COVID-19 in Missouri

2020-2021

A Perspective on Origins, Spread & Controversies

Part I

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The onset of the COVID-19 pandemic, which has taken more lives than any other event in United States history, was unexpected and insidious. We know that certain things are inevitable: death, taxes, and influenza pandemics, the latter of which typically occur thrice a century.

However, few anticipated the first pandemic caused by a coronavirus with the notable exception of Bill Gates.[1] Further, none predicted either the pandemic's duration or the extreme societal disruption and division it would precipitate.

Introduction

In early January 2020 as Missouri health care professionals were preparing for a busy winter influenza season, rumors started circulating about an outbreak in China of an exceptionally virulent form of pneumonia of unclear etiology. A few weeks after Chinese physicians began spreading word about the new disease, reports about the rapidly escalating epidemic were grim. Wuhan, an eastern Chinese city with more than 11 million inhabitants, quickly was overwhelmed by a lethal viral illness the world would soon come to know as COVID-19.[2] It was unclear if the outbreak would be contained in Asia, as had been the case with Severe Acute Respiratory Syndrome (SARS) in 2003, or whether a new pandemic was gathering steam and threatening Missourians.

In early 2020 the United States prepared for the possible arrival and spread of the novel coronavirus. The first U.S. case, on January 18, 2020 in Orange Country, California signaled the beginning of the worst pandemic to strike the country in more than a century. Subsequent blitzkrieg spread of COVID-19 ensued in the Pacific Northwest and, shortly thereafter, in the Northeast. The duration of a major conflict often is underestimated at the onset of hostilities. In early 2020 few could have predicted that COVID-19 would become the longest-lasting respiratory viral pandemic in recorded human history, and that after two years the end would not yet be in sight.

This manuscript, first in a series, will review current knowledge regarding the origin and spread of COVID-19, discuss patterns of disease incidence in Missouri and nationwide, and address controversies regarding optimal treatment strategies. Our opinions are based on information that was available as of early January 2022

Origins and Spread

Our understanding of the onset and early spread of COVID-19 is murky, as a result of concerted efforts by Chinese authorities to obfuscate the origins and minimize the severity of the pandemic.[2] Although the first case reportedly was diagnosed in Wuhan on December 8, 2019, in real time Chinese authorities delayed announcement of the outbreak for several weeks.[2] The initial reports describing the contagiousness and lethality of the new viral illness came from whistleblower physicians in Wuhan, subsequently ostracized, who privately shared information with their colleagues. News media leaks rapidly ensued.

Chinese health authorities began notifying local health care providers about the outbreak during the last week of December 2019, and scientists determined the genomic sequence of the new coronavirus, SARS-CoV-2, on January 3, 2020. However, as the outbreak unfolded the Chinese National Health Commission "ordered institutions not to publish any information … and (to) transfer any samples they had to designated testing institutions or destroy them."[2] The World Health Organization, in an apparent attempt to avoid angering the Chinese government, minimized the potential for widespread disease transmission as late as January 14, 2020. The situation subsequently deteriorated with lightning speed as cases were reported in Korea, Japan, and the U.S. on January 20, 2020. The disease exploded worldwide in February 2020, shortly after the WHO recommended against limitations of "trade or movement" from China. The delays in early action to contain the outbreak and to determine its source have been the subject of criticism worldwide.

The questions of when, where, and how SARS-CoV-2 was introduced into the human population have prompted extensive investigation and speculation

Figure 1. Closed Wuhan Huanan Seafood Market, January 1, 2020.
Source: Alamy

but our current state of knowledge about these issues remains quite incomplete. Human coronaviruses were discovered in the mid-1960s. Four have been recognized as seasonal endemic pathogens and have been estimated to account for approximately 15% of "common colds."[3] Most cases occur in the winter months and typically are associated with relatively mild upper respiratory symptoms.[4] Prior to COVID-19, two non-endemic coronaviruses were known to have infected humans. SARS-CoV caused an epidemic for several months in 2003 resulting in almost 800 deaths in 29 Asian countries. Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged in the Middle East in 2012 and sporadic small outbreaks of this viral illness have continued.

The two coronaviruses most closely genetically related to SARS-CoV-2 (albeit with only 96.3% sequence similarity) were identified in 2013 and 2019 in bats in Yunnan Province, China, 810 miles from Wuhan.[5, 6] Of note, SARS-CoV-2 has never been identified in a bat. Multiple early SARS-CoV-2 clinical isolates lacked substantial genetic variability, a finding consistent with the notion that SARS-CoV-2 first was introduced into the human population in late 2019 shortly prior to the earliest recognized cases in Wuhan.[7] Proposed potential explanations for initial human exposure to SARS-CoV-2 include 1) direct exposure from bats; 2) transmission from bats to an intermediate host and then to humans, or 3) inadvertent or deliberate release from a laboratory where the virus had been stored and perhaps manipulated.

Ascertainment of the source of the SARS-CoV-2 outbreak has been hampered by the absence of identified viruses with direct ancestral lineage to the novel 2019 virus.[8] However, phylogenetic

dating analyses suggest that SARS-CoV-2 diverged from related bat viruses sometime between 1948 and 1982 and subsequently has circulated in bats unnoticed for several decades.[9, 10] Although all human coronaviruses identified prior to the pandemic have had intermediate animal hosts, none has yet been identified for SARS-CoV-2. The rapid adaptation of SARS-CoV-2 to minks and other animals shortly after the pandemic's onset provides strong support to the concept that transmission to humans via an intermediate host is plausible.[5,10]

Epidemiologic investigation determined that the first confirmed human case, and about two-thirds of the first 41 cases, were linked to the Wuhan Huanan Seafood Market, where 38 species of live wild animals were kept in stalls and then sold. Raccoon dogs, subsequently found to be susceptible to SARS-CoV-2 infection, were caged in the western area of the 12-acre market, a location visited by many of the initial cases.[11] Multiple other animal species including hedgehogs, badgers, deer, and raccoons, but not bats, were sold at the market.[2,11]

To borrow an analogy from trauma care, the "golden hour" for elucidation of the epidemiology of the SARS-CoV-2 outbreak was in late December 2019.[12] Unfortunately, when the Huanan Market was closed on January 1, 2020, no live mammals were screened for SARS-CoV-2, an exercise which would have provided invaluable information about the potential intermediate host or hosts; thus the golden hour was squandered (Figure 1). The possibility that SARS-CoV-2 was not introduced into humans from an animal at the crowded market, but rather that an infected visitor initiated a superspreader event there, cannot be excluded but seems less likely based on the preponderance of available evidence.

An open question is whether an intentional or unintentional laboratory leak from the Wuhan Institute of Virology, where bat coronaviruses are studied, could have been the inciting event. Multiple lines of evidence, summarized by Holmes et al., do not support this theory.[8] No evidence that SARS-CoV-2 originated in a laboratory has been identified by multiple investigators using different lines of inquiry: epidemiologic investigation of laboratory workers; evaluation of the pathogenicity of SARS-CoV-2 in laboratory animals, including mice, necessary for serial passage in virology experiments; and assessment of the feasibility of altering an existing virus to attain the characteristics of SARS-CoV-2.[8] Prior gain-of-function experiments at the Wuhan Institute of Virology used viruses with different genetic backbones than that of SARS-CoV-2 and thus the widely promoted theory that this research caused the pandemic is unfounded.[8]

Was there an unidentified smoking gun in Wuhan, either at the virology institute or across the Yangtze River at the seafood market? Many scientists have concluded that currently available evidence does not support the hypothesis that manipulation or mishandling of a virus by laboratory workers triggered the pandemic.[6,8] The aphorism that common things occur commonly is an early lesson taught to health sciences students and clinicians. Initiation of a pandemic by transmission from other species to humans has been well-documented on multiple occasions.[13] Although the mystery of how SARS-CoV-2 first entered the human population remains unsolved, it seems likely that cross-species transmission occurred, either at the market or nearby, from an as-yet unidentified intermediate host. There is scant support for the theory that COVID-19 will prove to be the first pandemic in history caused by a laboratory leak.

Incidence in Missouri and U.S.

Once the first U.S. case was documented on January 26, 2020, on the west coast, it was only a matter of time until the new coronavirus would reach Missouri. On February 5, hundreds of thousands of Missourians celebrated with the Kansas City Chiefs at their first Super Bowl victory parade in half a century. The event's timing was fortuitous: scarcely a month later public gatherings ceased. The state's first case, reported on March 7, was a college student from the suburban St. Louis area who returned home from studying in Italy and then created a furor by attending a large social event in Clayton while possibly contagious.

From March until August 2020 Missouri benefited from its central location, far from the early hotspots on the east and west coasts, as case counts remained low; incidence was about half the national average[14] (Figure 2). In particular, COVID-19 rates in rural areas in central and southern Missouri were among the lowest in the country. Unfortunately,

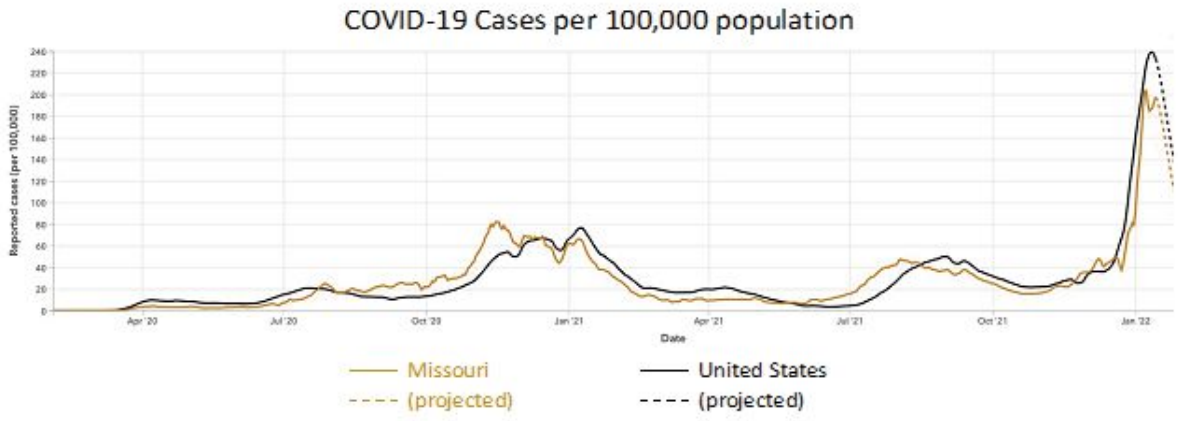

Figure 2. Epidemic Curve, Missouri and United States, 2020-21
Source: https://covid19.healthdata.org. Accessed 2/3/2022

spread of the novel coronavirus to all corners of the state soon ensued.

The epidemic curve in 2020 and 2021 was characterized by recurrent surges. As SARS-CoV-2 mutated successively more contagious variants, including Delta and Omicron, evolved and spread. Incidence in Missouri surpassed the rest of the nation from September 2020 to January 2021 in concert with widespread and increasing disdain for public health best practices (Figure 2). Initial optimism that COVID-19 would be a seasonal virus, confined to the cold weather months, was quashed as new infections occurred year-round. Cases spiked with the onset of cold weather in November 2020; after the December 2020 holiday season; in July 2021 when Southwest Missouri was the national epicenter for the Delta variant surge; and in December 2021 when the Omicron variant erupted[14] (Figure 3).

As of December 2021 approximately 780,000 COVID-19 cases were confirmed in Missouri; combined with an additional 180,000 probable cases, the total count approached one million, or roughly 17% of the state's population. Of note, many cases were undocumented and the actual case count undoubtedly was far higher. The state had 12,842 confirmed and 2,896 probable deaths by the end of 2021; COVID-19 was the third-leading cause of mortality in the state. Missouri ranked 19th among the 50 states in case rate per 100,000 population and its mortality rate ranked 27th.[14]

The epidemic curves in Missouri's two largest metropolitan areas, the St. Louis and Kansas City regions, largely were superimposable during the first two years of the pandemic with the exception of a steeper spike in Kansas City during the Delta variant surge in the summer of 2021 and a more rapid decline in cases in St. Louis at that time. In contrast, Springfield had lower disease incidence than Kansas City in the first 15 months of the pandemic but then experienced an exceptionally sharp spike in cases when the Delta surge began in July 2021.[14] Epidemic curves for Kansas City and Springfield are compared to that of New York City in Figure 3. New York City sustained a severe blow at an earlier phase of the pandemic as thousands of infected travelers arrived from Europe, and then implemented lockdown measures that were implemented for a lengthier period than in either of the Missouri cities.

Missouri is comprised of 115 counties plus the independent city of St. Louis. The highest regional incidence rates in Missouri were identified in rural counties. The top three counties in cases per 100,000 persons as of the end of 2021 were Gentry, Sullivan, and Lewis, each of which rank in the lowest 20% of the state's population. In contrast, the three most populous counties in the state (St. Charles, Jackson, St. Louis), and St. Louis City ranked 23rd, 32nd, 67th and 92nd, respectively.[14]. This data suggests that low population density was not protective.

Treatment

In March 2020 when COVID-19 arrived in Missouri, health care workers found themselves, metaphorically speaking, deep in one of the state's many dark limestone caves with only the faintest

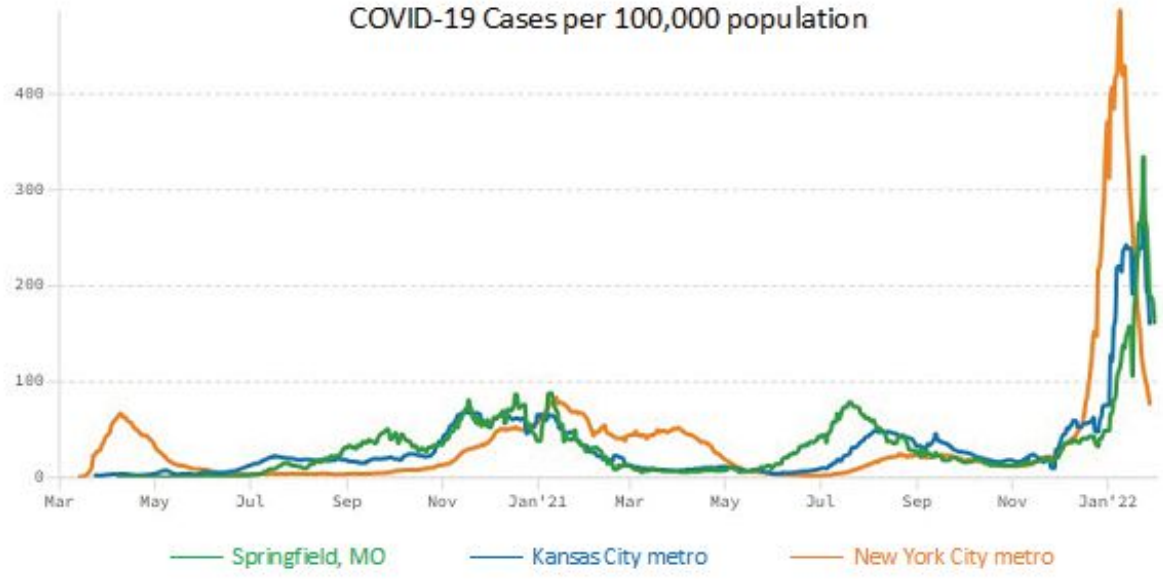

Figure 3. Epidemic Curves, Kansas City, Springfield, and New York City, 2020-21
Source: https://covid19.healthdata.org. Accessed 2/3/2022

flicker of light for illumination. There was no extant database about the formidable and unpredictable new viral adversary. As case counts inexorably increased, the evidence base regarding effective treatment options for SARS-CoV-2, and its many accompanying life-threatening inflammatory manifestations, evolved rapidly. A full discussion of treatment recommendations for COVID-19 is provided in guidelines published online by the National Institutes of Health (NIH) which are based on the highest caliber data available from clinical trials, are apolitical and unbiased, and are updated shortly after new data becomes available.[15]

Timing is a critically important factor impacting treatment decisions. During the initial phase of the illness antiviral therapies (oral paxlovid or molupiravir; intravenous remdesivir) reduce duration and severity of illness. Immune-based treatments (convalescent plasma, monoclonal antibodies) also are effective in many cases.[15,16,17] Blood banks are not currently collecting convalescent plasma, however. Steroid therapy is a double-edged sword. Although widely prescribed to outpatients, systemic corticosteroids prolong the duration of viral shedding and are not recommended.[15,18] However, for inpatients requiring supplemental oxygen dexamethasone reduces mortality and should be used routinely unless a contraindication exists. The interleukin-6 inhibitors tocilizumab and sarilumab and the JAK kinase 1 and 2 inhibitor baracitinib may be indicated for select cases in which gas exchange is deteriorating rapidly and there is evidence of systemic inflammation. Given the high risk for thromboembolic complications all inpatients should receive prophylactic anticoagulation unless contraindicated; a subset of inpatients appears to benefit from full anticoagulation.[15]

The pandemic has shined a bright light on health care workers' widely disparate perceptions about the most appropriate treatments for COVID-19. Multiple regimens not recommended in the NIH guidelines have been widely prescribed despite either the absence of quality evidence supporting their use, or even the suggestion of greater harm than benefit. The factors influencing physicians and other health care providers' treatment decisions have been studied extensively.[19] Experience during the pandemic has made it abundantly clear that discussion of certain treatments on podcasts, cable news, or social media by prominent public figures who possess a megaphone but lack scientific training or medical expertise appears to have an outsized influence on patient demand for certain medications and on prescribing practices by some providers. The apparent lack of widespread awareness

Table 1. Treatment for COVID-19: NIH Guidelines
February, 2022

Outpatient
Age > 65 or underlying medical conditions conferring high risk for severe COVID-19:
- Paxlovid
- Sotrovimab
- Remdesivir
- Molnupiravir

Inpatient
All patients:
- Prophylactic anticoagulation unless contraindicated

If requiring supplemental oxygen:
- Dexamethasone
- Remdesivir

Rapidly increasing oxygen requirement and systemic inflammation:
- tociluzumab or baricitinib
- alternatives: sarilumab or tofacitinib

Do Not Use
- Zinc
- Chloroquine or hydroxychloroquine
- Systemic steroid (outpatients)
- Azithromycin (unless bacterial infection)
- Anticoagulation/antiplatelet (outpatients)

Insufficient Evidence to Recommend For or Against Use
- Ivermectin
- Fluvoxamine
- Vitamin C
- Vitamin D

of the difference in caliber of various research studies and their applicability to practice has been striking.

In the era of instant worldwide dissemination of new information and ideas, accurate or not, rumors generated early in the pandemic often led to rapid and widespread implementation of new treatment practices. Some of these strategies should have been abandoned but their use has lingered despite evidence of potential harm. As an example, in 2020 French researchers who specialize in rickettsial infections reported favorable results of a pilot study of azithromycin and hydroxychloroquine, neither of which are antiviral drugs, for COVID-19.[20] Use of this regimen soon became commonplace. A subsequent randomized double-blind study demonstrated that azithromycin/hydroxychloroquine recipients were more likely to require mechanical ventilation or to die than those who received placebo, and a meta-analysis also found that hydroxychloroquine was associated with increased mortality. [21, 22] The senior author of the original manuscript is being investigated in France for possible disciplinary action. Nevertheless, hydroxychloroquine for COVID-19 is still advocated by some.[23]

The antiparasitic drug ivermectin has in vitro activity against SARS-CoV-2 at concentrations approximately 100-fold higher than are obtainable with standard human doses.[15] Ivermectin first received attention as a potential treatment for COVID-19 when a nonrandomized study in Egypt, subsequently retracted for inclusion of fraudulent data, reported a survival benefit.[25, 26] When this study and multiple other related publications with "significant methodological limitations" were scrutinized, the apparent benefits of the drug vanished.[15,24, 25,26] Ivermectin has not been shown to reduce viral clearance, progression to severe disease, or mortality, and its use is not recommended by the NIH or the Infectious Diseases Society of America.[26] Cases of ivermectin toxicity, manifested by gastrointestinal intolerance, ataxia, seizures, or coma, increased substantially in the U.S. during the pandemic, prompting an emergency reminder by the CDC to health care providers that the drug is not authorized by the Food and Drug Administration (FDA) for treatment of COVID-19.[27] The FDA web page states, "You are not a horse. You are not a cow. Seriously, y'all, stop it."[28] However, use of the human or veterinary formulations remains widespread. As an illustration of the highly politically charged environment surrounding ivermectin, the state health department in Missouri's eastern neighbor Illinois has threatened disciplinary action against providers who prescribe this medication whereas on our western border the Kansas House of Representatives has advanced legislation to prohibit the state's Board of Healing Arts from disciplining ivermectin advocates.[29]

Polypharmacy for COVID-19 appears to be widespread and may be associated with increased risk of adverse events.[30] Many vitamins, mineral supplements, and alternative medications which do not have antiviral activity have been used extensively for patients with SARS-CoV-2 infection. Vitamins

and alternative medicines have not been effective for treatment or prevention of COVID-19.[31] Concomitant medications have prompted extensive speculation as potential treatments for COVID-19. None have been shown either to improve or to worsen outcome.[15] Figure 4 summarizes current evidence-based management recommendations.

Conclusion

During the first two years of the historic and cataclysmic COVID-19 pandemic Missourians witnessed recurrent surges of disease that stretched our health care system almost to the breaking point on multiple occasions. Important questions remain unanswered, but dramatic advances have been made in our ability to treat COVID-19 and its complications. Although differences persist among health care providers regarding the best approach to treatment of COVID-19, these controversies are dwarfed by the highly politicized, divergent points of view about public health strategies for pandemic mitigation that will be addressed in the next article in this series.

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Disclosure

None reported.

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