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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

The COVID-19 Pandemic: What Comes Next? Lessons from Seasonal Coronaviruses

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: In temperate regions other than China, human seasonal coronaviruses circulate most heavily during the winter months, overlapping with influenza and respiratory syncytial virus — and this may be the eventual pattern for SARS-CoV-2.

SOURCE: Li Y, Wang X, Nair H. Global seasonality of human seasonal coronaviruses: A clue for post-pandemic circulating season of SARS-CoV-2 virus? *J Infect Dis* 2020; Jul 21:jiaa436. doi:10.1093/infdis/jiaa436. [Online ahead of print].

Speculation regarding the behavior of COVID-19 after the pandemic wave is brought into a semblance of stability continues and is of great importance for the future of this disease and the response to it. It is unlikely that SARS-CoV-2 will disappear from the face of the earth, thus leaving two major possibilities: ongoing year-round transmission with occasional regional spikes or seasonal transmission as has occurred after the appearance of influenza pandemic strains. One source of information that potentially can inform the debate on this issue is the behavior of the four endemic coronaviruses that primarily cause symptoms of a common cold.

Li and colleagues performed a systematic review to assess the global seasonality of existing seasonal human coronavirus infections (sCoV). They found that in temperate regions other than China, the winter months accounted for high sCoV activity, as measured by the annual average percentage. In China, sCoV activity occurred year-round.

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Infectious Disease [ALERT]

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In examining temperate regions (with the exclusion of China), researchers found that 53.1% of sCoV cases occurred during the influenza season and 49.6% occurred during the respiratory syncytial virus season. Lesser overlap occurred in tropical regions, as well as in temperate China (20% and 29% overlap, respectively). An examination of meteorological factors found that higher proportions of sCoV cases were associated with periods of low temperature and higher relative humidity.

■ COMMENTARY

A previous modeling study concluded that if, as has been demonstrated with sCoV, immunity to SARS-CoV-2 is not long-lasting, it will begin its circulation pattern beginning in 2021 or 2022 and will synchronize with circulation of the four human sCoV.[1] Thus, as also indicated by the empiric evidence discussed above, SARS-CoV-2 will cocirculate not only with sCoV but with influenza and respiratory virus infections. Since symptoms of infections due to these viruses overlap, clinical diagnoses cannot be relied on. Accurate, rapid-turnaround, and preferably point-of-care tests will be needed.

Get ready for a long, complicated, and never-ending ride. ■

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ABSTRACT & COMMENTARY

Dexamethasone for COVID-19 Inpatients Requiring Oxygen

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Dexamethasone administration is associated with reduced 28-day mortality in oxygen-requiring COVID-19 patients, including those receiving mechanical ventilation.

SOURCE: RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 — Preliminary report. *N Engl J Med* 2020; Jul 17. doi: 10.1056/NEJMoa2021436. [Online ahead of print].

As part of the RECOVERY trial designed to test multiple potential treatments for patients with COVID-19, the investigators randomized 2,104 patients to receive dexamethasone for up to 10 days in a dose of 6 mg per day, and 4,321 patients to receive usual care. Initially, hospitalized adults (including pregnant and breastfeeding patients) with proven or suspected COVID-19 were eligible. The age limitation was eventually eliminated. The mean age of the patients was 66.1 years and (strangely) only 36% were female. Fifty-six percent had a significant comorbidity: One-fourth each had diabetes mellitus or heart disease, and one-fifth had chronic lung disease. Sixteen percent were receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at the time of randomization, while 60% were receiving oxygen without invasive ventilation, and 24% received neither.

Dexamethasone was given for a median of seven days; 8% of usual care patients also received dexamethasone, and one-fourth of patients in each arm received azithromycin. Only a few patients received remdesivir.

At 28 days, 482 (22.9%) of the 2,104 dexamethasone recipients and 1,110 of the 4,321 (25.7%) usual care patients had died (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93, $P < 0.001$). Among those patients receiving mechanical ventilation, 95 of 324 (29.3%) dexamethasone recipients and 283 of 2,604 usual care patients (41.4%) died by 28 days (rate ratio = 0.64; 95% CI, 0.51 to 0.81). Among those who received oxygen without invasive ventilation, 298 of 1,279 (23.3%) dexamethasone recipients and 682 of 2,604 (26.2%) usual care recipients died (rate ratio = 0.82; 95% CI, 0.72 to 0.94). In contrast, there was no significant difference in outcomes among patients who had not required oxygen therapy at randomization.

■ COMMENTARY

Prior to the announcement of the results of this study, the use of corticosteroids in patients with COVID-19 was discouraged, based on prior negative experiences with their use as adjunctive therapy of infections due to influenza virus, SARS-CoV, and the Middle East respiratory syndrome (MERS) virus. Immediately upon receiving these results, official organizations such as the World Health Organization, the National Institutes of Health, and the Infectious Diseases Society of America (IDSA) reversed their positions, including a recommendation for dexamethasone use in COVID-19 in their guidelines. Congruent with the study results, the recommendation is limited to patients who require oxygen therapy at any level of care. It is not recommended for patients not requiring such therapy.

Thus, the IDSA recommends glucocorticoid therapy for hospitalized patients with severe COVID-19, with severe disease indicated by an $SpO_2 \leq 94\%$ on room air and/or a requirement for supplemental oxygen, mechanical ventilation, or ECMO.[1] IDSA further states that dexamethasone 6 mg intravenously or orally be administered until discharge for a maximum of 10 days. If dexamethasone is unavailable, alternative glucocorticoids can be used in equivalent doses. Thus, a total daily dose of 32 mg of methylprednisolone or 40 mg of prednisone may be given.

Of note, the study reviewed here does not address adverse events. In particular, there is no mention of the potential for superinfections due to corticosteroid administration. ■

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ABSTRACT & COMMENTARY

Repeat Infections with Endemic Coronaviruses and Possible Implications for COVID-19

By Stan Deresinski, MD, FACP, FIDSA

Clinical Professor of Medicine, Stanford University

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Repeat infection with endemic seasonal coronavirus occurs commonly and raises concerns about immunity to SARS-CoV-2 as well as about the efficacy of vaccines in the protection against infection due to this virus.

SOURCE: Galanti M, Shaman J. Direct observation of repeated infections with endemic coronaviruses. *J Infect Dis* 2020; July 7. doi:10.1093/infdis/jiaa392

Galanti and colleagues examined data from the Virome project carried out in Manhattan from October 2016 to April 2018 to determine the frequency of recurrent infection with endemic coronaviruses. In this study, 214 healthy individuals had regular sampling for respiratory virus infection, with self-reporting of symptoms and episodes of clinical care. The cohort included children attending two daycare centers, as well as their parents and siblings; students and teachers

from a high school; adults working in emergency departments at a pediatric and an adult hospital; and adults working at a university medical center.

Nasopharyngeal samples were collected weekly and, using a respiratory virus panel, were tested for the presence of nucleic acid from 18 respiratory viruses, including the α-coronaviruses 229E and NL63 and the β-coronaviruses HKU1 and OC43. Participants also self-reported symptoms each day.

Of the 191 participants who contributed samples at least six times in the same season, 86 had evidence of at least one episode of infection by a coronavirus, with OC43 the most frequently identified. The probability of a test-positive episode of OC43 infection during the 80 weeks of the study was 0.47. Twelve of the 86 tested positive for the same virus during at least two episodes, with OC43 accounting for nine of these 12. Of the nine people with repeated OC43 episodes, six people had two episodes and three people had three such episodes. The median interval between episodes was 37 weeks (range, 4 to 48 weeks).

[Although limited evidence indicates that pre-existing antibodies may correlate with some degree of protection, the occurrence of repeat infection with the same serotype suggests that any protection is limted.]

Repeat episodes did not appear to be associated with either worse or milder symptoms, but there was a significant association between symptom severity and inclusion within the same family cluster. In individuals whose initial coronavirus infection was asymptomatic, all subsequent infections with the same virus also were asymptomatic.

■ COMMENTARY

Seroconversion to one or more of the endemic seasonal coronaviruses first occurs at an early age and, overall, more than nine in 10 people in the general population are seropositive. Although limited evidence indicates that pre-existing antibodies may correlate with some degree of protection, the occurrence of repeat infection with the same serotype suggests that any protection is limited.

To the extent that these data are relevant to COVID-19, they raise concern regarding the long-term protective nature of antibody to SARS-CoV-2 — with obvious implications for dealing with this infection and for the efficacy of vaccines. Although almost all patients who recover from COVID-19 develop antibodies to the virus, and these antibodies often are neutralizing, evidence indicates that their serum levels rapidly decay, at least in those people with mild or asymptomatic infection.

Ibarrondo et al found that the serum half-life of IgG antibody in patients with clinically mild COVID-19 was only 36 days, while Long and colleagues found that 40% of patients with asymptomatic infection and 12% of those whose infection was symptomatic lost detectable serum antibody during the early convalescent period.[1,2]

The finding by Galanti and colleagues of clustering within families of symptomatic infection due to seasonal endemic coronaviruses suggests the possibility of human genetic influences on the inflammatory response elicited via the innate immune system. Some evidence suggests that genetic factors affecting that system may play a role in COVID-19. Van der Made and colleagues evaluated two sets of brothers in the Netherlands who, despite being young and previously healthy, required mechanical ventilation for their management.[3] They were found to have putative loss-of-function mutations in the gene encoding TLR7, and this was associated with an impaired interferon response to agonists of this toll-like receptor.

Thus, just as with endemic coronaviruses, the necessary elements of immune protection against SARS-CoV-2 remain undefined. ■

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ABSTRACT & COMMENTARY

Respiratory Syncytial Virus — Effective Prevention Still Needed

By Philip R. Fischer, MD, DTM&H

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Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Prevention of respiratory syncytial virus infection is needed but challenging. New studies show some favorable effectiveness on infant outcomes with both vaccination of healthy pregnant women and passive single-dose immunization of prematurely born babies.

SOURCES: Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N Engl J Med* 2020;383:426-439.

Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med* 2020;383:415-425.

Respiratory syncytial virus (RSV) is a main cause of seasonal respiratory tract infection and hospitalization in infants. Worldwide, RSV prompts more than 3 million hospitalizations each year, and more than 100,000 children die of RSV infection each year. Young infants, especially those born preterm with chronic lung disease or congenital heart disease, are at particular risk of infection and death. For more than five decades, vaccines have been developed and tested, still with just limited effectiveness. RSV-specific immune globulin is used in monthly injections to reduce severe disease in high-risk premature babies during the winter season, but there is no feasible, useful preventive measure for more widespread use.

Two new studies demonstrate novel strategies to reduce RSV-related morbidity and mortality. First, healthy pregnant women due to deliver near the start of the RSV season were given an RSV vaccine. Second, an extended half-life RSV-specific monoclonal antibody was given to preterm babies.

Madhi and colleagues vaccinated healthy women at 28 to 36 weeks of gestation with a single-dose intramuscular, RSV fusion protein nanoparticle vaccine in a randomized trial comparing offspring of vaccine-vaccinated and placebo-vaccinated (2:1 ratio) women. A total of 4,636 women were randomized, most in South Africa and the United States. Injection-site reactions were more common with vaccine than placebo injection, but other side effects were not detected with vaccine use.

During the first 90 days of life, medically significant RSV infection was seen in 1.5% of offspring of vaccinated women and 2.4% of offspring of women

who received placebo injections. Infection requiring hospitalization (2.1% vs. 3.7%) and infection requiring oxygen use (0.5% vs. 1.0%) were similarly lower in offspring of women who received the true vaccine. The differences were statistically significant but did not reach the pre-determined criterion to be considered "successful." Nonetheless, severe RSV illness was less likely in offspring of mothers who were vaccinated.

Griffin and colleagues evaluated nirsevimab, an extended half-life monoclonal antibody, in 1,453 infants born following gestations of 29 through 34 weeks. They, too, used a 2:1 ratio of vaccine recipients to placebo recipients. The vaccine consisted of 50 mg of nirsevimab given intramuscularly at the beginning of an RSV season. There were no notable hypersensitivity-type reactions. Infection requiring medical care was less common with vaccine than with placebo (2.6% vs. 9.5%), as was RSV-related hospitalization (0.8% vs. 4.1%).

■ COMMENTARY

RSV is an RNA virus with two surface proteins responsible for much of its pathogenesis and infectivity.[1] The fusion protein accounts for viral entry into the host cell and is the target of natural neutralizing antibodies.[1] This protein was the basis of the vaccine tested in pregnant women by Madhi's group and of the monoclonal antibody used by Griffin's group. These preventive efforts are more likely to be useful than the attempted 1960s vaccine that prompted formation of non-neutralizing antibodies and, sadly, enhanced T cell responses with worsened disease.[1] Although each of these new trials demonstrated statistically significant favorable effects as compared to placebo, each intervention was only about 70% effective in preventing serious RSV illness. Prevention efforts will continue.

So far, prevention efforts have failed to prevent actual infection to a significant degree. But, vaccination still can be useful, since it reduces the risk of being sick enough with infection to require medical care, hospitalization, or oxygen supplementation. And, prevention of illness, even if not preventing all infection, could be effective in saving many of the 100,000-plus lives of children currently dying each year with RSV bronchiolitis.

At the same time, treatment of RSV infection has evolved. While supportive care (fluids, nutrition, comfort measures, oxygen as needed) is all that has proven efficacy, various disproven treatments have generated widespread (though ineffective) use — such as bronchodilators, hypertonic saline, steroids, antibiotics, and high-technology oxygen delivery systems.[2-5] Quality improvement efforts can be effective in reducing unnecessary treatments.[6-8]

All around the planet, there is eager expectation of a vaccine for SARS-CoV-2. It is hoped that such a vaccine will soon be available, effective, and practical. However, one hopes not to see too many correlates with COVID-19 and RSV bronchiolitis. Yes, each is caused by an RNA virus with important surface proteins that can serve as vaccine targets. Yes, each illness has prompted the widespread use of costly, unproven, and potentially dangerous treatments. It is hoped, though, that it will not take decades to find a SARS-CoV-2 vaccine that actually reduces illness — as has been the case for RSV vaccines.

In the meantime, the widespread isolation, masking, and social distancing implemented to reduce COVID-19 also likely will reduce the incidence of RSV bronchiolitis this coming fall and winter. ■

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ABSTRACT & COMMENTARY

A Novel Rifabutin-Containing Combination Regimen Is Effective for Eradicating *H. pylori* Infection

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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Dr. Watkins reports no financial relationships relevant to this field of study.

SYNOPSIS: A Phase III, randomized, controlled trial found a significantly higher eradication rate for *H. pylori* with a 14-day regimen of rifabutin, amoxicillin, and omeprazole compared to 14 days of amoxicillin and omeprazole.

SOURCE: Graham DY, Canaan Y, Maher J, et al. Rifabutin-based triple therapy (RHB-105) for *Helicobacter pylori* eradication: A double-blind, randomized, controlled trial. *Ann Intern Med* 2020;172:795-802.

The treatment of *Helicobacter pylori*, the most common cause of peptic ulcers and gastric cancer, has become more challenging because of the spread of antibiotic resistance. Indeed, several antibiotics that were previously used empirically, such as clarithromycin, metronidazole, and levofloxacin, are no longer effective in many cases. Previous studies have shown that rifabutin is active in vitro against *H. pylori*, and resistance is slow to develop. After promising results from a pilot study, Graham and colleagues conducted a clinical trial to compare a treatment regimen that contained rifabutin to a standard combination for eradicating *H. pylori*.

The study was a Phase III, double-blind, randomized, controlled clinical trial that enrolled adults with dyspepsia and confirmed *H. pylori* infection. Patients were randomly assigned in a 1:1 ratio to receive a fixed dose combination of amoxicillin 3 g, omeprazole 120 mg, and rifabutin 150 mg (AOR) or amoxicillin plus omeprazole (AO), four capsules every eight hours for 14 days. A follow-up 13C urea breath test was performed at the test-of-cure visit (conducted between days 43 and 71 after initiation of treatment) to determine *H. pylori* eradication. Plasma concentrations of the drugs were measured at baseline and at day 13 visits. Also, pharmacogenetic testing was done at baseline to assess the status of CYP 2C19, which is the liver enzyme that metabolizes omeprazole. Exclusion criteria included prior *H. pylori* treatment; alarm symptoms (e.g., anemia, melena, weight loss, or dysphagia); more than two active gastric or duodenal ulcers; a history of esophageal or gastric surgery; previous gastric cancer; and recent receipt of antibiotics, a proton-pump inhibitor, or a bismuth-containing medication. Also, persons of Asian descent were excluded because of concerns about polymorphisms in cytochrome P450 genes that can affect omeprazole metabolism.

[In the United States, there has not been a new therapy approved by the Food and Drug Administration to treat *H. pylori* since 1997.]

Two hundred twenty-eight patients received AOR and 227 received AO. The treatment groups were well-balanced in terms of demographic characteristics. The mean age was 46.5 years (standard deviation [SD], 13), 62.2% were

women, and 60.0% were Hispanic. At baseline, 22 (6.4%) of the patients were infected with amoxicillin-resistant *H. pylori* strains. No isolates were resistant to rifabutin. The mean adherence rate, determined by pill counts, was 97.5% (SD, 14.2%) in the AOR group and 97.9% (SD, 13.1%) in the AO group.

The eradication rate was higher in the AOR group compared to the AO group (83.8%; 95% confidence interval [CI], 78.4% to 88.0% vs. 57.7% [95% CI, 51.2% to 64.0%], respectively; $P < 0.001$). Interestingly, the eradication rate with the AOR regimen was high even for strains that were resistant to amoxicillin (80%), but predictably was much worse for the AO regimen (25%). The rates of adverse events were similar between the two groups, with diarrhea and headache more common in the AOR group vs. the AO group (10.1% and 7.5% vs. 7.9% and 7.0%, respectively), while nausea, abdominal pain, and dizziness were more frequent in the AO group. More rashes were seen with AOR (1.3%) than with AO (0). Finally, no adverse events were found to be related to the CYP 2C19 genotype.

■ COMMENTARY

The dwindling number of effective drugs to treat *H. pylori* infection is an increasing concern. In the United States, there has not been a new therapy approved by the Food and Drug Administration to treat *H. pylori* since 1997. Therefore, the study by Graham and colleagues is welcome since it provides evidence for the effectiveness of a novel, fixed-combination regimen. Another highlight was that the adherence rate, tolerability, and adverse event profile of the three-drug regimen compared favorably to the two-drug regimen. Moving forward, it will be important to see how much the novel regimen will cost and if the rate of adverse events will remain low once it becomes widely prescribed. Moreover, while none of the *H. pylori* strains demonstrated rifabutin resistance, this undoubtedly will occur with increasing use and will need to be recognized and monitored by clinical microbiology laboratories.

Despite the robust design, there are a few limitations to the study that deserve mention. First, since the investigators excluded people of Asian descent, it is not clear if the drug will be safe and effective for this group of patients. Second, there were limited data on the clinical breakpoints for the amoxicillin-resistant strains. Third, quadruple therapy that includes bismuth is the regimen prescribed most frequently for *H. pylori* in the United States. How AOR would compare to this regimen is unknown. Finally, all of the clinical sites were in the United States, so the results might not be applicable to other geographic areas.

A new combination treatment option for *H. pylori* infection appears to be on the horizon. Although it is a cause for optimism, whether the results from the randomized clinical trial will hold up in real-world settings remains to be elucidated. Further studies that compare AOR to current first-line regimens also seem warranted. ■

ABSTRACT & COMMENTARY

Respiratory Syncytial Virus — Not Just a Disease of Children

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Respiratory syncytial virus is a significant cause of morbidity and mortality in the elderly.

SOURCE: Tseng HF, Sy LS, Ackerson B, et al. Severe morbidity and short- and mid- to long-term mortality in older adults hospitalized with respiratory syncytial virus infection. *J Infect Dis* 2020; Jun 27. doi: 10.1093/infdis/jiaa361. [Online ahead of print].

Tseng and colleagues examined the rates of morbidity and mortality in individuals older than 60 years of age with documented respiratory syncytial virus (RSV) infection who were hospitalized in the Kaiser Permanente Southern California system. Of the 664 patients, 64.1% were > 75 years of age, 60.5% were female, > 30% had chronic underlying illness, and 35%

were current smokers. Only 2.6% had coinfection with another virus.

The most frequent presenting respiratory features were cough, tachypnea (> 20 breaths per minute), and shortness of breath. Fifty-six percent of patients had very severe tachypnea, with respiratory rates > 26 breaths per minute. Approximately one-half of patients had radiographically confirmed pneumonia, with possible pneumonia in 10.5% and 13.8% of those ages 60-74 years and ≥ 75 years, respectively. Ventilatory support was required by 20.4%, with a similar proportion requiring intensive care. Eighteen patients had documented bacteremia. The overall in-hospital mortality was 5.6%, while the 30-day mortality was 8.6%. Among survivors, there was a frequent need for home health services or placement in a nursing home after discharge.

■ COMMENTARY

RSV infection is frequently thought of as a pediatric disease, which it is. However, data such as this confirm that RSV also affects adults and frequently is severe and may be life-threatening. Tseng and colleagues cited publications indicating that there are an estimated 61,000 to 177,000 hospitalizations in the United States each year, with 10,000 to 14,000 deaths attributed to RSV in individuals ≥ 65 years of age.

Underlying cardiopulmonary conditions are common in the elderly, and these are exacerbated by superimposed RSV infection. It has been reported that the frequency of complications and severe outcomes due to RSV in the elderly is similar to that observed in association with influenza virus infection. Patients with severe immunocompromise are at high risk of death from RSV infections.

We have vaccines (albeit imperfect) for the prevention of influenza, as well as modestly effective antiviral therapy. Although these are not available for dealing with RSV infection, both currently are under investigation. ■

Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Things Do Not Always Go Better with Cola

SOURCE: Wuthiekanun V, Amornchai P, Langla S, et al. Survival of *Burkholderia pseudomallei* and pathogenic *Leptospira* in cola, beer, energy drinks, and sports drinks. *Am J Trop Med Hyg* 2020;103:249-252.

In response to reports generating fears of canned beverages contaminated with rat feces and urine leading to human bacterial infection, these authors examined the survival of *Leptospira* spp. and *Burkholderia pseudomallei* in canned drinks. Two different species of *Leptospira* were chosen, in part because these organisms can survive for months in fresh water and soil, and have been linked to contaminated potable water in several countries. In addition, two different strains of *Burkholderia pseudomallei* (BP) were selected, because this organism is fairly hardy and known to survive for long periods of time in the environment. Studies have shown that BP can survive in normal saline at a pH 2.0 for one day and at a pH 3.0 for up to one week.

Four different beverages were selected, including cola (Coca-Cola original), beer (Singha original), an energy drink (Red Bull Extra), and a sports drink (Gatorade lemon-lime), as well as distilled water for a control. Aliquots of BP and *Leptospira* at 10^4 and 10^8 colony-forming units (CFU)/mL in 0.3 mL sterile water and in EMJH broth, respectively, were inoculated into 2.7 mL of each liquid and kept at 4°C and 37°C. These temperatures are comparable to that for refrigeration and ambient tropical breezes. The spiked beverages were aliquoted and cultured at various intervals for up to four weeks.

Both organisms survived longer at the higher concentrations, although there were significant differences between the survival of the two organisms. The two species of *Leptospira* survived only briefly in the four beverages (< 15 minutes) at 4°C and less than five minutes at 37°C. But they survived much longer in distilled water at 37°C. In contrast, BP survived for up to four weeks when refrigerated at 4°C in all four canned beverages, and for shorter periods of time in distilled water. However, at 37°C, BP survived for less than three days in beer and Red Bull and less than two hours in Coca-Cola, even at the higher bacterial concentrations. This may be because

of the increased acidity of Coca-Cola (pH 2.71) compared to the other beverages (pH range, 3.08-6.49).

Canned beverages could theoretically be contaminated with bacteria during the canning process or in storage if the packaging is disrupted, but most bacteria on the surface of a can will not survive. As with all canned goods, make sure the can is intact before opening. It is not necessary to wash your cans with soap and water, but given the current COVID experience, some compulsive consumers may continue to do so. And, as suggested by the following study report, laboratory inoculations with 10^8 organisms, such as were used in this experiment, are way beyond the typical scanty bacterial contamination observed in the real world.

'Hygiene Theater'

SOURCES: Thompson D. Hygiene theater is a huge waste of time. *The Atlantic,* July 27, 2020.
Goldman E. Exaggerated risk of transmission of COVID-19 by fomites. *Lancet Infect Dis* 2020;20:892-893.

I received an email from clinic administrators the other day, wondering whether disinfection of the chairs in the clinic waiting room every 30 minutes during COVID was sufficient. Two fabric paintings, gifted by a patient, were removed from the walls, and the magazines in the waiting room were confiscated lest SARS-CoV-2 virus jump off and infect visitors. The New York subway system is spraying seats, walls, and poles with disinfectant. Yet, people are still riding the subway … and standing next to each other. But the pole is clean.

[Although surface contamination resulting in COVID-19 may be possible, most people acquire infection through person-to-person spread.]

In an immediate notice on May 22, 2020, the Centers for Disease Control and Prevention (CDC) sought to assuage people's fears that their cereal boxes were not going to infect them by attempting to clarify that although surface contamination resulting in COVID may be possible, most people acquire infection through person-to-person spread.[1] Sadly, this statement did not go far enough, and my friend is still washing her store-bought fruits and vegetables with soap and water, my sister lets her groceries sit in the garage for two days before unpacking them, and my neighbor is wearing gloves to get the mail. It reminds me of those televised scenes of the Chinese government spraying disinfectant throughout the city streets during H1N1 in 2009.

This amusing article and a *Lancet* editorial point out how such actions are completely misguided (hygiene theater), and mistakenly make some people feel safer while obscuring the real risk for infection — which is other people. Such activities also waste time, energy, and valuable resources. Your real risk is your friends, family, and co-workers — not your mail.

The press has made much about the risk of COVID viral particles surviving for days on surfaces and objects. However, none of the relevant studies are based in realistic scenarios of viral surface contamination or our understanding of respiratory infection. The longest survival of SARS-CoV-2 on surfaces required a large laboratory inoculation of 10^7 viral particles, and viable virus was found out to six days. Another study applied 10^6 viral particles to surfaces, and retrieved viable virus four days later. Aerosols spiked with a large inoculum of 10^5 to 10^7 of SARS-CoV-2 particles found viable virus on surfaces two days later. But, as the editorialist points out, this would be like 100 people sneezing onto that surface, and then you quickly lick it or rub it in your eye.

In a study where surfaces were contaminated by an actual patient, no viable virus could be found. Similar studies of common community coronavirus found virus survived < 1-3 hours after drying on various surfaces, including surgical gloves and aluminum. People's fears have been exaggerated by bad science and worse public policy.

Theoretically, high-touch surfaces may pose a risk. Realistically, fomites carrying small amounts of virus that have not been in contact with their owner for > 1-2 hours do not. Ask yourself, how many cases of COVID have been traced to fomites as the cause for infection? As the columnist states, "the extreme infrequency of evidence may indeed be evidence of extreme infrequency."

REFERENCE

1. Centers for Disease Control and Prevention. CDC updates COVID-19 transmission webpage to clarify information about types of spread. Media Statement. May 22, 2020. https://www.cdc.gov/media/releases/2020/s0522-cdc-updates-covid-transmission.html

Geodynamics of COVID-19 in Brazil

SOURCE: Candido DS, Claro IM, de Jesus JG, et al. Evolution and epidemic spread of SARS-CoV-2 in Brazil. *Science* 2020; July 23:eabd2161.

Public health measures to reduce the transmission of SARS-CoV-2 virus, such as restrictions on travel and shelter-in-place, may be useful — but at a cost. Trying to determine which measures are most useful, and when and where, is important. As of July 12, 2020, Brazil had the second largest number of cases of COVID (> 1.8 million cases), second only to the United States. More than one-third of these cases have occurred in São Paulo, in the southeastern part of the country.

Delays in reporting, changes in reporting requirements, and lack of access to testing sites render a real-time assessment of viral movement throughout the country impossible. Instead, these authors looked to genomics and molecular clock phylogenetics compared with a global data set, which allowed a retrospective estimate of the timing of viral introductions into the country and subsequent movement of virus throughout. Movement of people throughout the country was estimated based on four mobility indices (including a social isolation index from Brazilian geolocation company In Loco, and Google mobility indices for time spent in transit stations, parks, and the average between groceries and pharmacies, retail, and recreational and workspaces).

A total of 26,732 samples obtained from public and private laboratories were tested, identifying 7,944 (29%) SARS-CoV-2 infections. From these, 427 new genomes were constructed, comprising isolates from March 5 to April 30. In addition, 63 Brazilian sequences entered into the GISAID database were included, for a total of 490 sequences. These represented viral genomes from 85 different municipalities across 18 of 27 federal states, and were representative of the outbreak across the country. Only five genomes were found to be lineage B, and the rest were lineage A. The majority of isolates fell into three clades (including clade 1 [38%], clade 2 [34%], and clade 3 [4%]).

Time-based phylogenetic analysis revealed at least 102 introductions of virus into Brazil — even before the first cases were recognized. More than half of these were from Italy (26%) and the United States (28%). By the time international travel restrictions were put in place in March, widespread community transmission was occurring already, especially in São Paulo and the southeastern part of the country. Although the introduction of international isolates declined with international travel restrictions, increasing virus transmission, both locally and within state borders, continued to occur.

[Although the introduction of international isolates declined with international travel restrictions, increasing virus transmission, both locally and within state borders, continued to occur.]

During the second phase of the epidemic in Brazil, multiple different virus lineages were observed to move outside of large urban areas and the southeastern states to infect other areas within Brazil. This occurred coincident with a 25% observed increase in national travel, especially an increase in longer-distance travel. Nonetheless, within-state travel remained 5.1-fold more frequent than between-state travel.

This interesting study demonstrates how genomics and mobility data can be combined to measure the effect of regional and national travel movement on the evolution of a pandemic throughout a country. Brazil's efforts to restrict international travel in March were too late; more than 100 different viral lineages had already been introduced into the country, with ongoing increasingly widespread community transmission. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. Which of the following is true regarding respiratory syncytial virus?

a. Infection is preventable now by vaccination of pregnant women.

b. Infection is preventable now by passive immunization of newborns.

c. Illness (bronchiolitis) is effectively treated by bronchodilators, steroids, and high-flow nasal cannula oxygen.

d. Illness (bronchiolitis) is a cause of more than 100,000 childhood deaths worldwide each year.

2. Which of the following groups of COVID-19 patients were *not* found to benefit from receipt of dexamethasone?

a. Patients requiring mechanical ventilation

b. Patients requiring ventilatory support and supplemental oxygen

c. Patients requiring supplemental oxygen but not invasive ventilatory support

d. Patients not requiring supplemental oxygen

3. Which of the following is correct regarding infections with the four endemic coronaviruses?

a. Infection with one type provides subsequent lifelong protection against all four viruses.

b. Infection with one type provides lifelong protection, but only to that type.

c. Infection fails to provide lifelong protection.

d. Repeat infection is associated with increased severity.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.