 Infection, Hospitalization, and Death, Compared to White People in the United States

Source: CDC, 4/29/2022.
COVID-19 Among Children (<18 Years) in the United States

- Reported cases: 15,005,523
- Hospital admissions: 126,809*
- Multisystem Inflammatory Syndrome in Children (MISC-C) cases: 8,210
- Deaths: 1,527

*Data for Aug. 1, 2020 – May 24, 2022

<table>
<thead>
<tr>
<th>WHO name</th>
<th>Earliest documented samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>9/2020</td>
</tr>
<tr>
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</tr>
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</tr>
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<td>Delta</td>
<td>10/2020</td>
</tr>
<tr>
<td>Omicron</td>
<td>11/2021</td>
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Source: WHO
## WHO SARS-CoV-2 Variants of Concern (VOCs)

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<td><strong>Omicron</strong></td>
<td><strong>11/2021</strong></td>
</tr>
</tbody>
</table>

Source: WHO
SARS-CoV-2 Spike Protein Mutations

Delta (B.1.617.2) 

Omicron (BA.1)

Source: COG-UK/Mutation Explorer, May 2022
Timecourse of SARS-CoV-2 Variant Distribution, Global

Source: GISAID, 5/24/2022
Daily New Confirmed COVID-19 Cases, United States

7-day rolling average

Source: Our World in Data
SARS-CoV-2 Variant Proportions, United States, Feb. 20 - May 28, 2022

BA.2.12.1 - 59.1%
BA.1.1 - 28.7%
BA.1.1.529 - 7.5%
BA.2 - 34.7%
Other - 5.2%

*CDC Nowcast modeling estimate

Source: CDC
South Africa: BA.4, BA.5 Now Dominant

Prevalence of SARS-CoV-2 sequences by lineage and epiweek

Epiweeks in 2021 – 2022

Source: Network for Genomic Surveillance in South Africa (NGS-SA), May 27, 2022
SARS-CoV-2 Variants: Ladder of Transmissibility

- Alpha
- Delta
- Omicron BA.1
- BA.2
- BA.2.12.1
- BA.4 and BA.5

Adapted from E Topol: Groundtruths Substack, May 4, 2022
Increase in COVID-19 Cases

- Waning immunity to prior infection and/or vaccination
- Increased transmissibility of new variants
- Relaxation of mitigations (masking, indoor congregating)
Medical Management of the SARS-CoV-2-Infected Patient
Medical Management of the SARS-CoV-2-Infected Patient

- Control of symptoms
- End-organ support
- Antivirals and immunomodulators
COVID-19 Treatment: WHO and NIH Guidelines

Therapeutics and COVID-19

Living Guideline
14 January 2022

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
Key COVID-19 Therapeutics, June 2022

Targeting the virus

- Remdesivir – FDA approved
- Paxlovid – EUA
- Molnupiravir – EUA
- Anti-SARS-CoV-2 monoclonal antibodies
  - Bebtelovimab (EUA)

Moderating host responses

- Dexamethasone – recommended for hospitalized patients on oxygen
- Tocilizumab (EUA) or baricitinib (FDA approved) – recommended for certain patients on dexamethasone
- Other immunomodulators – clinical trials
- Anticoagulants – recommended for certain hospitalized patients
Therapeutic “Toolkit” for Non-Hospitalized Patients with COVID-19 in the Omicron Era
Fact Sheet: Biden Administration Launches Nationwide Test-to-Treat Initiative Ensuring Rapid ‘On the Spot’ Access to Lifesaving COVID Treatments

More info: aspr.hhs.gov/COVID-19/Therapeutics
COVID-19 Vaccines
<table>
<thead>
<tr>
<th>Platform</th>
<th>Immunogen</th>
<th>Developer</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleic Acid (mRNA)</td>
<td>S2P</td>
<td>Moderna</td>
<td>BLA (Age 18+)</td>
</tr>
<tr>
<td></td>
<td>S2P</td>
<td>BioNTech/Pfizer</td>
<td>BLA (Age 16+); EUA (Age 5-15)</td>
</tr>
<tr>
<td>Adenovirus Vector</td>
<td>S2P</td>
<td>Johnson &amp; Johnson</td>
<td>EUA (Age 18+)</td>
</tr>
<tr>
<td></td>
<td>Wild-type spike</td>
<td>AstraZeneca</td>
<td>EUA/BLA TBD</td>
</tr>
<tr>
<td>Recombinant Protein</td>
<td>S2P</td>
<td>GSK/Sanofi</td>
<td>EUA request 2/2022</td>
</tr>
<tr>
<td>and Adjuvant</td>
<td>S2P</td>
<td>Novavax</td>
<td>EUA request 1/2022</td>
</tr>
</tbody>
</table>

- Deaths: 2,265,222
- Hospitalizations: 17,003,960
- Infections: 66,159,093
- Health care costs: $899.4 billion

Vaccination Profile in the United States

<table>
<thead>
<tr>
<th>Age Group</th>
<th>At least one dose</th>
<th>Fully vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>78%</td>
<td>67%</td>
</tr>
<tr>
<td>5 and up</td>
<td>83%</td>
<td>71%</td>
</tr>
<tr>
<td>65 and up</td>
<td>95%</td>
<td>91%</td>
</tr>
</tbody>
</table>

Source: CDC COVID Data tracker, 5/31/2022.
FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC): Upcoming Meetings on COVID-19 Vaccines for Children

- **June 14, 2022** – Discussion of Moderna’s Emergency Use Authorization (EUA) request for children 6 years through 17 years of age

- **June 15, 2022** – Discussion of Moderna’s EUA request for children 6 months through 5 years of age and Pfizer-BioNTech’s EUA request for children 6 months through 4 years of age
Share of People Vaccinated Against COVID-19 as of May 30, 2022

- **Upper middle income:** 77.7% complete protocol, 4.5% partly vaccinated, 82.2% total
- **High income:** 74.8% complete protocol, 5.0% partly vaccinated, 79.8% total
- **Lower middle income:** 53.5% complete protocol, 7.8% partly vaccinated, 61.3% total
- **Low income:** 12.9% complete protocol, 3.3% partly vaccinated, 16.2% total

Source: Our World in Data
Booster Shots for SARS-CoV-2 Vaccines
Waning Immunity after COVID-19 Vaccination Among U.S. Veterans, 2021

Waning immunity against infection

Vaccine effectiveness (VE) against SARS-CoV-2 infection declined from 87.9% to 48.1% from Feb. to Oct., 2021

From July to October 2021 (Delta predominant period), VE against COVID-19 death:

- age <65 years: 73.0% for Janssen, 81.5% for Moderna, 84.3% for Pfizer-BioNTech
- age ≥65 years: 52.2% for Janssen, 75.5% for Moderna, 70.1% for Pfizer-BioNTech

Numerous studies of the real-world effectiveness COVID-19 vaccines show that booster doses reconstitute waning immune protection for at least several months.

The effect of booster doses is most pronounced against severe disease, hospitalization and death.
Age-Adjusted Rates of COVID-19-Associated Hospitalizations by Vaccination Status in Adults Ages ≥18 Years, October 2021–January 2022

- **Unvaccinated**
- **Fully vaccinated without additional or booster dose**
- **Fully vaccinated with additional or booster dose**

Rate per 100,000 population

Source: CDC
COVID-19 Vaccination and Boosters Work!

COVID-19 weekly death rate/100,000 population by vaccination status, USA, 1/2022

- Unvaccinated: 12.06
- Fully vaccinated, no booster: 1.83
- Fully vaccinated + booster: 0.45

Sources: CDC; Our World in Data
Impact of COVID-19 Booster Doses in the United States

In March 2022 (Omicron variant predominant):

- Unvaccinated people aged 18+ years had a 5x increased risk of COVID-19-associated hospitalization compared to people vaccinated with a primary series and a booster dose.

- Unvaccinated people aged 12+ years had a 17x increased risk of dying from COVID-19 compared to people vaccinated with a primary series and a booster dose.

Source: covid.cdc.gov/covid-data-tracker, May 2022
FDA Expands Eligibility for Pfizer-BioNTech COVID-19 Vaccine Booster Dose to Children 5 through 11 Years
Considerations for a Second COVID-19 Booster Shot
Waning Effectiveness of 1st COVID-19 Vaccine Booster Restored by 2nd Booster Dose

First booster doses restore the waning vaccine effectiveness of a primary vaccination series, including against severe disease and hospitalization associated with the Omicron variant.

However, the effectiveness of a first booster dose wanes over time.

Growing evidence indicates that a second COVID-19 vaccine booster dose can restore vaccine effectiveness for certain populations, at least in short term.
Protection by a Fourth Dose of BNT162b2 against Omicron in Israel
YM Bar-On, R Milo et al.

- >1.2 million people aged 60+ years and eligible for fourth dose, Israeli Ministry of Health database
- An additional booster dose of Pfizer/BioNTech vaccine at 4 months after a 1st booster resulted in a 3.5-fold lower rate of severe illness
- Protection against severe illness did not wane during 6 weeks of follow up
Fourth Dose of BNT162b2 mRNA COVID-19 Vaccine in a Nationwide Setting

O Magen, N Dagan et al.

- 365,000 members of Clalit Health Services aged 60+ years

- Relative effectiveness of a 4th vaccine dose after 14-30 days compared to a 3rd third dose given at least 4 months earlier
  + 61% vs. symptomatic COVID-19
  + 72% vs. COVID-19–related hospitalization
  + 64% vs. severe COVID-19
  + 76% vs. COVID-19–related death
Cumulative COVID-19 Mortality Rates in Israeli Adults 60+ Years Receiving 1 or 2 Booster Doses of BNT162b2 Vaccine

![Graph showing cumulative incidence of COVID-19 mortality rates over days since dose 4.](image_url)

Primary analysis begins

Vaccination Group:
- First booster
- Second booster

Source: O Magen et al. *NEJM* 386:1603, 2022
CDC Recommends Additional Boosters for Certain Individuals

CDC Strengthens Recommendations and Expands Eligibility for COVID-19 Booster Shots
<table>
<thead>
<tr>
<th>Number of doses</th>
<th>0-4</th>
<th>5-11</th>
<th>12-17</th>
<th>18-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Second dose</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Third dose/booster</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Fourth dose/booster</td>
<td>X</td>
<td>X</td>
<td>✓*</td>
<td>✓*</td>
<td>✓</td>
</tr>
</tbody>
</table>

Source: CDC

* If moderately or severely immunocompromised
News Release

NIH Begins Clinical Trial Evaluating Second COVID-19 Booster Shots in Adults

Study Includes Multiple Variant Vaccines

- COVID-19 Variant Immunologic Landscape (COVAIL) trial
- Assessing different 4th dose vaccine regimens—prototype and variant vaccines alone and in combinations—to see if they broaden immunity in adults who have already had one booster dose
The Future
Perspective

Universal Coronavirus Vaccines — An Urgent Need

David M. Morens, M.D., Jeffery K. Taubenberger, M.D., Ph.D., and Anthony S. Fauci, M.D.
In the past 20 years, three coronaviruses have caused major disease outbreaks – **SARS, MERS, COVID-19**

Since September 2020, five SARS-CoV-2 **Variants of Concern** have emerged – alpha, beta, gamma, delta, omicron

Innovative approaches are needed to induce broad and durable protection against coronaviruses, known and unknown

**Pan-Coronavirus Vaccines**
Coronavirus Phylogenetic Tree

Human coronaviruses

Source: SM Gygli, PhD, NIAID. Based on 440 bp nucleotide sequences of RNA-dependent RNA polymerase.
WHO Variants of Concern:
- Alpha
- Beta
- Gamma
- Delta
- Omicron
Pan-Sarbecovirus Vaccine

Sarbecoviruses

Beta-CoV
- SARS-CoV-1
- SARS-CoV-2
- β-CoV-Pangolin-CoV
- β-CoV-SD-Pangolin-CoV
- Bat-CoV-RaTG13

Delta-CoV
- Gamma-CoV
- Deltacoronavirus 073-2015
- Deltacoronavirus 073-2016
- HCoV-HKU1
- HCoV-OC43

Alpha-CoV

SARS-CoV-3

Genus Sarbecovirus

Genus Betacoronavirus

Genus Alphacoronavirus
Example of a Pan-Coronavirus Vaccine Concept

Nanoparticle with different spike protein fragments

Vaccine

Diverse antibody response

Source: Bjorkman et al. 2021 Science
Example of a Universal Beta-Coronavirus Vaccine Concept

Inactivated, whole virus vaccine consisting of SARS-CoV-2 and several different coronaviruses delivered by intranasal mist

Broad protection against human and animal beta-coronaviruses

Source: Taubenberger, et al. 2022 Unpublished
The Antiviral Program for Pandemics (APP) aims to catalyze the development of new medicines to combat COVID-19 and prepare for other pandemic threats.
Bolstering COVID-19 Therapeutic Armamentarium: New Targets for Antivirals

Entry Inhibitors

Protease Inhibitors

Polymerase Inhibitors

Spike protein

RNA

SARS-CoV-2

ACE2

TMPRSS2

Viral protease

Viral protease cleavage

Replication-transcription complex

Translation & RNA replication

Uncapping/virion RNA translation

Endoplasmic reticulum

Golgi apparatus

Packaging & lysosomal trafficking

Viral entry

Virion release
COVID-19

The End Game for 2022 and Beyond
Pandemic Phase

Deceleration of New Cases

Control

Elimination

Eradication
Pandemic Phase

Deceleration of New Cases

Control

Elimination

Eradication
Pandemic Phase

Deceleration of New Cases

Control

Elimination

Eradication
Smallpox Eradication

- Lack of animal reservoir
- Phenotypically stable virus
- Widely accepted global vaccination campaign
- Durability of vaccine- and infection-induced immunity
Pandemic Phase

Deceleration of New Cases

Control

Elimination

Eradication
Elimination of Polio and Measles in the United States

Polio elimination: 1979

- Lack of animal reservoir
- Phenotypically stable virus
- Widely accepted national vaccination campaign

Measles elimination: 2000

- Durability of vaccine- and infection-induced immunity
- Established animal reservoirs
- Evolution of genotypically and phenotypically diverse variants
- Lack of a wide acceptance of safe and effective vaccines
- Waning of vaccine- and infection-induced immunity
Common sense respiratory hygiene, voluntary masking, attention to ventilation

Return to “Normalcy”

Requirement for intermittent vaccination

Endemicity

Availability of effective antivirals and monoclonal Abs

Similar to other respiratory viruses: RSV, common cold coronaviruses, influenza, etc.
Emerging Infections: A Perpetual Challenge

DM Morens, GK Folkers, and AS Fauci