COMMENTARY

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The perfect storm: An unseasonably early RSV annual epidemic, a severe annual flu epidemic, and a smoldering COVID-19 pandemic

"And now these three remain: faith, hope and love. But the greatest of these is love." 1 Corinthians 13:13

Some seasonal respiratory viruses can assure a perfect storm, as has been the case most recently with an unseasonably early respiratory syncytial virus (RSV) epidemic, a severe annual influenza virus epidemic, and a smoldering coronavirus (COVID-19) pandemic.[1] Much has been discussed since last October about this looming "tridemic" or "triple-demic" of RSV, influenza, and COVID. Given the predominance of these 3 respiratory viruses during the late fall, winter, and early spring, I will henceforth limit my comments to just these 3 viruses, although this by no means implies that other respiratory viruses are of less significance.

The following clinical scenarios are meant to emphasize the overlapping clinical manifestations of respiratory viral infections that make clinical diagnosis challenging.

THREE CLINICAL SCENARIOS

Scenario 1

A 50-year-old male patient who underwent kidney transplantation 10 years prior to presentation developed low-grade fever and nasal congestion on a Friday afternoon, the last week of November 2022, after exposure to an office coworker with similar symptoms. He was up-to-date on COVID vaccine recommendations and the annual influenza vaccine. A single nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), RSV, and influenza detection by polymerase chain reaction (PCR) was collected, and he was promptly started on oseltamivir. Molnupiravir could not be prescribed without a documented positive PCR test for SARS-CoV-2. His symptoms did not change over the subsequent 12 hours. Once SARS-CoV-2 was confirmed and RSV and influenza were not detected, he was treated with molnupiravir for 5 days starting Saturday morning, and symptoms rapidly improved.

Scenario 2

A 40-year-old, healthy internist developed sudden-onset fever, headache, and cough on a Thursday evening, the second week of December 2022. She had diagnosed multiple patients earlier that week and in the preceding weeks with COVID and influenza. She was up-to-date on COVID vaccine recommendations and the annual influenza vaccine. An astute clinician, she self-diagnosed influenza A, had a nasopharyngeal swab for SARS-CoV-2 and influenza PCR collected, and started taking oseltamivir the same night her symptoms started. Influenza A was detected by PCR, and SARS-CoV-2 was not detected. Her symptoms did not improve until the third day of oseltamivir treatment. She was afebrile without the use of antipyretics by the fourth day of treatment and returned to work after completing 5 days of therapy.

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Scenario 3

A 61-year-old husband and wife developed nasal congestion, cough, and malaise without fever in the third week of November 2022. Both were up-to-date with COVID vaccine recommendations and the annual influenza vaccine. Both completed home rapid antigen-detection tests for SARS-CoV-2 that were negative. Their symptoms slightly improved, and they decided not to cancel their 5-day vacation in sunny Florida the following week around Thanksgiving. The husband's 79-year-old mother joined them on their vacation. Shortly after returning home, she developed similar symptoms. She was up-to-date on COVID vaccine recommendations and annual influenza vaccine. Her home rapid antigen-detection test for SARS-CoV-2 was negative, and a nasopharyngeal swab PCR test did not detect influenza or SARS-CoV-2. Her symptoms lingered for 10 days despite treatment with over-the-counter analgesics, nasal decongestants, and cough suppressants. She completely recovered by the end of the second week of illness.

The first and second patients had PCR-confirmed COVID and influenza A, respectively. No microbiologically confirmed diagnosis was made for the 3 patients in the third clinical scenario, but the epidemiology and clinical course suggest RSV infection.

TRIPLEDEMIC

Outdoor seasonal climate and human behavior impact the seasonality of many respiratory viruses, including SARS-CoV-2,[2] but modern living partially shields us from climate extremes of temperature and humidity.[1] Several respiratory viruses, including RSV, human metapneumovirus, and human coronaviruses (strains 229E, NL63, OC43, HKU1) display biennial variations.[1] Some, such as metapneumovirus, display cyclical subgroup predominance every 1 to 3 years. Seasonality of other respiratory viruses is less evident.

Overlapping of epidemiology and clinical presentation of various respiratory viruses makes clinical diagnosis a matter of statistical probability rather than certainty, particularly in immunocompromised individuals.[3] Immunity following acute infection is short-lived, so repeated infections do occur. Vaccines and specific antiviral agents are available to prevent and treat SARS-CoV-2 infection and influenza. These vaccines prevent severe infections requiring hospitalization but are less successful in preventing mild or asymptomatic infections, prevent exacerbation of underlying lung and heart diseases, and prevent secondary bacterial pneumonia. While natural infections may be more effective than vaccines in preventing a subsequent infection by the same virus,[4] choosing intentional exposure for the purpose of acquiring natural immunity over vaccine-induced immunity should not be condoned, as fatal outcomes can occur in healthy individuals.[5] Vaccines and therapeutics for other respiratory viruses are not currently available.

Behavioral measures successfully applied during the early peak of the COVID pandemic were at least partially successful in reducing infection spread, particularly before preventive vaccines and effective therapeutics became available. Collateral benefit of these behavioral measures was a concomitant reduction in incidence of other respiratory viruses. However, these measures kept us "cocooned," resulting in a current exposure-immunity "debt" or "gap." Inching closer to SARS-CoV-2 infection- and vaccine-induced herd immunity, decreased SARS-CoV-2 virulence, and behavioral restriction fatigue are pushing us out of that cocoon, and hence a greater proportion of the population is more susceptible to other respiratory viruses, including RSV and influenza.

Another collateral damage of the COVID pandemic is decreased uptake (49.4%) of influenza vaccination in adults during the 2021 to 2022 influenza season, a decrease of 0.8% percentage points from the previous influenza season.[6]

RESPIRATORY SYNCYTIAL VIRUS

Chimpanzee coryza agent was discovered in 1956 as a cause of colds in chimpanzees, and was renamed RSV in 1957 after it was identified as the most common cause of pediatric bronchiolitis.[7,8] RSV is currently the most common cause of lower respiratory tract infections (LRTIs).[9] Symptomatic treatment results in recovery in the vast majority of children, but RSV is associated with severe disease in certain high-risk children and adults, resulting in up to an estimated 120,000 hospitalizations and 10,000 deaths annually in older US adults,[9] similar to or surpassing the impact of influenza.[8]

Peak months of seasonal RSV activity typically occur in December or January. However, for the 2022 to 2023 season, an increase in RSV cases began in late August and surged 5-fold by November of 2022,[10] stretching resources and capacity of healthcare facilities that were already grappling with rising cases of COVID and influenza. Although hospitalization from RSV in seniors in the early fall of 2022 was significantly lower than that for children, this was still 10 times higher (about 6 of every 100,000) for that

time in the season than in years before the COVID pandemic.[10]

Because seniors had been appropriately concerned about the spread of the COVID omicron variant and maintained previously adopted preventive public health measures like masks and social distancing, their exposure to children with the RSV infection was delayed. When the population began loosening their adherence to these measures in the fall of 2022, the rate of hospitalization from RSV infection in seniors increased.

RSV Prevention

Palivizumab is the most widely used monoclonal antibody used prophylactically to reduce RSV hospitalizations and protect against severe disease in high-risk infants with a history of premature birth or bronchopulmonary or hemodynamically significant congenital heart disease.[11,12]

A randomized phase 1/2 study with an RSV prefusion F vaccine for maternal immunization showed it was well-tolerated and immunogenic in adults.[11] A randomized, double-blinded, placebo-controlled phase 3 study with the same vaccine evaluated vaccination during pregnancy against medically attended LRTIs in newborn infants and enrolled 7,358 maternal participants and found no safety concerns for both vaccinated mothers and their newborns, with 81.8% and 69.4% vaccine efficacy during the first 3 and 6 months of life, respectively.[13–15] As noted at a national meeting in October 2022, preplanned interim analysis of a phase 3, global, multicenter, randomized, double-blinded, placebo-controlled study with the same vaccine in adults age 60 and older showed 66.7% and 85.7% efficacy against LRTI with 2 or more and 3 or more symptoms, respectively, with no safety concerns.[16] RSV vaccines by 2 other manufacturers have recently been shown to be similarly effective in adults age 60 and older.[17,18] Calculating the number needed to vaccine to prevent 1 case of LRTI with these 3 investigational vaccines ranged from 96 to 385. In February 2023, the US Food and Drug Administration (FDA) Vaccines and Related Biological Products Advisory Committee proposed provisional approval of one of these vaccines in adults age 60 and older[19] and set an action date for August 2023, following the acceptance of the marketing authorization application for this vaccine candidate by the European Medicines Agency under accelerated assessment for both older adult and maternal immunization.[20]

Treatment for the vast majority of cases of RSV LRTIs is supportive, and early therapy with ribavirin and intravenous gamma globulin may be associated with improved survival in immunocompromised persons. Rilematovir (JNJ-53718678), a novel, oral, selective small-molecule RSV fusion protein inhibitor displays very potent antiviral activity and low cytotoxicity against RSV A2 strain and strains from both A and B subtypes.[21] A randomized, dose-varying, placebo-controlled study with this molecule administered once daily for 7 days to 69 healthy adult volunteers inoculated with RSV substantially reduced mean and peak viral load, time to peak viral load, duration of viral shedding, mean overall symptom score, and nasal secretion weight.[22] However, the manufacturer of rilematovir terminated 3 studies in early 2022 in hospitalized pediatric patients, adult outpatients, and patients with hepatic impairment, stating that this decision was not based on safety concerns.

INFLUENZA

Despite a misnomer that the 1918 "Spanish flu" pandemic originated in birds and was transmitted to humans and then to pigs, the first human cases were detected in a soldier's camp in Kansas in March 1918.[23,24] Human influenza A virus was not discovered as a "filterable organism" for another 15 years, until 1933, when an influenza virus was demonstrated by Alphonse Raymond Dochez to be producible in humans.[23] In 1977 at the Armed Forces Institute of Pathology, Taubenberger and Reid[23] sequenced 9 fragments of 1918 influenza viral RNA from 4 of 8 virus gene segments from a US serviceman's preserved lung tissue after he succumbed to "influenza and pneumonia" in September 1918 and from lung tissues of Alaskan Inuit Natives who died from influenza A during the 1918 pandemic, were buried in a mass grave, and frozen in permafrost.[24]

Fast forward to 2022, the influenza A (H3N2) virus circulated earlier than during seasons preceding the COVID pandemic in certain countries in the Southern Hemisphere, such as Chile.[25] Also in Tennessee, the influenza season began earlier than usual, resulting in higher rates of pediatric symptomatic illness and hospitalizations compared with adults and prior seasons.[26] By early December 2022, it became clear that the current influenza season was more severe and associated with 1.6 times more hospitalizations than the highest cumulative rate in the last 13 years.[27] Consequently, the percent fill rate for oseltamivir became almost 15 times higher than it had been in previous years,[28] and the US Department of Health and Human Services through the Administration

for Strategic Preparedness and Response announced at the end of 2022 that they are making additional supplies of oseltamivir to ensure supply for states, territories, and tribes owing to increased demand for the antiviral during this influenza season.[29]

COVID IS NOT GOING ANYWHERE

Human cases of COVID, the coronavirus disease caused by SARS-CoV-2, were first reported in Wuhan, China, in December 2019 and most likely had their ecological reservoir in bats.[30] Because humans do not have much interaction with bats, it is believed that SARS-CoV-2 jumped the species barrier to humans through an intermediate animal host that is more likely to be handled by humans.[30]

On December 30, 2019, Dr. Li Wenliang warned in an online chat group (WeChat) that he had seen a report showing positive test results of SARS in 7 patients.[31,32] However, he did not formally report the outbreak to the authorities at that time and was reprimanded at that time for disrupting public order. On December 26, 2019, Dr. Zhang Jixian, Director of the Respiratory and Critical Care Medicine Department of Hubei Provincial Hospital of Integrated Chinese and Western Medicine, diagnosed a senior couple living in a residential community near that hospital with viral pneumonia. The computed tomography (CT) chest images reminded her of similar CTs in patients she had cared for during the 2003 SARS outbreak, also in Wuhan.[32] After "summoning" the couple's son for "mandatory" chest CT that showed findings similar to his parents' CT, and hospitalization of a fourth patient with similar clinical and CT findings within the next day, and after excluding influenza in all 4 patients, Dr. Jixian reported her concern, and on December 30 at 3:10 pm, the Wuhan Municipal Health and Health Commission issued the official "emergency notice reporting the treatment of pneumonia of unknown cases."[32] Dr. Jixian is thus considered the first physician to report the novel coronavirus before its outbreak.

COVID seasonality in temperate countries is now well established, with data showing that with an increment of 1°C above the average temperature is associated with a reduction of about 61 COVID deaths per million annually.[2] Some findings suggested that COVID transmission is inversely proportional to temperature and absolute humidity.[33] Even though epidemiologic data were consistent with COVID as a seasonal low-temperature infection, seasonality alone was not sufficient to curtail viral transmission to the extent that nonpharmacologic interventions were no longer needed.[34]

In an unprecedented approach to containing the COVID pandemic, the US government provided free COVID home antigen testing kits to any resident who requested. This likely facilitated home testing for many people, possibly allowing for early medical intervention for those who seek care if they test positive. However, there were several drawbacks to the widespread use of home testing:

- Posttest probability depends on pretest probability, and people interpreted results indiscriminately, whether they got tested for asymptomatic screening before family gatherings or for acute illness.
- Sick people with negative tests may not have pursued PCR testing as recommended, mistakenly accepting negative tests as guaranteed "ruleout," even if they remained ill.
- Tests may not have been performed accurately per the manufacturers' instructions.
- Tests may have been used beyond their labeled expiration dates (which was actually recommended by the US government at one point during the pandemic).
- Since reporting results of these home tests was not required, people could have—intentionally or unintentionally—spread the infection to others.

It was not until December 2022 that the National Institutes of Health launched a website for users to anonymously report the result of at-home COVID tests.[35] However, this is merely an option and not mandatory. Granted that antigen test results likely underestimate infection prevalence, I think we missed a golden opportunity to track the results of these home tests to allow better contact-tracing and possibly tackle disease containment. The National Health and Nutrition Examination Survey collects SARS-CoV-2 serology data and self-reported vaccination and disease history among adults.[36] In doing so, they have provided preliminary insights about disease prevalence and vaccine uptake and noted that 43.7% of respondents were possibly asymptomatically infected, and healthy young adults and ethnic minorities may have had less access to testing and unknowingly exposed others, amplifying disparities in infection rates and outcomes.[36]

Frequent SARS-CoV-2 mutations resulting in new variants sweeping the country and the impact of vaccination, infection, and therapy on the incidence and severity of infection[37] have fueled misinformation about viral transmission and complacency toward preventive behaviors, such as "mask fatigue."[38] Data have shown that lifting universal masking mandates in schools resulted in a 5% increase in cases.[39]

The current dominant variant nationwide is XBB.1.5, accounting for half of cases, followed by BQ.1.1, accounting for about a quarter of cases,[40] while the original omicron variant has almost disappeared. Fortunately, these latest variants don't appear to cause more serious disease than their predecessors. Nevertheless, even though the ongoing COVID pandemic in the United States is mostly associated with mild illness, it is certainly not just a nuisance, with 300 to 500 related current daily deaths, which cumulatively exceed severe seasonal influenza epidemic-associated deaths.[41] We also should not forget that influenza and SARS-CoV-2 coinfections occur and can result in more serious illnesses if not promptly recognized and treated.[42]

COVID VACCINES WORK AND WILL BE ADMINISTERED ANNUALLY

Public trust in the almost unprecedented safety and protective efficacy rates of the initial COVID vaccines has been partially dampened after breakthrough infections and reactogenicity data accumulated. However, the majority of scientists and, hopefully, the population believe that these vaccines prevented an unknown number—likely in the millions—of hospitalizations and deaths worldwide.[43] Interim analysis of a prospective observational cohort study conducted at Kaiser Permanente Southern California comparing more than 900,000 individuals age 18 and older who received 2 doses of mRNA-1273 vaccine through June 2021, and who were matched 1:1 to randomly selected unvaccinated individuals followed through September 2021, showed 88.0% vaccine effectiveness against SARS-CoV-2 infection at 0 to < 2 months and 75.5% at 6 to < 8 months.[44]

Studies assessing "booster" doses (admittedly a moving target) of vaccine showed that additional doses conferred additional protection compared with "primary series" (which differs depending on age and underlying diseases) in immunocompetent adults[45] as well as nursing home residents.[46] Those who were not up-to-date with recommended COVID vaccines had a 30% to 50% higher risk for acquiring SARS-CoV-2 infection compared with those who were up-to-date with COVID vaccines.[46]

Natural COVID infection confers some immunity against subsequent infections. While antibody levels wane over time following natural infection or vaccination, data have shown that COVID vaccination confers higher and long-lasting antibody levels, including in pregnant women and cord blood, particularly when natural infections are mild.[47] COVID vaccine correlate of protection has been illusive, but accumulating data support using neutralizing antibodies (which increase after vaccination only) and not anti-spike protein antibodies (which increase after natural infection or vaccination) as the agreed-upon correlate of protection, which would merit its use for near-term decisions about vaccines.[48]

Recent data showed cross-neutralization ability of the omicron-containing bivalent booster vaccine that was introduced in late 2022 against emerging omicron subvariants that are not contained in the vaccine.[49] Early estimates of bivalent mRNA vaccine booster dose are showing vaccine effectiveness in preventing symptomatic infection,[50] COVID-associated emergency department or urgent care encounters, and COVID-associated hospitalizations,[50–52] including infections attributable to omicron BA.5 and XBB/XBB.1.5-related sublineages.[40]

Latest estimates from the World Health Organization show that 4 of 5 people who died from COVID were over age 60, but only 3 in 4 people in that age group completed primary vaccine series.[40] Unfortunately, only about two-thirds of healthcare professionals who received primary COVID vaccines received a booster dose, and only about 80% received influenza vaccination during 2021 to 2022 season.[53] It does not seem probable that we can convince vaccine-skeptical patients to get vaccinated unless we ourselves "walk the talk."

We may finally be getting clarification on what to expect regarding future COVID vaccines instead of the roller coaster we have been riding for the last 3 years and the number of doses of the monovalent vaccine needed to maintain vaccine effectiveness, from 1 to 5 doses to the most recent bivalent vaccine. The FDA Vaccines and Related Biological Products Advisory Committee stated in a briefing document released in January 2023, ahead of a meeting with its vaccine advisors, that their intended approach would be similar to that of the annual influenza vaccination program, with the goal to predict in the spring of 2023 which SARS-CoV-2 strain would be expected to pose the greatest threat in the winter of 2023 to 2024.[54] A vaccine targeting that strain would then be distributed in the fall of 2023, with annual updates to that COVID vaccine expected in each future year. Reducing uncertainty about future vaccines would hopefully improve vaccine uptake.

COVID TREATMENT OPTIONS, SOME ALREADY OBSOLETE

The first SARS-CoV-2 monoclonal antibody, bamlanivimab, received emergency use authorization (EUA) by the FDA in November 2020 for patients with mild COVID-related illness who had certain medical conditions that put them at risk for progression to severe illness, with the intent to prevent emergency department and urgent care visits, hospitalizations, and deaths. Subsequently, other monoclonal antibodies were sequentially developed in what seems like lightning-speed succession to catch up with SARS-CoV-2 mutations and new variants, from casirivimab-imdevimab later on in November 2020, to bamlanivimab-etesevimab in February 2021, to sotrovimab in May 2021, to bebtelovimab in February 2022. In addition, tixagevimab-cilgavimab was authorized by the FDA in December 2021 for pre-exposure prophylaxis for patients who are not expected to mount a protective response to vaccines and are at risk for severe illness if they get infected. SARS-CoV-2 finally outsmarted us, and newer variants became resistant to the last 2 available monoclonal antibodies, bebtelovimab and tixagevimab-cilgavimab, within 10 to 12 months of their EUA, resulting in withdrawal from the market by the FDA in December 2022. We are currently in a "monoclonal antibody void," and we have to manage our patients with other agents currently available on the market.

Our current antiviral armamentarium is limited to intravenous remdesivir, oral nirmatrelvir-ritonavir, and oral molnupiravir.[55–58] Intravenous remdesivir is fully approved by the FDA, while the oral agents received EUA. Retrospectively analyzed data following EUA of oral nirmatrelvir-ritonavir showed 51% lower hospitalization rates in adults within 30 days after diagnosis when prescribed within 5 days of diagnosis, compared with those who were not prescribed this drug.[55] Preliminary disturbing data are showing up to 5% risk of rebound COVID-related illness that may be severe enough to require hospitalization in patients who initially improve with either oral antiviral agent.[56] New mutations conferring resistance to remdesivir have been described,[57] and time will tell to what extent this may impact future effectiveness of SARS-CoV-2 therapeutics. Interim analysis of a randomized, multicenter placebo-controlled phase 3 clinical trial showed that sabizabulin, an oral novel microtubule disruptor that has antiviral as well as anti-inflammatory properties, when administered to hospitalized patients with moderate to severe COVID who were at high risk for acute respiratory distress syndrome and death, resulted in a 25% absolute reduction and a 55% relative reduction in mortality compared with placebo.[58] The study was stopped for efficacy earlier than what had been planned by the independent data-monitoring committee. Data were submitted to the FDA for approval, and more data and analysis were requested.

A phase 3, multicenter, noninferiority, observer-blinded, randomized clinical trial conducted in China during the outbreak of omicron (B.1.1.529) SARS-CoV-2 variant showed that VV116 (an orally bioavailable deuterated remdesivir hydrobromide) was noninferior to nirmatrelvir-ritonavir to alleviate symptoms in adults with mild-to-moderate COVID at high risk for progression to severe disease.[59] The majority of COVID patients do not require hospitalization, and the supply of oral nirmatrelvir-ritonavir, molnupiravir, and intravenous remdesivir clearly falls short of the global demand for outpatient management. If VV116 is approved, it would help fill at least part of the current void for outpatient treatment; and given the familiarity of both healthcare providers and the public with the worldwide successful track record of intravenous remdesivir, VV116 stands a better chance for acceptance and widespread use in patients with mild-to-moderate COVID.

There is no question that we must continue recommending, particularly to our most vulnerable and immunocompromised patients, the COVID preventive and treatment options that are accepted by the majority of scientists,[60] at least until the pandemic is declared over.

THE PANDEMIC AFTER THE PANDEMIC

Worldwide prevalence of long COVID, defined as persistence of symptoms or development of new symptoms more than 4 weeks after initial infection, ranges up to 45%.[61] Even patients with mild COVID are at higher risk compared with uninfected people for persistence of anosmia and dysgeusia during the first 6 months after infection and for persistence of dyspnea and weakness in the second 6 months after infection, regardless of the SARS-CoV-2 variant, but the majority of symptoms resolve within a year.[62] Adults have persistent symptoms early on more than children, and women and men are roughly equally affected. Vaccinated patients with breakthrough infection have a lower risk of persistent symptoms than unvaccinated patients,[63] particularly those pre-

senting with moderate or severe symptoms of acute illness. Some patients who have had one COVID-related infection and subsequently let down their guard regarding preventive measures and compliance with recommended vaccination doses erroneously think they are invincible to reinfection and that there is no potential added protection from subsequent doses of the vaccine. Regardless of vaccination status, data have shown that compared with no reinfection, reinfection increases risk of all-cause mortality, hospitalization, and risk of pulmonary, cardiovascular, hematologic, gastrointestinal, renal, psychological, musculoskeletal, and neurologic sequelae.[5] Also, compared with noninfected controls, cumulative risk increased according to number of reinfections.

LIGHT AT THE END OF THE TUNNEL

Despite the early and potentially looming fear of a "tripledemic," US surveillance data showed a different situation. The earlier and more-severe RSV season declined after peaking during the second week of November 2022, influenza declined after peaking during the first week of December 2022, and the uptick in COVID-related hospitalization after Christmas 2022 was short-lived and nowhere near surges of this pandemic in the last 3 years.[64] Needless to say, the future is unpredictable, with a second peak of RSV commonly occurring in the spring, and with influenza B cases typically peaking in late winter, early spring.

THE BOTTOM LINE

All three viruses—RSV, influenza, and COVID—can cause severe illness requiring hospitalization and can be fatal, whether as a result of severe viral pneumonia or secondary bacterial or fungal pneumonia, or by exacerbation of underlying chronic cardiopulmonary diseases. Despite the presumed absence of human natural immunity to SARS-CoV-2, the lack of current FDA-approved vaccines and treatment options for RSV, and the availability of several vaccines and a handful of antiviral agents active against influenza, I still believe that influenza takes the prize of "worst actor."

Influenza is pervasive

Influenza is unpredictable, pervasive, and endemic in wild birds—which are all around us, and their droppings are unavoidable. Further, human consumption depends on manufacturing and technology and more widespread travel, and with birds in all parts of the world, in one way or another, all of this contributes to annual influenza epidemics. We fully anticipate annual influenza virus antigenic drift(s) accounting for annual epidemics and potential antigenic drift(s) that result in pandemics. Highly pathogenic avian influenza epidemics with potential pandemic spread occur with concerning frequency.[65]

The majority of influenza vaccine production remains the archaic egg-based process. We are annually playing "catch-up," with the Northern Hemisphere targeting predominant influenza serotypes in the Southern Hemisphere during the preceding flu season, and vice versa. Year-round influenza activity near the equator and global warming add to the complexity and shortcomings of this process. Also, half of US influenza vaccine suppliers manufacture their vaccines outside of the United States, making the implementation of quality control measures more challenging.

Although annual influenza vaccination is the most effective prevention, public and healthcare workers' annual influenza vaccine uptake remain suboptimal. Despite multiple decades of influenza vaccine research, ample immunogenicity, and protective efficacy data, public trust in vaccine is both weak and unrealistic (100% protective efficacy and protection from other viral respiratory tract infections should not be expected), and continued myths about inaccurate associations with certain side effects or subsequent disorders persist.

Antiviral agents and resistance

Adamantane resistance among circulating influenza A (H3N2) viruses has rapidly increased over the last 3 decades, becoming universal during the 2005 to 2006 season, and has persisted since then.[66] Therefore, amantadine and rimantadine are no longer recommended. Neuraminidase resistance mutations in seasonal influenza A (H1N1) increased during the 2007 to 2008 influenza season, conferring resistance to oseltamivir, but not zanamivir. Fortunately, the 2009 pandemic influenza A (H1N1) that has since essentially completely replaced the previously circulating seasonal influenza A (H1N1) is susceptible to the neuraminidase inhibitor oseltamivir, the current primary antiviral agent used to treat influenza. Patients who do not respond to the antiviral medications they are receiving may need to have their treatment regimens altered to fit their clinical circumstances.[66]

For additional perspective, in examining and comparing the impact of the 1918 influenza pandemic, the ongoing acquired immunodeficiency syndrome worldwide epidemic that started in 1981, and the cur-

TABLE 1
Comparing 1918 influenza pandemic, AIDS worldwide epidemic, and COVID-19 pandemic

	1918 Influenza A (H1N1) pandemic	AIDS epidemic (cumulative, ongoing since 1981)	COVID pandemic (ongoing)
World population	1.8 billion	7.8 billion	7.8 billion
Number of deaths	50 million	40.1 million	6.9 million
Percent deaths	2.5%	0.5%	0.9%
Duration	2 years	42 years	3 years
Epidemic curve	"W": young adults and extremes of age	Inverted "U": young adults	"U": extremes of age
Number infected	500 million	84 million	670 million
Percent infected	30%	1.1%	8.6%

AIDS = acquired immunodeficiency syndrome

rent COVID pandemic (Table 1), it becomes clear that the 1918 influenza pandemic had the worst outcomes.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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