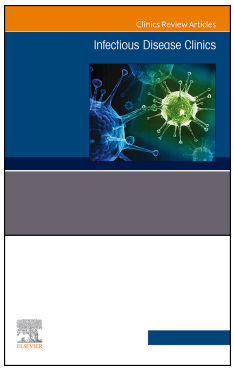
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Epidemiology and Clinical Presentation of COVID-19 in Older Adults

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Yasin Abul: None to declare

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Keywords: COVID-19, older adults, epidemiology, clinical presentation

Key points:

- The range of presentation with SARS-CoV-2 infection, from asymptomatic infection to critical illness, changes with age. Older adults will more commonly have an atypical clinical presentation, nonspecific symptoms, and blunted fever response to SARS-CoV-2 infection.
- Most COVID-19 hospitalization and mortality occur in older adults, with severity compounded by underlying illnesses.
- Although vaccination significantly reduces risk of severe COVID-19 and mortality in older adults, it may take three or more exposures for the spike protein as antigen to develop an antibody repertoire that can neutralize a broader range of variants.

Synopsis

SARS-CoV-2 infection remains asymptomatic in 33 to 90% of older adults depending on their immune status from prior infection, vaccination and circulating strain. Older adults symptomatic with SARS-CoV-2 often both present atypically, such as with a blunted fever response, and develop more severe disease. Early and late reports showed that older adults have increased severity of COVID-19 with higher case fatality rates and higher intensive care needs compared to younger adults. Infection and vaccine-induced antibody response and long-term effects of COVID-19 also differ in older adults.

INTRODUCTION

History/ Background

Coronaviruses, enveloped positive-stranded RNA viruses, infect both people and animals. In December 2019, the World Health Organization (WHO) identified a new coronavirus, reported first in Wuhan, China, as a cause of pneumonia in several countries including Thailand and Japan [1, 2] The International Committee on Virus Taxonomy named the new virus “severe acute respiratory syndrome coronavirus-2” (SARS-CoV-2) [3]. WHO designated the disease it caused “COVID-19” (coronavirus disease 2019) [4]. On January 21, 2020, the Centers for Disease Control and Prevention (CDC) reported the first confirmed travel-related case in the United States (US), in the state of Washington [5]. n January 31st, WHO issued a Global Health Emergency. This was followed by a US public emergency declaration on February 3rd [2].

The similarity of SARS-CoV-2 coronavirus’ RNA sequence to that of coronaviruses found in bats leads scientists to consider bats as the primary reservoir of SARS-like coronaviruses [6] and the original source of the 2019 SARS-CoV-2 Wuhan strain [7] . SARS-CoV-2 binds to the human cell angiotensin-converting enzyme 2 (ACE2) host receptor as a primary mechanism to gain entrance [8]. SARS-CoV-2 continues to evolve over time, acquiring mutations that improve efficiency in infection and evasion of immunity in people. CDC’s data projection tool, Nowcast, identifies and tracks emerging variants, and predicts more recent proportions of circulating variants to inform appropriate public health action plans (**Figure1**) [9]. The Omicron variant’s added

capacity to evade humoral immunity give it a replication advantage over prior variants that can improve infectiousness and fuel its spread [10-12]

Conservatively, in the US, SARS-CoV-2 has killed over one million of the more than 90 million people infected by September, 2022 [13]. Older adults suffered the greatest morbidity and mortality early in the COVID-19 pandemic [14]. Although adults >65 years old represent only about 16% of the US population, they account for 31% of reported cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of COVID-19-associated deaths [15]. CDC reports a considerably higher incidence of COVID-19 deaths per 100,000 population in those >65 years old compared with younger individuals (**Figure 2**) [16]. In the subset living in nursing homes (NH), SARS-CoV-2 infected over one million, 13% of whom subsequently died by August 2022 [17]. This article will discuss epidemiology and different clinical presentations of COVID-19 in older adults.

Definitions (see Table 1 and below)

CDC and WHO Definitions of COVID-19 Stages [18, 19]

Acute COVID-19: Symptomatic SARS-CoV-2 infection, with symptoms that last up to four weeks following illness onset

Long COVID or Post-COVID Conditions

Some individuals infected with SARS-CoV-2 have persistent or new symptoms that last two to three months beyond their initial infection [27, 29, 30]. More formally known as

post-acute sequelae of COVID (PASC), it is also called Long COVID, long-haul COVID, post-acute COVID-19, long-term effects of COVID, and chronic COVID [20].

EPIDEMIOLOGY

Risk for SARS-CoV-2 infection in older adults

Immunosenescence and Immunity in Older Adults with COVID-19

Immunosenescence refers to a multifactorial process with aging that results in immune dysfunction [21-23]. Examples of consequences of immune senescence include alterations in inflammatory response, infection severity and recovery, and reduced vaccine response [24], such as occurs with influenza and other causes of pneumonia [25-27]. Also, immune memory from prior infections and vaccination wanes over time, with a consequent increasing susceptibility to re-infection. For example, prior betacoronavirus infection that causes the common cold could offer some protection against SARS-CoV-2 by providing naturally acquired cross-protective immunity. Immunosenescence contributes to reduced initial vaccine response with age and also the more rapid decay in antibody levels following vaccination [28-30]. Poor or decreased capability to mount a cytokine response in the case of severe infection likely contributes to older adults' proneness to atypical presentations of severe COVID-19 infection, and lesser or delayed symptoms and blunted fever response [31, 32]. Both cellular senescence, which leads to permanent cell growth arrest with aging, and decreased antibody response in older adults that occurs within immunosenescence, seem to play a significant role in SARS-CoV-2's impact on the host-pathogen interaction [32-34]. Natural killer (NK) cells, participants in innate immunity, serve as first line defenders

against viral infections in the human body [35, 36]. The phenotype and function of NK cells change and decay during aging by way of transformed surface molecules, which reduces their capacity to bind to virally infected cells [35]. SARS-CoV-2 also exhausts NK cell phenotypes. This may potentiate the severity of disease by allowing the virus to escape from the NK cells' first line cellular antiviral reactivity [37-39]. Therefore, both aging and SARS-CoV-2 impair functioning of the antiviral cytotoxic NK cells in a way that can increase severity of COVID-19 in older adults [32].

Aging also impairs T cell receptor (TCR) diversity, an essential mechanism that facilitates the immune system's ability to detect foreign antigens. TCR diversity, driven by thymic stimulation of T cells in the first decades of life, persists with the homeostatic proliferation of naïve T cells [40] .

Progressive regression in thymic size and senescence of certain T cell clones results in a declining output of new naïve T cells and reduces TCR diversity [41]. COVID-19 patients have significantly less TCR diversity compared to healthy controls, a feature compounding the reduced diversity resulting from aging. Thus, the COVID-19 pathophysiology seen in older adults appears to relate to the impairment in TCR diversity [42, 43].

Aging lymphocytes have lower capacity of proliferation in defense against viral infections, and higher proportions of B and T lymphocytes become apoptotic with aging [44]. Adults ≥65 years old have impaired coordination of SARS-CoV-2 antigen-specific immune responses, and aging and poor COVID-19 outcomes are associated with paucity of naïve T cells [45].

Vaccination in Older Adults with COVID-19

Four manufacturers produce COVID-19 vaccines for the US. For the initial vaccination series, available vaccines include two mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), an adjuvant recombinant protein vaccine, NVX-CoV2373 (Novavax), and an adenoviral vector vaccine, Ad26.COV2 (Janssen/Johnson & Johnson) [46-50]. The mRNA vaccines also have been used to boost the initial series until September, 2022, when the booster doses were replaced by bivalent mRNA vaccines that include code for both the ancestral strain used in the original series and the then circulating Omicron BA.4 and BA.5 strains. For individuals unvaccinated against COVID-19, infection provides only fleeting or partial protection from recurrent infection and disease [51]. Older individuals vaccinated with BNT162b2 mRNA vaccine without prior SARS-CoV-2 infection (infection naïve) have significantly lower antibody levels than infection naïve younger adults. Unsurprisingly, the negative correlation between age and post vaccination antibody levels with SARS-CoV-2 vaccination occurs with other vaccines, too [28, 30] This lower antibody response in older adults likely signifies less absolute and less durable protection from infection, with shorter intervals of protective titers and increased likelihood of breakthrough infection [28]. Antibody decline occurs from two weeks to six months after administration of the initial pair of BNT162b2 mRNA vaccine in NH residents. NH residents experienced a more than 81% drop of anti-spike, receptor-binding domain, and neutralizing antibody level regardless of prior COVID-19 infection status during these six months (**Figure-4, Figure-5**) [28, 29]. While antibody levels may wane, booster doses appear to improve clinical protection in nursing home residents [52]. Future boosting strategies, particularly for

older adults, need to address the relative drop in antibody levels and other measures of immunity following vaccination to their relevance for clinical protection, especially in the context of their relevance to the evolving virus.

Aging (affecting clearing of virus)

Mucociliary clearance, a first line of defense against lower respiratory tract infections, functions by sweeping mucus, particles, and microorganisms up and out of the lungs. Both aging and SARS-CoV-2 impair mucociliary clearance and affect older adults' ability to clear the virus [53-55]. This reduced clearance of microorganisms can also increase the risk of co-infection with age. In Hong Kong, the risk of hospitalization with dual infection increases with age, where under 35% of hospitalizations with dual infection occur in the group under age 65, and 65% occurs in older adults who represent only 19% of the overall population [56, 57]. SARS-CoV-2 infection introduces the possibility of dual infections and thereby worse outcomes [58]. As older adults experience worse outcomes overall with SARS-CoV-2 infection, the association of co-infection with COVID-19 severity may have an amplified risk in older adults.

Hearing and visual changes with age

Sensory changes with age can indirectly affect SARS-CoV-2 infection risk. For example, presbycusis may lead individuals to shout or lower their masks to facilitate communication for those with the most hearing impairment, increasing risk for more efficient virus aerosolization and thereby transmission [59-61]. Potential and frequent SARS-CoV-2 transmission can also occur via ocular droplet deposition, a feature that remains considerably underestimated as a mode of transmission [62]. However,

because visual impairment also occurs more commonly with advanced age, the consequent increased use of eyeglasses [63] could offer a modicum of protection against SARS-CoV-2 inoculation [64, 65].

Multiple morbidities (affecting immune competence, clearance of virus)

COVID-19 severity, defined as hospitalization due to COVID-19, intensive care unit admission, need for intubation/mechanical ventilation, and COVID-19 related mortality, depends in part, on underlying conditions and morbidities. Severe COVID-19 occurs more often with the following risk factors that we also see more commonly in older adults [66-70]:

- Cancer
- Cerebrovascular diseases
- Chronic kidney disease
- Chronic lung diseases (including COPD, interstitial lung diseases, bronchiectasis, pulmonary embolism, and pulmonary hypertension)
- Chronic liver diseases (including cirrhosis, alcoholic hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease)
- Type-2 diabetes mellitus
- Disabilities
- Congestive heart failure, coronary artery disease, and other cardiomyopathies
- Dementia
- Obesity (BMI ≥30 kg/m2)
- Physical inactivity

- Smoking history
- Use of immunosuppressive medications including steroids

Underlying morbidities in older adults have added significance, given the synergies of aging and morbidities on COVID-19 severity. The February 28 and March 18, 2020 long-term care facility SARS-CoV-2 outbreaks in Washington State offer an example of this. The hospitalization rate of 55% and fatality rate of 34% occurred in a group with a median age of 83 years (n=101) and with 94% having an underlying chronic condition [71]. State and territorial jurisdiction cases reported through July 21, 2022 show a 330-times higher rate of death in individuals ≥85 years old, compared with individuals 18-29 years old [68]. Even vaccination doesn't entirely overcome the more severe age-associated outcomes in late life. Risk for a severe COVID-19 outcome after primary vaccination was higher in individuals >65 years old and in individuals with at least one underlying condition [72].

Exposure and transmissibility

Older adults in long-term care settings endure common and uncommon respiratory disease outbreaks [73-75]. SARS-CoV-2 spreads by direct contact and respiratory droplets or secretions. Transmission occurs via fomites from contaminated hands or by contact with contaminated surfaces before self-inoculation, such as through touching the eyes, nose, or mouth [76]. Frequent and close contact between healthcare staff and nursing residents with functional impairments increase the risk of COVID-19 transmission [77-79]. Some patients with cognitive impairment cannot maintain social distance or use personal protective devices, impacting their risk for getting infected or infecting others once infected, thus increasing transmission risk in the long-term care

setting. Cognitive impairment and delirium can complicate proper use of personal protective equipment (PPE), and thereby could result in higher rates of transmission [80]. The long-term care workforce has many challenges that can leave it unprepared to manage infectious outbreaks, from adequate PPE resources to high turnover which affects the ability to keep staff trained, increased use of per diem staff and the risk of unexpected vectors of infection [81-87]. Frail older adults with functional impairment, particularly those in long-term care settings, are at significantly higher risk of SARS-CoV-2 infection, such as when they receive close, hands-on care from asymptomatic health care workers who could unwittingly inoculate them [77, 88].

Data from 44,672 confirmed cases of COVID-19 during the first COVID-19 transmission surge in China showed that an initial overall case-fatality rate of 2.3% increased to 8.0% among older adults aged 70-79 years, and 14.8% for those 80 years and older [89]. Older individuals not only experience higher fatality rates but also appear more likely to spread infection [90]. The higher old-age dependency ratio (the number of individuals >64 years old relative to the number of working-age individuals (15–64 years old)), suggests a higher level of transmission among the older population. This conceivably could influence both the severity and longevity of COVID-19 symptoms in older adults. Those with sustained increased risk of close contact transmission (higher inoculum) may have asymmetrically greater risk for infection and more severe outcomes. This risk could occur especially in situations where individuals live in close quarters or share bedrooms, bathrooms, and dining areas [91].

Reinfection and Breakthrough Infection in older adults

Reinfection with SARS-CoV-2 that causes COVID-19 occurs when a SARS-CoV-2-infected individual recovers, and later becomes re-infected [92]. Breakthrough infection, or vaccine breakthrough infection, occurs after an individual is vaccinated against SARS-CoV-2 and nevertheless becomes infected and symptomatic with SARS-CoV-2 [93]. Prior to the Omicron variant wave of infections, risk for reinfection was less. Apparently, the level of added protection reduced the risk of reinfection for pre-Omicron variants by around 80%, lasting six to nine months [94, 95]. However, the reduced reinfection risk did not pertain to infection with Omicron, a feature attributed to Omicron's immune evasion characteristics [10-12] .

CLINICAL CHARACTERISTICS of COVID-19 IN OLDER ADULTS

Multi-morbidity, frailty and immunosenescence combine to increase the vulnerability to COVID-19 with advanced age [96]. SARS-CoV-2 infection often remains asymptomatic, a likelihood that changes with underlying immunity from infection, such as acquired from infection with its betacoronavirus cousins and vaccination [97-100].

When SARS-CoV-2 infection produces symptoms, i.e., COVID-19, they may include any combination of fever, cough, fatigue, shortness of breath, myalgia, anorexia, sore throat, headache, chills, and loss of taste and smell sensation [101] (Figure 3). During the early surge of COVID-19, shortness of breath occurred more frequently among adults >60 years old (12%), compared to younger adults (3%) [102]. A research collaboration of 86 emergency departments (ED) in 27 US states used the RECOVER Network registry for a multicenter cohort study. Older adults in this study had more

atypical presentations; neurological symptoms, especially confusion and altered mental status, and more malaise and dyspnea compared to younger individuals [96]. Additionally, clinicians may miss shortness of breath in older adults when it presents as functional decline with impaired mobility or frequent falls, rather than a more obvious respiratory symptom that occurs with SARS-CoV-2 infection [103].

Changes with advanced age can blunt fever response, dyspnea, and cough with COVID-19 [96, 104]. A study of Veterans living in 134 CLCs operated by the Veterans Administration (VA) evaluated temperatures through the course of SARS-CoV-2 infection. One fourth of them did not have meaningful temperature elevations over baseline. Also, the temperature for 75% of these NH residents with SARS-CoV-2 infection never exceeded 38°C at any time during the two weeks before and after their maximum temperature (**Figure-6)** [104]. Thus, in older adults, particularly those in NH settings where SARS-CoV-2 may be circulating, using a lower temperature threshold to 37.2°C will alert staff to consider early testing and will improve sensitivity for screening by temperature for SARS-CoV-2 infection [105]. A second elevated reading improves specificity for infection. CDC suggests that isolation and further evaluation for COVID-19 should be triggered by more than two temperatures >37.2°C, especially with the presence of atypical symptoms of worsening malaise, new dizziness, or diarrhea [106], but temperature elevation alone should be enough to trigger isolation and further evaluation for COVID-19 if there is an index of suspicion from known contact .

As noted above, older adults can remain asymptomatic with SARS-CoV-2 infection or develop symptoms more slowly. At a long-term care skilled facility in King County, Washington, 56% of residents with SARS-CoV-2 infection had no symptoms at the time

of testing, while 77% were presymptomatic at time of testing. Screening by fever and symptom-based criteria would have missed half of these cases [107].

COVID-19 Complications

COVID-19 can lead to many complications. In a retrospective cohort study, individuals 65 years old and older who were continuously enrolled in a Medicare Advantage plan with prescription drug coverage from January 2019 to the date of SARS-CoV-2 diagnosis, had higher risk of complications that include respiratory failure, fatigue, hypertension, memory problems, kidney injury, mental health problems, hypercoagulopathy, and cardiac rhythm problems, compared to matched comparison groups without COVID-19 [108]. A nationwide study from Sweden reported higher incidence of deep vein thrombosis and pulmonary embolism in older adults with highest rate of pulmonary embolism in the age group 50 to 70 years. The increase in incidence rate ratio with age specific to deep vein thrombosis during 1-90 days after SARS-CoV-2 infection was greatest for the first compared with the second and third pandemic waves in Sweden [109].

Severity of COVID-19

National Institute of Health (NIH) guidelines define individuals with severe COVID-19 as having "...SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%." NIH defines individuals with critical COVID-19 as having "...respiratory failure, septic shock, and/or multiple organ dysfunction." Underlying morbidity modulates the risk for severe COVID-19 in older adults such as

cardiopulmonary disease, diabetes, cancer, obesity, or chronic kidney disease [67]. Although COVID-19 vaccination reduces the risk of severe illness, vaccine immunogenicity and efficacy to BNT162b2 mRNA declines with advanced age leaving some people vulnerable to a breakthrough infection that can result in severe illness [29, 110].

COVID-19 in Older Adults: Risk Stratification, Risk Factors, and Prevention

Initial Chinese, United Kingdom (UK), and US COVID-19 cohorts show that among all the risk factors, age dominates as the most important determinant of severity [15, 89, 111]. Individuals 70-79 years old and >80 years old had hospitalization and case fatality rates at least four-fold that among the entire Chinese cohort [89]. Among adults >80 years old in a UK cohort, the risk of mortality was 20-fold that among adults 50-59 years old [111]. In the US cohort, individuals >65 years old accounted for 80% of total deaths [15]. In older adults, comorbidity burden also contributes to the risk for severe COVID-19. Individuals with both advanced age and a high comorbidity burden commonly experience severe COVID-19. Individuals with one reported underlying condition have a six-fold higher hospitalization rate and 12-fold higher mortality rate than those with no underlying conditions (45.4% vs 7.6%, and 19.5% vs 1.6% respectively) [112].

Primary prevention offers the best approach to counter introduction and spread of COVID-19 and has proven especially effective in the long-term care setting. In NHs, implementation of basic and fundamental prevention methods begins with setting policy, education, and adherence to and monitoring of best practices. Best practices address vaccination, surveillance, and other policies (Vaccines for prevention is the focus of another chapter in this issue.) Staff should seek to maximize and track resident and

staff vaccination rates while keeping vaccines up-to-date. Routine symptom screening can directly trigger testing for SARS-CoV-2 or other infections. When a test result identifies a SARS-CoV-2 infection, it should trigger contact tracing if not broader testing of other residents on the ward or in the facility. Staff also should model and promote appropriate use of masks and restrict visitors according to prevailing CDC or local health department guidelines. As a sole strategy to determine who to isolate or mask, symptom-screening alone will fail to prevent transmission of SARS-CoV-2 in NHs since symptom screening alone will fail to detect 40% or more of SARS-CoV-2 infections [113, 114]. These findings remind us that more than 50% of NH residents infected with SARS-CoV-2 were asymptomatic or presymptomatic at time of testing. And, given that some have non-diagnostic tests followed by a diagnostic test day [115] which means neither symptoms nor testing fully discriminate those infected with SARS-CoV-2 infection from those who are not at a given moment. Taken together, these point to a very important contributory factor of the transmission of SARS-CoV-2 in this population, i.e., the failure to recognize the limitations to our approach to surveillance, and consequent premature relaxation of policies that limit transmission.

Successful masking strategies in NH residents and health care professionals can critically limit the opportunity for SARS-CoV-2 transmission. N-95 respirators offer better protection for care activities with NH residents than surgical masks. However, masking, along with distancing and hand washing, reducing time in shared air spaces (reduced ventilation), high efficiency air filtration, and other strategies collectively can reduce the likelihood of transmission [114]. On the other hand, NH residents can be infected with

low inoculum viral load and may stay asymptomatic despite of all those precautions [91].

Atypical Clinical Presentation of COVID-19 in Older Adults

Older adults with COVID-19 present to the ED with more atypical symptoms. Health care providers should consider COVID-19 in differential diagnosis in the ED and/or NH settings when faced with older adults with non-specific symptoms such as falls, confusion, delirium, and worsening of functional impairment, especially when SARS-CoV-2 is known to be circulating in the community [96, 103, 116]. Gastrointestinal symptoms are less commonly reported in older adults compared to younger adults, and older adults more commonly present to the ED with neurological symptoms including altered mental status and confusion. Older adults presenting to the ED more often have abnormal laboratory findings, including elevated troponin and leukocyte levels, compared to younger individuals presenting to the ED [96]. Radiological differences are also noted between younger and older individuals with COVID-19; older adults with COVID-19 also more often have extensive lung involvement, and subpleural line and pleural thickening [117], with one study showing that in older adults with COVID-19, pleural effusion can be used as a distinctive prognostic marker [118]. In NHs and other settings with older adults, awareness of these atypical findings and clinical presentations can help identify additional indications for early screening and other preventive measurements to support infection control efforts and improve patient outcomes [116].

Long COVID or Post-Acute Sequelae of COVID-19 (PASC) Older Adults

The risk for Long COVID, formally called PASC, in older adults differs depending on the data sources. Reportedly, one in four older adults experience at least one potential PASC condition compared to one in five younger adults [119]. However, new data from the US Household Pulse Survey performed by the National Center for Health Statistics indicate older adults less often reported PASC conditions than younger adults, with approximately three times as many adults ages 50-59 having Long COVID relative to individuals >80 years old [120]. In data on Veterans living in CLCs where daily symptom surveillance and trigger and sweep testing protocols are in place to optimally detect COVID, data suggests that around one in five of these older Veterans has one or more new PASC symptoms more than two months from their initial diagnosis [121]. This rate exceeds that of the observational study and underlines the limitations in surveying older adults for PASC, where a variety of reasons can lead to their non-participation and undercounting, from issues that relate to privacy, illness, ability to respond through technology or telephone [120]. As such, the relative risk for PASC with age remains uncertain. A recent study suggests that nearly 55% of patients have at least one post-COVID sequelae two years after SARS-CoV-2 infection [122]. Another study suggests that risk for this outcome increases with each additional infection. Those with Long COVID symptoms at two years scored lower on quality-of-life metrics, had worse exercise capacity, more mental health abnormalities, and increased healthcare use after discharge, compared to survivors without Long COVID symptoms [122-125]

A universally acceptable definition will need to wait until we know more about the symptoms, etiology, and risk factors of PASC [126]. Some of the physical and mental symptoms of PASC include fatigue, muscle weakness, shortness of breath, chest pain,

cough, anxiety, depression, posttraumatic stress disorder (PTSD), poor memory, sleep disturbances, and concentration deficiency [127, 128]. Depression, insomnia, dyspnea, myalgias, anxiety, cognitive impairment, and fatigue are the most common PASC symptoms, in descending order among older Veterans living in Community Living Centers (CLCs) [121]. Risk factors for developing PASC include increased age, number of acute phase symptoms (>5), BMI, and female sex [129]. Notably, severity of illness in the initial infection has not correlated with the risk of developing PASC, although initial reports of PASC after hospitalization seem to indicate greater susceptibility to outcomes of PASC for hospitalized patients. Evidence linking the development of PASC to elevated inflammatory markers such as red cell distribution width (RDW), Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) remains inconclusive [130].

PASC in older adults compared to those under age 65, as extracted from the CERNER electronic health record database, more often includes renal failure, thromboembolic events, cerebrovascular disease, type 2 diabetes, muscle disorders, neurologic conditions, and mental health conditions (including mood disorders, anxiety, other mental conditions, and substance-related disorders) [119]. Persistent impaired cognitive functions in older adults have been reported for up to one year after acute COVID-19 [131].

FUTURE DIRECTIONS

- COVID-19 vaccine frequency and acceptance to optimize immunologic response and clinical effectiveness need further studies that emphasize outcomes in older adults.

- The refinement of definitions for PASC, its epidemiology, impact, and approaches to management will evolve as new data become available.
- We need to better understand what drives the severity of SARS-CoV-2 infection in older adults, especially as it relates to frailty, immune senescence, and inflammation.

CLINICAL CARE POINTS

- Older adults with COVID-19 have higher hospitalization and case fatality rates than younger adults [132]
- SARS-CoV-2 infection remains asymptomatic from 33 to 90% of older adults, depending on underlying immune status from prior infection, vaccination, and circulating strain [133].
- The high frequency of asymptomatic SARS-CoV-2 infection makes symptom based testing ineffective as a sole means for early outbreak detection of SARS-CoV-2 in NH populations [113].
- Fever response is blunted in older adults with COVID-19; setting a lower threshold for triggering SARS-CoV-2 testing in older adults in NH settings improves sensitivity and can alert staff to consider the need to test for SARS-CoV-2 days earlier [104, 105].
- Older adults with underlying morbidities disproportionately suffer the most severe COVID-19 outcomes [134, 135] .
- Healthcare providers should consider adding COVID-19 to the differential diagnosis of clinical presentations such as falls, confusion, delirium, and worsening of functional impairment. This should drive SARS-CoV-2 testing,

treatment, and measures to reduce spread (e.g., distancing, masking, isolation) [116].

- Older adults more often experience any of a broad range of sequelae of respiratory failure, fatigue, hypertension, memory problems, kidney injury, mental health problems, hypercoagulopathy, cardiac dysrhythmias, deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19 [108, 109].
- In older adults, vaccination reduces SARS-CoV-2 incident infection and subsequent severity [134, 135], effects bolstered by booster vaccines [52].
- N-95 respirators provide superior protection to other masks and can protect users from getting infection when caring for or visiting those infected with SARS-CoV-2 [114]. In conjunction with social distancing, minimizing time in rooms with infected individuals, frequent hand washing, and proper use of other PPE, individuals can avoid becoming infected. Absent N-95 respirator availability, other masks still can offer some protection. The use of masks should follow the greater standard of personal preference of health department guidelines.

FIGURE LEGENDS AND TABLE

Figure 1: Regional proportions from specimens collected week of 9/24/2022 in CDC page with a model that estimates more recent proportions of circulating variants. *(From CDC Data Tracker: Monitoring Variant Proportions. Available from: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#circulatingVariants , Accessed on July 20, 2022)*

Figure 2: Covid-19 Weekly Deaths per 100,000 Population by Age Group, United States between March 01,2020, and September 27, 2022. *(Adapted from CDC Data Tracker: Monitoring Variant Proportions. Available from: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-proportions.html#circulatingVariants , Accessed on July 20, 2022)*

Figure-3: Organ and systems which are affected by SARS-CoV-2 in the long term with symptoms and signs of COVID-19 [121, 127, 136-143]. *(Designed by Freepik)*

Figure-4: Humoral immune assessment of BNT162b2 messenger RNA (mRNA) vaccine vaccination in NH residents.

Post-vaccination anti-spike, anti-receptor-binding domain (RBD) and serum neutralization titers are shown.

Control: vaccinated younger healthcare workers or unvaccinated SARS-CoV-2-convalescent individuals.

The dotted lines: median preimmunization value in the SARS-CoV-2-naive subjects.

Abbreviations: AU, antibody unit; NH, nursing home; pNT50, pseudovirus neutralization titer [28].

Figure-5: Antibody levels two weeks and six months after BNT162b2 mRNA vaccination in healthcare workers (HCWs) and NH residents with and without SARS-CoV-2 infection prior to vaccination.

Abbreviations: AU, arbitrary unit; BAU, binding arbitrary unit; NH, nursing home; pNT50, pseudovirus neutralization; RBD, receptor-binding domain [29].

Figure-6: Temperature trends according to maximum temperature. This compares daily temperatures relative to the maximum temperature. The shaded area denotes the 95% confidence intervals, and T0 refers the testing date for SARS-CoV-2. *(Adapted from Rudolph, J.L., et al., Temperature in Nursing Home Residents Systematically Tested for SARS-CoV-2. J Am Med Dir Assoc, 2020. 21(7): p. 895-899.e1; with permission)*

Table 1: Definitions.

Term	Definition	
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) named by the International Committee on Virus Taxonomy is the virus that causes COVID-19 [3].	
COVID-19	Coronavirus disease 2019 is an infectious disease, designated by WHO as COVID-19, that is caused by SARS-CoV-2, a coronavirus discovered in 2019 [4].	
Asymptomatic infection	Infection while having no symptoms. Includes both presymptomatic individuals and individuals who will never develop symptoms.	
Presymptomatic infection	Infection prior to inevitable development of symptoms.	
Transmission [144]	**Presymptomatic**	An index case has no symptoms during the exposure period of their close contacts, but later develops symptoms.
	Asymptomatic	An index case never develops symptoms or signs of infection.
	Post-symptomatic	An index case has no symptoms during the exposure period of their close contacts, but previously had symptoms.
Criteria of Suspected Cases of SARS-CoV-2 Infection [101, 145] When suspicious: new onset fever and/or respiratory symptoms (eg, sore throat, cough, nasal congestion, rhinorrhea, shortness of breath). Other common non-respiratory symptoms: new changes in taste or smell, diarrhea, chills, anorexia, headache, and muscle pain.	**Clinical Criteria** **Epidemiologic Criteria**	Acute onset of fever and cough **OR** Acute onset of any three or more of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea, diarrhea, anorexia. Contact of a probable or confirmed case or linked to a COVID-19 cluster.
	Illness	Severe acute respiratory illness (SARI)
	Testing	No clinical signs or symptoms, nor meeting epidemiologic criteria, with a positive professional use or self-test SARS-CoV-2 antigen-RDT
Clinical criteria in the absence of a more likely diagnosis (CDC) [146] (Organ systems and associated symptoms and signs by all ages and older adults are summarized in Figure 3. As discussed later in this article, older adults may present differently.)	Acute onset or worsening of at least two symptoms or signs	Fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion, runny nose
	OR	
	Acute onset or worsening of at least one symptoms or sign	Cough; shortness of breath; difficulty breathing; olfactory disorder; taste disorder; confusion or change in mental status; persistent pain or pressure in the chest; pale, gray, or blue-colored skin, lips, or nail beds, depending on skin tone; inability to wake or stay awake
	OR	
	Severe respiratory illness with at least	Clinical or radiographic evidence of pneumonia, or acute respiratory distress syndrome (ARDS)
Laboratory Criteria (CDC) [146, 147] Laboratory evidence using methods approved or authorized by the US Food and Drug Administration (FDA) or designated authority	Confirmatory laboratory evidence	Detection of SARS-CoV-2 ribonucleic acid (RNA) in a post-mortem respiratory swab or clinical specimen using a diagnostic molecular amplification test performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified provider **OR** Detection of SARS-CoV-2 by genomic sequencing
	Presumptive laboratory evidence	Detection of SARS-CoV-2 specific antigen in a post-mortem obtained respiratory swab or clinical specimen using a diagnostic test performed by a CLIA-certified provider
	Supportive laboratory evidence	Detection of antibody in serum, plasma, or whole blood specific to natural infection with SARS-CoV-2 (antibody to nucleocapsid protein) **OR** Detection of SARS-CoV-2 specific antigen by immunocytochemistry in an autopsy specimen

		OR Detection of SARS-CoV-2 RNA or specific antigen using a test performed without CLIA oversight
Epidemiologic Linkage [146]	One or both of the following exposures in the prior 14 days (CDC)	Close contact***** with a confirmed or probable case of COVID-19 disease **OR** Member of an exposed risk cohort as defined by public health authorities during an outbreak or high transmission
	Probable case (WHO) [145]	An individual who meets clinical criteria of suspected case AND is a contact of a probable or confirmed case, OR is linked to a COVID-19 cluster
	Confirmed case (WHO) [145]	An individual with a positive Nucleic Acid Amplification Test (NAAT), regardless of clinical criteria or epidemiological criteria **OR** A person meeting clinical criteria and/or epidemiological criteria with a positive professional use or self-test SARS-CoV-2 Antigen-RDT
	Symptomatic case (WHO) [145]	An individual who is infected with SARS-CoV-2 and has symptoms
Case Classification (CDC) [146]	**Suspect**	Meets supportive laboratory evidence with no prior history of being a confirmed or probable case
	Probable	Meets clinical criteria and epidemiologic linkage with no confirmatory or presumptive laboratory evidence for SARS-CoV-2 **OR** Meets presumptive laboratory evidence **OR**
		Meets vital records criteria with no confirmatory laboratory evidence for SARS-CoV-2
	Confirmed	Meets confirmatory laboratory evidence
Testing	**Positive Test**	A positive test indicates likelihood of present or past SARS-CoV-2 infection whether symptomatic or recovered.
	Types of Tests [148-151]	**Direct detection of SARS-CoV-2 RNA** by nucleic acid amplification tests (NAATs) or reverse- transcription polymerase chain reaction (RT-PCR) from the upper respiratory tract)
		Serological tests detecting antibodies to the virus in the blood. Usually used to detect previous infection or response to vaccine
		Antigen tests detecting SARS-CoV-2 antigen with nasal swab or saliva sample,
		Breathalyzer that uses gas chromatography-mass spectrometry to detect exhaled volatile organic compounds specific to SARS-CoV-2 infection
		Interferon-gamma release assay
Definition of COVID Stages (CDC and WHO) [18, 19]	**Acute COVID-19**	Symptoms of COVID-19, up to four weeks following the onset of illness
	Long COVID or Post-COVID Conditions (PCC)	(See text for details) (Also called long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term effects of COVID, chronic COVID) [20].

*Close contact is generally defined as being within six feet for a cumulative period of at least 15 minutes over a 24-hour period. However, this is dependent on a number of exposure and setting variables (eg, in the setting of an aerosol-generating procedure in a healthcare setting without proper personal protective equipment (PPE), it may be “any period of time.”

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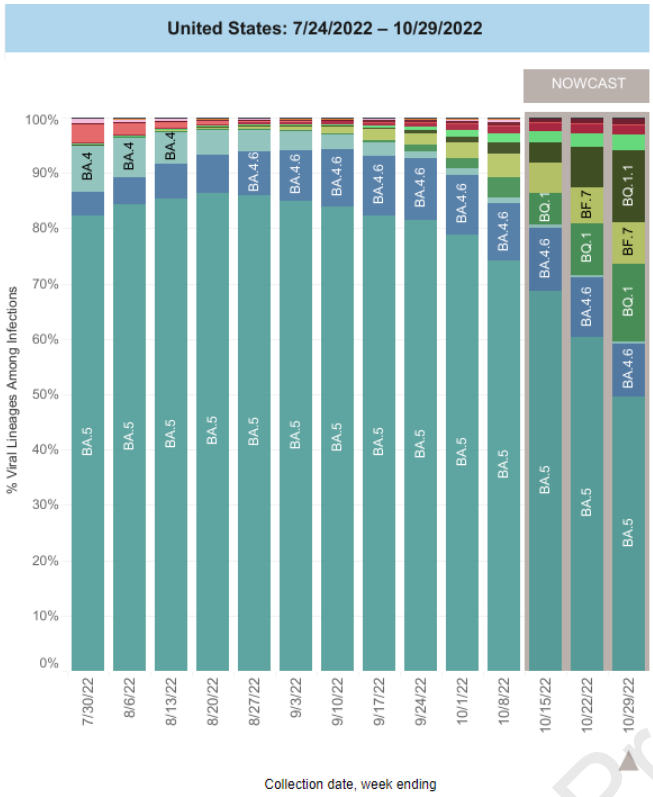


United States: 10/23/2022 – 10/29/2022 NOWCAST

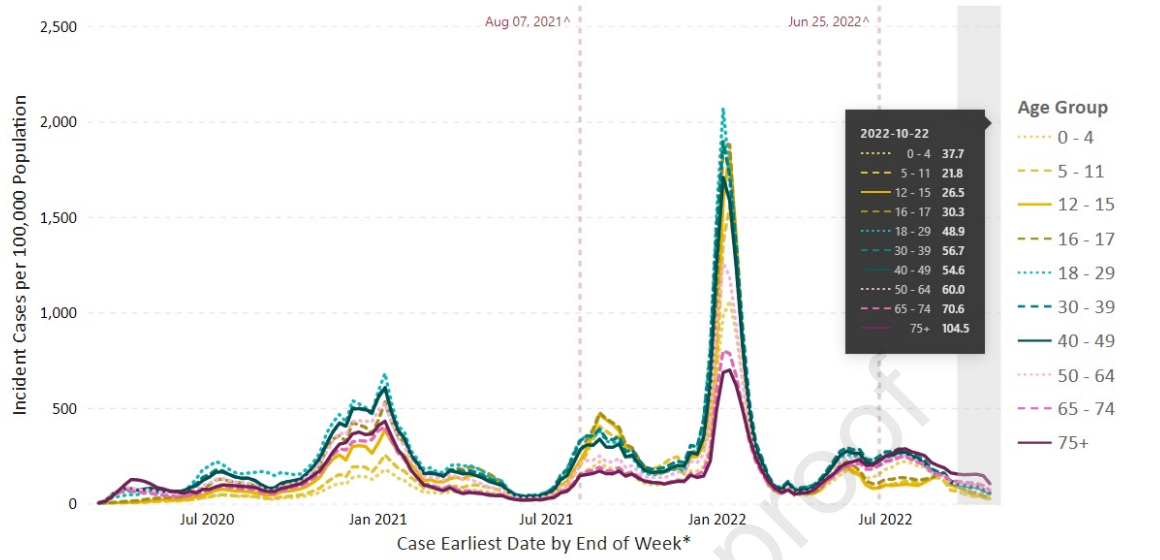
USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	49.6%	45.3-53.9%
	BQ.1	VOC	14.0%	11.2-17.5%
	BQ.1.1	VOC	13.1%	9.8-17.3%
	BA.4.6	VOC	9.6%	8.6-10.7%
	BF.7	VOC	7.5%	6.6-8.5%
	BA.5.2.6	VOC	2.8%	2.3-3.5%
	BA.2.75	VOC	1.8%	1.5-2.2%
	BA.2.75.2	VOC	1.2%	0.9-1.6%
	BA.4	VOC	0.2%	0.2-0.3%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2 and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, BA.5.2.6 were aggregated with BA.5. Lineages BA.2.75.2, BA.4.6, BF.7, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

COVID-19 Weekly Cases per 100,000 Population by Age Group, United States

March 01, 2020 - October 22, 2022*



US: Includes data up to the week ending on Oct 22, 2022. Percentage of cases reporting age by date - 99.91%.

US territories are included in case and death counts but not in population counts. Potential six-week delay in case reporting to CDC denoted by gray bars. Weekly data with five or less cases have been suppressed. *Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC. The date for the current week extends through Saturday. ^Case rates for South Dakota during the week ending Aug 07, 2021, and Texas during the week ending Jun 25, 2022, are reflective of a data reporting artifact. Surveillance data are provisional, and as additional clinical date data becomes available, the case rates over time are subject to change.

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public Health Science Team