

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists and pharmacy technicians will be able to:

- List developments related to treatments that are currently being investigated for COVID-19
- Recognize changes to the CDC's recommendations and risk criteria
- Describe non-pharmacologic interventions to reduce the spread of SARS-CoV-19



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.1 CEU (1 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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\$3 for technicians

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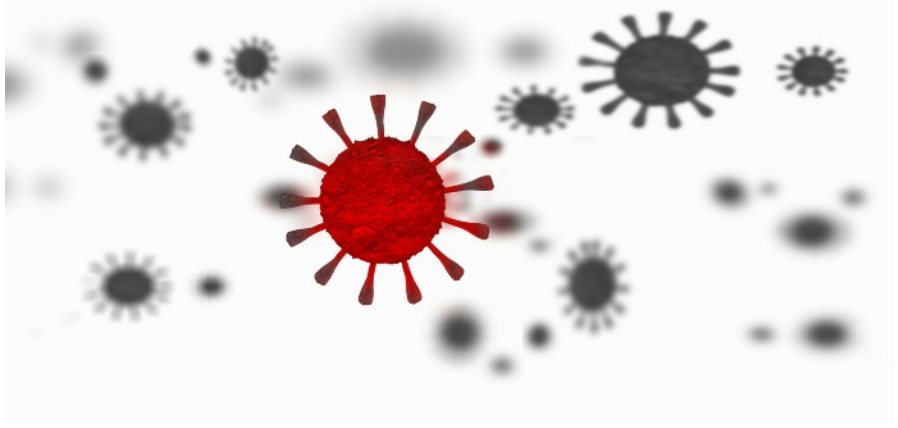
Use your NABP E-profile ID and the **session code 20YC44-XTX29 for pharmacists or 20YC44-YKT48 for pharmacy technicians**

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For questions concerning the online CPE activities, email joanne.nault@uconn.edu.

You Asked for It! CE

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UConn UPDATE #3: SARS-CoV-2 and COVID-19

ABSTRACT: UConn faculty assembled this homestudy in response to a high demand to reliable education on coronavirus. It answers questions submitted by our learners.

FACULTY: Jeannette Y. Wick, R.Ph, MBA, FASCP, is the Assistant Director, Office of Pharmacy Professional Development, UConn School of Pharmacy, Storrs, CT. C. Michael White, Pharm.D., FCP, FCCP; Professor and Chair, Pharmacy Practice, UConn School of Pharmacy, Storrs, CT and Director, HOPES Collaborative Group, University of Connecticut and Hartford Hospital, Hartford, CT. Jeffrey R. Aeschlimann, Pharm.D. Is an Associate Professor, UConn School of Pharmacy, Adjunct Associate Professor, UConn School of Medicine, UConn Health, Division of Infectious Diseases.

FACULTY DISCLOSURE: All faculty have no actual or potential conflicts of interest associated with this article.

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INTRODUCTION

This is the third update to UConn's running series on SARS-COV-2 and COVID-19. In previous continuing education (CE) activities, we discussed the virus (SARS-CoV-2), the disease it causes (COVID-19), and frequently asked questions. It's been an interesting two weeks, with change afoot daily. We appreciate your questions and interest, and have done our best to provide evidence-based information. Please feel free to share the CEs with others.

Interested individuals can find the original activity here:

<https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/03/CORONAVIRUS-MAR2020-FINAL.pdf>.

And the first update here:

<https://pharmacy.uconn.edu/wp-content/uploads/sites/2740/2020/03/CORONAVIRUS-UPDATE-1-30MAR2020-FINAL.pdf>

And the second update here:

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TO REGISTER and PAY FOR THIS CE, go to: https://pharmacyce.uconn.edu/program_register.php

Are there any changes to the information you provided in previous continuing education activities?

Just this week, the Centers for Disease Prevention and Control (CDC) updated their list of at-risk individuals.¹ **Table 1** lists the new information. The CDC has also added to its list of presenting symptoms (see **Table 2**).

In the last update, you discussed the preliminary data associated with hydroxychloroquine? What happened? Why is this no longer in the news?

As noted in our last update, the data on hydroxychloroquine was preliminary and based on two studies that had not been peer reviewed. In the interim, researchers released four additional manuscripts, and we remind readers that these documents are also preliminary and yet to be peer-reviewed.

Table 3 compares two of the four studies.

The other two studies were randomized, controlled trials conducted in China and Brazil that enrolled 75 and 41 patients respectively.^{5,6} The most important similarity between the two studies is this: their Interim data Monitoring Committees stopped both studies at interim analysis. In the Chinese study, the overall rate of symptom alleviation within 28 days

(text continues on page 4)

Table 1. CDC Criteria for Highest Risk for Severe COVID-19¹

- Adults 65 years of age and older, with those 80 and older and those who live in nursing homes at considerably higher risk for developing COVID-19
 - Many people, especially younger people, contract SARS-CoV-2 but remain asymptomatic or have only mild symptoms
- People who have chronic medical conditions (particularly if they are not well controlled) like:
 - Heart disease
 - Diabetes
 - Lung disease
 - Cancer
 - Liver disease
 - Kidney disease requiring dialysis
- Older adults (age 80 or older) and older adults who have underlying medical conditions were and continue to be at highest risk. Other populations now considered at elevated risk include the following:
 - People who are immunocompromised or who are living with HIV*
 - People with disabilities*
 - People whose body mass index ≥ 40 *
 - People experiencing homelessness*
 - Racial and ethnic minority groups*

*Newly added

Table 2. Signs and symptoms of COVID-19²

Stage 1 is a flulike prodrome that begins 2-14 days after incubation, lasts 3-7 days, and is characterized by the following:

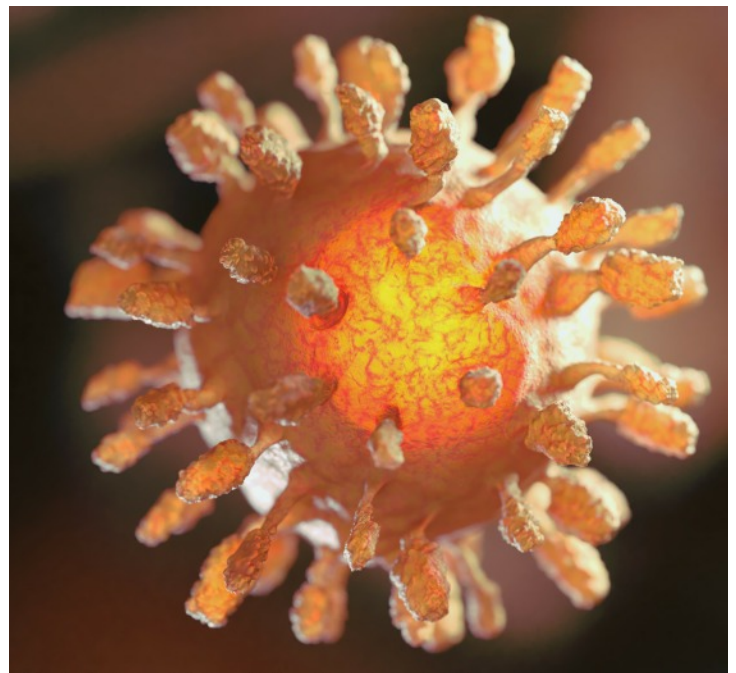
- Fever ($>100.4^{\circ}\text{F}$ [38°C])
- Fatigue
- Headaches
- Chills (and/or repeated shaking with chills)*
- Myalgias (muscle aches and pains)*
- Malaise (a feeling that you are slightly sick, although you cannot say what exactly is wrong)
- Cough
- Sore throat
- New loss of taste or smell*
- Anorexia (lack of appetite)*

*Newly added

Some patients may also have increased sputum production and coryza (an inflammation of the mucous membrane lining the nose usually associated with nasal discharge). Nausea and vomiting, dizziness, and diarrhea are also possible but rarely seen in this outbreak.

Stage 2 occurs when the infection migrates into the lower respiratory tract. Symptoms include the following:

- Dry cough
- Dyspnea
- Progressive hypoxemia in many cases
- Respiratory failure that requires mechanical ventilation in some cases

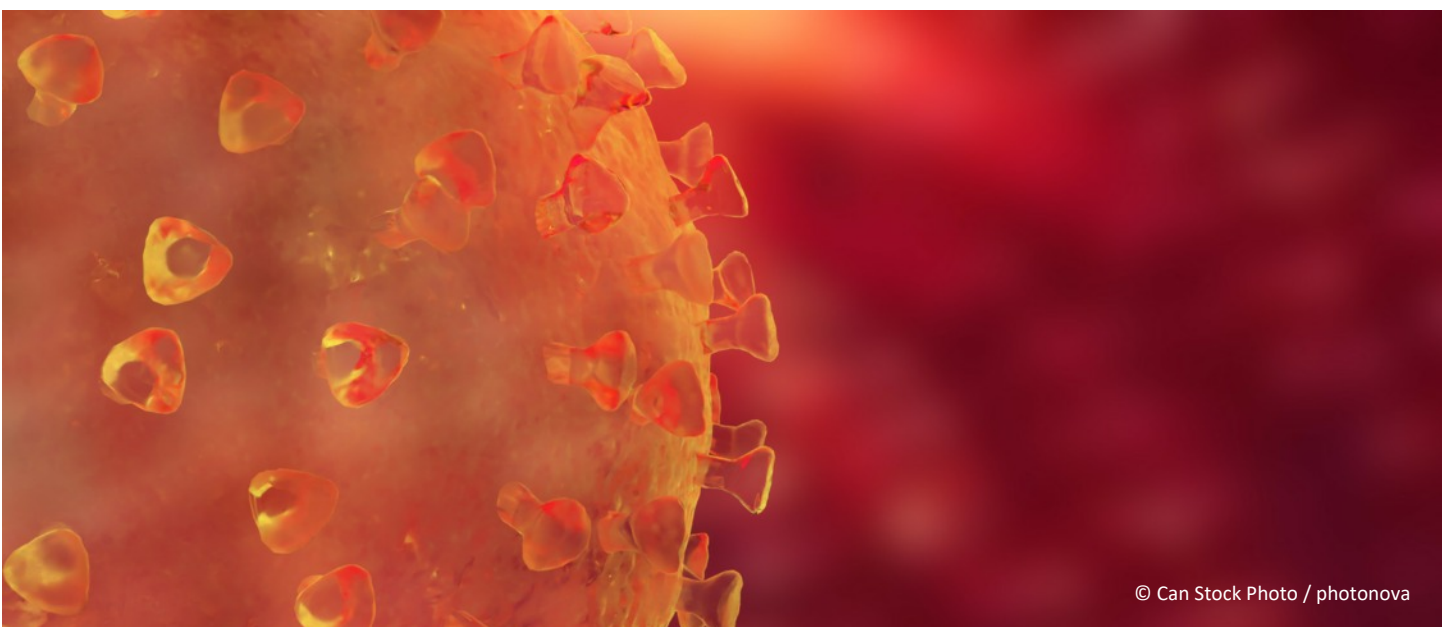


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Table 3. Recent Retrospective Studies of Hydroxychloroquine for COVID-19^{3,4}

Study Location and Design	N/n	Key points
<p>French Tertiary Care Centers Retrospective review of adults (18-80 years old) requiring admission and oxygen by mask/nasal prongs</p>	<p>N = 181 HCQ group n = 84 No-HCQ group n = 97</p>	<ul style="list-style-type: none"> □ Groups determined by receipt/no receipt of HCQ within 1st 48 hours of admission □ Median time of symptoms before hospitalization was 7 days <ul style="list-style-type: none"> ● 20.2% patients in the HCQ group were transferred to the ICU or died within 7 days ● 22.1% patients in the no HCQ group were transferred to the ICU or died within 7 days ● In the HCQ group, 2.8% of the patients died within 7 days and 27.4% developed ARDS ● In the no-HCQ group, 4.6% died within 7 days and 24.1% developed acute respiratory distress syndrome ARDS within 7 days ● Eight patients in the HCQ groups (9.5%) experienced ECG modifications requiring HCQ discontinuation ● The results failed to support HCQ use in patients hospitalized with SARS CoV-2-positive hypoxic pneumonia.
<p>U.S. Veterans Administration Retrospective analysis of data from veterans hospitalized with confirmed SARSCoV-2 infection in all U.S. VA medical centers until April 11, 2020</p>	<p>N = 368 HC group n = 97 HC +AZ group n = 113 No HC group n = 158</p>	<ul style="list-style-type: none"> □ 32% of “No HCQ group” received AZ □ Groups were highly imbalanced; there were high percentages of missing data for many important factors associated with COVID-19 severity (so proper adjustments for differences in groups could not be made) <p>Rates of death in the</p> <ul style="list-style-type: none"> ● HCQ group was 27.8% ● HCQ + AZ group was 22.1% ● No HCQ group 11.4% <p>In non-ventilated patients, rates of progression to need for ventilation in the</p> <ul style="list-style-type: none"> ● HCQ group was 13.3% ● HCQ + AZ group was 6.9% ● No HCQ group 14.1% <p>Compared to the no HCQ group, risk of death from any cause was 2.61 times higher in the HC group but not in the HCQ + AZ group</p>

ABBREVIATIONS: ARDS = acute respiratory distress syndrome; AZ = azithromycin; ECG = electrocardiogram; HCQ = hydroxychloroquine; ICU = Intensive care unit



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Table 4. Key Points from the *ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19*¹⁴

At admission	<ul style="list-style-type: none"> ▪ Measure D-dimer level, PT, and the platelet count (in decreasing order of importance) in all patients who present with COVID-19 infection ▪ Consider underlying conditions such as liver disease and medications when interpreting results
During admission	<ul style="list-style-type: none"> ▪ Measure fibrinogen as a marker for disseminated intravascular coagulation ▪ Fibrinogen may be a marker for worsening prognosis ▪ Consider more aggressive critical care support is warranted and consideration should be given for more “experimental” therapies and blood product support ▪ Consider prophylactic dose LMWH, in all patients (including non-critically ill) hospitalized for COVID-19 infection, in the absence of any contraindications
If clotting occurs	<ul style="list-style-type: none"> ▪ Treat following institutional treatment guidelines
If bleeding develops	<ul style="list-style-type: none"> ▪ Follow accepted guidelines concerning blood transfusions
ABBREVIATIONS: LMWH = low molecular weight heparin; PT = prothombin time	

was similar for patients who received standard of care with and without hydroxychloroquine. In the Brazilian study, which used chloroquine, QTc prolongation was a problem for 10.7% of patients receiving low-dose therapy (450 mg BID on day one, then 450 mg on days two through four), and 25% of those receiving high-dose therapy (600 mg BID for ten days).⁶ These researchers wrote, “[O]ur study raises enough red flags to stop the use of a high-dosage regimen (i.e., 12 g of CQ during 10 days), because the risks of toxic effects overcame the benefits.”⁶ They found elevated creatine phosphokinase (CK) and myocarditis (defined as a creatine kinase-MB more than twice the upper limit of normal) in more than 30% of chloroquine-treated patients, and prolonged QTc levels in 15% of patients.⁶ It is important to note that even though the trial was randomized, at the point of study stoppage, the higher-dose CQ patient group was substantially sicker and had more comorbidities than the low dose group. It also lacked a placebo control arm.

The bottom line is that all of these smaller preliminary studies are plagued by numerous and significant limitations. Larger randomized, controlled studies are ongoing—at least one of which is nearing achievement of its targeted sample sizes. We anticipate that results from these studies may begin to be reported in as soon as mid- to late May. At this time, it seems that hydroxychloroquine has no overwhelmingly positive effects, and may have some significant risks associated with its use in COVID-19 infected patients (which we could predict from knowledge of the adverse effects based on decades of experience with the drug).

Thrombosis has emerged as a problem in patients with COVID-19. Can you summarize the issues and current management techniques?

Numerous clinicians have raised the issue of thrombotic complications seen in patients with COVID-19. Research from China indicates infected patients frequently develop thrombocytopenia (36.2%); many infected individuals develop elevated

D-dimer levels (46.4%). In patients with severe COVID-19, thrombocytopenia and elevated D-dimer levels have been reported in 57.7% and 59.6% of patients, respectively.⁷ A study from the Netherlands found similar results in 184 patients admitted to the ICU. They reported a 31% incidence of thrombotic complications despite systematic thrombosis prophylaxis.⁸ Such changes increase risk for disseminated intravascular coagulation (DIC),⁷ and have been linked to poor prognosis.^{9,10}

As with many of the things we know about coronaviruses, history is helping here. Previous data from the SARS-CoV-1 and MERS-CoV epidemics indicate that coronavirus infections can be associated with coagulation disorders, including pulmonary embolism, deep vein thrombosis, widespread multi-organ infarcts, and ischemic stroke. Researchers suggest that coagulation problems develop pursuant to a prothrombotic response. Humans and animals mount a prothrombotic response in an attempt to prevent scattered alveolar hemorrhage, but the action may go awry and lead to overt clot formation.¹¹

When coagulopathy develops secondary to COVID-19, it typically presents with pronounced elevation of D-dimer and fibrin/fibrinogen degradation products.¹² Rising D-dimer often indicates grim prognosis, and any rapid drop in fibrinogen usually suggests DIC; these changes occur within 7-11 days after onset of symptoms or 4-10 days after hospitalization.¹³ The International Society of Thrombosis and Haemostasis (ISTH) has issued the *ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19*.¹⁴ Complete coverage of the information contained in this guidance is beyond the scope of this CE activity, but **Table 4** lists key points.

What is new concerning remdesivir?

On April 10, 2020, a multinational group of investigators published preliminary results describing compassionate use of remdesivir in patients (N = 61) with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who received oxygen support. They administered remdesivir 200 mg intravenously on day 1, followed by 100 mg daily for an additional 9 days. They could not analyze data from eight patients, leaving an analyzable sample of 53 patients. Of the remaining patients

- 22 were from the United States
- 22 from Europe or Canada
- 9 from Japan

At baseline, 30 patients (57%) were receiving mechanical ventilation and four patients (8%) were receiving extracorporeal membrane oxygenation. Median follow-up was 18 days. At that time, 36 patients (68%) had an improvement in oxygen-support class; among these patients, 17 of 30 patients (57%) who had been on mechanical ventilation were extubated. Nearly one-half (47%) were discharged. Seven patients (13%) died, reflecting a mortality rate of 18% among patients receiving invasive ventilation and 5% among others. The authors report clinical improvement in 36 of 53 patients (68%).

Pharmacy staff who have been following the news may have heard about “leaked” data from China regarding remdesivir. That data have now been published in *The Lancet*.¹⁵ This is a randomized study in which 158 patients received remdesivir and 79 received placebo. The researchers emphasize three key findings:

- Patients in the remdesivir arm who had symptoms for 10 days or fewer improved faster than those in the placebo arm, but the difference was not statistically significant.
- Adverse event rates were similar in both arms, with 102 reports (66%) from remdesivir recipients and 50 reports (64%) from placebo recipients.
- Eighteen patients (12%) stopped remdesivir early pursuant to serious adverse events that included gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin increases, and worsened cardiopulmonary status. Four patients (5%) stopped placebo early.

On the same day that *The Lancet* published the Chinese study online, the U.S. National Institutes of Health issued a press release describing preliminary data from its a randomized, placebo-controlled trial involving 1063 patients, which began on February 21, 2020.¹⁶ Called the Adaptive COVID-19 Treatment Trial, or ACTT, this trial is being conducted under the auspices of the National Institute of Allergy and Infectious Diseases. Sixty-eight sites are conducting this trial—47 in the United States and 21 in countries in Europe and Asia. The trial’s structure is similar

to those used to assess treatments for influenza, and examines time to recovery as the primary endpoint. Preliminary analysis of the primary outcome measure indicate that remdesivir-treated patients had recovery times that were 31% faster (11 vs. 15 days) than placebo-treated patients. An analysis of mortality rates was also promising (8% for remdesivir-treated patients versus 11.6% for placebo-treated patients)—this difference approached statistical significance ($p=0.059$).

I keep hearing conflicting news about SARS-CoV-2’s ability to survive on surfaces. Are any new studies available?

We hear conflicting information, too, and we hear all kinds of recommendations about sanitizing. SARS-CoV-2 can be detected on different surfaces and researchers continue to attempt to determine its viability in different environmental conditions. Two recent studies have looked at survival times.

The first study measured SARS-CoV-2’s stability at different temperatures, and found that the virus is highly stable at 4°C (39.2°F), but sensitive to heat.¹⁷ At 4°C, there was only around a 0.7 log-unit reduction of infectious titer on day 14. The researchers increased the incubation temperature to 70°C (158°F), the time for virus inactivation was reduced to five minutes. So heat—extreme heat—can kill SARS-CoV-2.¹⁷

To test its viability on different surfaces, researchers placed it on various surfaces at room temperature (22°C or 71.6°F) with a relative humidity of around 65%. They checked the surfaces (carefully) periodically. Here’s what they found¹⁷:

- On tissue paper, no infectious virus after a 3-hour incubation
- On wood and cloth, no infectious virus on day 2
- On glass and banknotes, no infectious virus on day 4
- On stainless steel and plastic, no infectious virus on day 7

One unexpected finding was a detectable level of infectious virus was present on the outer layer of a surgical mask on day 7. However, the researchers indicated that using disinfectants at their working concentration was universally effective.¹⁷ That’s a key point—using disinfectants at their working concentration. Another key point: leaving the disinfectants in place for the amount of time the product label designates.

The second set of researchers looked at five environmental conditions (aerosols, cardboard, copper, plastic, and stainless steel).¹⁸ They found similar survival times, and indicated the virus survives for approximately two hours in aerosolized droplets; for eight hours on copper; for 24 hours on cardboard ($t_{1/2} \sim 3.5$ hours); and roughly three days on stainless steel and plastic ($t_{1/2} \sim 5.5$ to 7 hours). They noted that decay was logarithmic, and the residual amounts dropped quickly.¹⁸

Since coronavirus can survive on clothing and surfaces, can we use steam or a microwave to kill it?

For example, can I microwave my facemasks?

Finally, we can have a bit of fun with this question. First, let's be sure you know that a facemask is a disposable mask generally reserved for healthcare providers, and different from a cloth face covering. Make note of this, as it will be on the test! It's difficult to find definitive studies on this topic. Microwaving is unlikely to work because it relies on the water content of the item being microwaved. Microwaving a facemask or a cloth face covering is unlikely to kill coronavirus, as the virus and the mask's materials are usually devoid of water molecules. And, some masks—paper or cloth—have little metal staples or metal nose frames in them. Metal + microwave = no, no, no!

Many healthcare facilities are using steam to sterilize reusable cloth masks, but note that they use an autoclave. Autoclaves use a combination of steam and pressure—usually with the internal pressure at 15 pounds per square foot and the temperature reaching 121°C (250 °F).¹⁹ Reaching this temperature at home would be difficult (and yes, we anticipate the next round of questions to include a question about using a pressure cooker, and we will ignore that for now). If you have a steam machine or garment steamer at home, you would need to determine the steam's temperature and then find the length of time necessary to kill the virus. That data is elusive, but 175°F for three minutes seems to be a general guideline.

One of the best articles we have found concerning what kills coronavirus in the home was published online by the prestigious medical journal, *Reader's Digest*.²⁰ Find it here: <https://www.rd.com/advice/what-kills-bacteria/>. Please note that while our allegation that *Reader's Digest* is a medical journal is facetious, the integrity of this article is beyond reproach. We know for a fact the authors and editors at *Reader's Digest* are very careful to fact check, and they have done a great job on this article. This article stresses a number of important facts:

- Soap and water will kill bacteria and viruses if used properly; the soap incapacitates the virus, ample water flushes it from the skin
- Alcohol, bleach, and hydrogen peroxide will, too, provided they are allowed to sit for recommended sit times
- Vinegar and ammonia will not help
- Heat from the dishwasher and clothes dryer will work
- Burning sage will kill many bacteria, but not viruses

Why did the CDC do a U-turn on its stance on wearing masks in public?

The CDC did not initially recommend that people other than healthcare providers wear masks in public because they are only mildly effective at preventing the wearer from becoming infected in the presence of infected air droplets. After numerous studies found that many individuals who were infected with coronavirus were asymptomatic or pre-symptomatic, it became clear



that these people could transmit the virus to others.²¹⁻²⁷ In this case, a face covering has been shown to be effective at preventing you from infecting others. The CDC amended its previous recommendation to recommend wearing cloth face coverings in public settings where other social distancing measures are difficult to maintain (e.g., grocery stores and pharmacies). The CDC emphasizes this is **especially important** in areas of significant community-based transmission. This measure protects others from people who simply may not know they are infected.¹⁹

People can use cloth face coverings fashioned from household items or common low cost materials. Find the CDC's directions on how to make face coverings here: <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html>. People who comply with this recommendation are good citizens exercising a voluntary public health measure.¹⁹ Maintaining six feet of social distancing remains important. When social distancing is impossible, the combination of a face covering and social distancing as much as possible can reduce the impact of exponential spread. If one person spreads COVID-19 to 2.5 people after ten days in normal circumstances, than that first infected person will indirectly cause 244 people to be infected by day 60. However, a 50% reduction in the infection rate will result in just four infections over those 60 days. At a more aggressive 75% reduction in the infection rate (which is achievable with face coverings and social distancing), only 0.06 infections occur per originally infected person.²⁹

Surgical masks and N-95 respirators are critical supplies that continue to be reserved for healthcare workers and other medical first responders.¹⁹ The CDC also issued a *Guidance for Pharmacies* on April 14, 2020. **Table 5** lists its key points, but we advise you to read the entire document on the CDC's web site.

We'll conclude this update with a reminder that people who are afraid and desperate will often do things that are unwise or ignorant (meaning they simply do not know better). For example, the U.S. Food and Drug Administration is reminding all people who manufacture hand sanitizers—and manufacturing hand sanitizer has become a cottage industry, with many breweries and distilleries jumping into the fray³⁰—to add a bitter ingredient so that people will not drink them.³¹ The FDA's guidance indicates these products must have an unpalatable odor and taste and mandates the use of denatured alcohol.

And, of course, people should not consume products meant for topical use or cleaning or go to a tanning booth set for “extra crispy.”

CONCLUSION

We continue to stay abreast of developments. In the last few days, we have heard news reports about trials involving famotidine with no real explanation why it might work³²; an investigational drug called sobetirome that mimics thyroid hormone and may have effects on lung tissue³³; and some truly ridiculous suggestions in the press. All of these suggestions and allegations lack evidence at this time. Should they develop into significant developments, we will provide an additional update.

We welcome your questions. Please submit questions or comments to jeannette.wick@uconn.edu.

Table 5. Summary of the CDC's Guidance for Pharmacies

- Everyone entering the pharmacy should wear a face covering, regardless of symptoms. Cloth face coverings should not be placed on young children under age 2; anyone who has trouble breathing; or is unconscious, incapacitated or otherwise unable to remove the mask without assistance.
- Pharmacists and pharmacy technicians should always wear a facemask while they are in the pharmacy for source control.
 - Facemasks (if available) are generally preferred over cloth face coverings
- Pharmacies should postpone and reschedule some routine clinical preventive services, such as adult immunizations, which require face-to-face encounters
- Staff who are sick should STAY HOME
- Maintain social distancing when interacting with customers
 - Use engineering controls (signage, barriers, clear plastic shields, frequent cleaning, self-service registers, drive-through windows)
 - Use administrative controls (protocols and changes to work practice, policies or procedures)
 - Limit the number of customers allowed in the pharmacy at one time
 - Close self-serve blood pressure units

See the complete list of recommendations here: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/pharmacies.html>

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