Coronavirus – What You Need to Know
as of: 03/30/20

Virion Structure: Size

Coronavirus virions are spherical with diameters of approximately 125 nm (0.125\(\mu\) or 0.00000492125 inches) as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy \[2,3\].

Virus virion is invisible in this photo of salt grains!
Virion Structure: Internal Model
Video Overview: https://www.youtube.com/watch?v=aPvpfC7NfR0
Source: Dr. John Campbell CV at https://uk.linkedin.com/in/dr-john-campbell-5256223b

Basic information about the novel Coronavirus, currently in China. (But spreading worldwide!)

**Coronaviruses (CoV):**
A large family of viruses that cause illness ranging from the common cold to more severe respiratory diseases.

A new novel virus identified from humans 29th December 2019, 2019-nCoV

**Human respiratory viral infections:**
Cold often caused by rhinovirus
Influenza (flu) caused by influenza virus

**Coronaviruses virion:**
CoV is a single stranded RNA
Protein envelope (protein shell or capsid)
Crown shaped virions
Less than 100 nm

Coronaviruses are zoonotic
MERS Middle East Respiratory Syndrome, 2012
SARS Severe Acute Respiratory Syndrome, 2003
Novel previously unidentified in humans, 2019 – nCoV

**Clinical features:**
Fever 98%
Cough 76%
Myalgia or fatigue 44%
Sputum production 28%
Headache 8%
Haemoptysis 5%
Diarrhoea 3%
Dyspnoea 55%
Severe acute respiratory infection – pneumonia
Acute respiratory distress syndrome
Radiology

Median duration from illness onset to dyspnoea 8·0 days
Median time from onset of symptoms to first hospital admission 7·0 days
Time from onset of symptoms to mechanical ventilation was 10·5 days
Leucopenia less than $4 \times 10^9$/L 25%
Lymphopenia less than $1·0 \times 10^9$/L 63%

Transmission:
Direct from animals, vectors
Human to human
Droplet, nasal or mouth mucosa, eyes
Coughs and sneezes spread diseases - over 2 metres
Catch it - bin it - kill it
Surfaces - hands - mucous membranes
Virus contained in an envelope, so virus can stay dormant for 5 days
Fomites
Closed environments, less likely outside

Sometimes people with mild or no symptoms can be carriers

Contagious for a few (2-5-14) days of incubation period, feeling well but still contagious.

Protection:
1. Stay home, avoid planes, buses, trains, busy areas
2. No visitors avoid close contact with symptomatic people or potential carriers
3. Wear a quality medical mask
4. Wrap around glasses
5. Gloves and meticulous hand hygiene, don’t touch eyes, nose mouth
6. Don’t trust hand sanitizers
7. Avoid hospitals

Same infectiousness as SARS, lower mortality (SARS) 10% v 3%

2 to 3 people get new infection for every infected case

Treatment:
Supportive
Keep warm
Hydration
Eat if hungry
No specific coronavirus antiviral drugs
Oxygen for hypoxaemia
3% mortality
No vaccine as yet
Viruses didn’t become ubiquitous by being wimps: From the rhinoviruses that cause the common cold to the new coronavirus that has spread across the world, they are able to survive on surfaces far away from the living cells that they need in order to reproduce.

How long they can lurk before a living organism comes along to infect depends on the kind of surface and the properties of the virus: The Covid-19 virus, according to a new study, sticks around on plastic surfaces for up to three days, but for a shorter period on metals.

Rhinoviruses can survive on human skin for hours, which is why shaking hands with someone who has a cold is a good way to catch it. Influenza viruses remain infectious for up to 48 hours after landing on nonporous surfaces such as stainless steel or plastic such as that in computer keyboards, but that seems like the outer limit: A 2011 study found that the H1N1 flu virus that caused the 2009 pandemic could be recovered from glass, stainless steel, plastic, and aluminum for up to 48 hours, but most was gone after nine hours. Both cold and flu viruses survive for much shorter times on porous surfaces such as cloth, paper, or tissue, with very little infectious virus remaining after four hours.

Viruses covered in “envelopes” have the most trouble surviving outside a living cell. On surfaces, the surrounding light, heat, and dryness break down the envelope, killing the virus. (Porous surfaces pull moisture away from viruses that land on them, accelerating the destruction of the envelope.) Most rhinoviruses have such envelopes; so do some influenza viruses. Norovirus doesn’t, enabling it to last longer in the environment.

Then there’s the new coronavirus. Its survival on surfaces is similar to that of the SARS virus, to which it’s related. On plastic, after eight hours only 10% of what researchers deposited was still there, according to a study published on Tuesday in the New England Journal of Medicine. But the virus didn’t become undetectable until after 72 hours. On stainless steel, the numbers began plummeting after just four hours, becoming undetectable by about 48 hours. On copper and cardboard, virus was undetectable by eight hours and 48 hours, respectively.

The fewer the virus particles on a surface, the lower the chances that someone touching it will become infected. “You have to get a certain level of virus exposure to be infected,” said Ross McKinney, chief scientific officer of the American Association of Medical Colleges. And infection cannot happen through the skin: to “self inoculate,” one must transfer virus from, say, the fingers to the nose or eyes, where it can enter the body via mucus membranes.

But because the virus that causes Covid-19 is, like other microbes, so durable, thoroughly washing hands after touching surfaces that anyone else might have touched — or not touching them in the first place — is the first line of defense against infection.
How long does coronavirus live outside the body?

Touching any surface suddenly seems dangerous in the era of the new coronavirus. Fingers might pick up the microbe, which could lead to COVID-19 — the illness spreading around the world — when a person touches his or her face.

The Centers for Disease Control and Prevention estimates it could be viable for “hours to days.” A preliminary study published this week found the virus could be detected in the air for up to three hours after it was aerosolized with a nebulizer, up to four hours on copper, up to 24 hours on cardboard and up to two to three days on plastic and stainless steel.

The newest research, which has not yet been peer reviewed, was conducted by scientists at the National Institutes of Health, Princeton University, the University of California and the CDC. Previously published studies have indicated coronaviruses in general — not specifically the new one — can last up to nine days on surfaces depending on the surface type, the heat, the humidity, exposure to sunlight and other factors, said Joseph Fair, a virologist, epidemiologist and NBC News Science contributor.

“Coronaviruses have been with us for millions of years — not this one, but other coronaviruses,” Fair told TODAY.

Since there’s no definitive data on the new bug yet, scientists have to err on the side of caution about how long it can stay active, he added.

It’s important to note there hasn’t been a documented case of a person getting infected from a surface contaminated with the new coronavirus, according to the CDC.

Transmission usually happens when people come in direct contact with respiratory droplets produced when a nearby infected person coughs or sneezes.

How does that compare to other germs?

The flu virus can stay active on some surfaces for up to 48 hours, according to the CDC.

The Ebola virus can survive on doorknobs and countertops for several hours.

The norovirus can survive up to four weeks on surfaces, said Charles Gerba, a professor of microbiology and immunology at The University of Arizona.

Some bacteria can last much longer, Fair said.
What affects how long the coronavirus stays active?

Fair called sunlight “nature’s greatest disinfectant” because the ultraviolet light inactivates bacteria and viruses.

Higher heat and humidity, on the other hand, will help it to stay active longer, he noted.

Disinfecting surfaces can kill the virus. More on that below.

Does the type of surface make a difference?

Yes, the less porous a surface, the more virus you will get on your hands when you touch it, Gerba said.

“You will pick up on your finger 70% of the viruses on stainless steel surfaces versus only 1% from a cloth surface or money,” he noted.

That being said, Fair advised people to avoid handling cash, which he called “one of the most filthy things in our society, period.” Paper money is made of cotton, an absorbable surface that can get wet. The new coronavirus can potentially stay active on it for up to nine days just like on other surfaces, he said.

Which surfaces are the most infectious?

Any that are touched the most often, Fair said. That includes bathroom faucet handles, doorknobs, elevator buttons, hand rails and touchscreens on phones, tablets, and ATMs.

They’re the dirtiest surfaces we come into contact with because so many people touch them.

What kills viruses?

Common cleaners with either bleach or alcohol as their active ingredient inactivate infectious viruses, Fair said.

Coronaviruses are fairly sensitive to most disinfectants, including bleach, hydrogen peroxide and quaternary ammonium compounds, Gerba added. If the label says the cleaner will kill the influenza virus or norovirus, it will work against coronaviruses, too.

“I would use disinfecting wipes because then you use the right dose of disinfectant and you usually let it dry so you get the right contact time for the disinfectant to work,” he noted.
How often should you disinfect surfaces?

Several times per day, especially frequently-touched items like a computer keyboard, phones and tablets, Fair advised.

“It’s very good practice because those are the filthiest areas in your life,” he said.

COVID-19: your questions, answered

Source https://www.weforum.org/agenda/2020/03/covid-19-your-questions-answered

With so much conflicting information about the coronavirus pandemic swirling around the internet, we invited the Forum's Instagram followers to put their questions about the crisis to a panel of medical experts from around the world.

Can you have COVID-19 and show no symptoms?

You can have it and display no symptoms depending on your age, how strong your immune system is and how recently you have been exposed. Because it is extremely contagious, the virus can be transmitted easily - even by individuals without symptoms - which is why it is important to practice preventative measures even if you feel fine.

- Dr David Walcott, World Economic Forum Global Shaper and founder of NovaMed

Yes - because the time from when you catch the COVID-19 virus to when you begin to show symptoms is five days on average. However, this time period, also called the incubation period, has been known to vary between 1-14 days - and people can be infectious during this period. Additionally, if you have no symptoms but are a carrier of the virus, you could risk passing it on to others, for whom it could be fatal. So, follow the advice of your local and national governments and practice social distancing.

- Dr Kate Tulenko, CEO of Corvus Health

Can one get coronavirus for a second time?

Currently it is unknown how long the immunity of COVID-19 patients can last. However, the virus could potentially mutate in such a way as to cause patients to become susceptible again.

There are reports of recovered COVID-19 patients being tested positive again in China, South Korea and Japan. However, solid scientific evidence is needed to address questions like: How accurate were the test results? Was the recovered patient reinfected with the virus, or did they have an infection that simply lasted a long time? Are there variations in immune response among different people? How many different versions of COVID-19 may be spreading around? These questions could help us understand the immune response of the virus.

- Dr Xifeng Wu, Dean and Professor of School of Public Health, Vice President of The Second Affiliated Hospital, Director of National Institute for Data Science in Health and Medicine, Zhejiang University, Hangzhou, China
How long can the virus survive on surfaces?

This depends on the surface material and the amount of virus present. A recent study investigated the persistence of coronavirus on stainless steel, plastic, cardboard and copper. The authors used an initial virus concentration similar to that found in the respiratory tract of infected people. The virus remained detectable for between 10 hours and three days, with the shortest persistence on copper and the longest on plastic. Another study that looked at the related virus SARS-CoV - the virus responsible for the SARS outbreak in 2003 - found it was detectable for up to nine days. However, just because a virus is detectable does not mean it poses a health risk.

So an interesting related question is: How long should we worry about becoming sick from touching a contaminated surface? The answer to this is probably shorter than three to nine days. One reason is that the virus concentration on surfaces declines over time as it dries out, so the longer the time since contamination, the lower the risk. A second reason is that only a portion of the total virus will transfer from the surface to your hand to your mouth or nose. Nevertheless, risks from surface contamination in highly trafficked areas provide additional motivation to wash your hands frequently with soap and water and disinfect surfaces regularly.

- Dr Tim Julian, Group Leader of Pathogens and Human Health, Department Environmental Microbiology, Eawag - Swiss Federal Institute of Aquatic Science and Technology
How has attention to other major illnesses (like cancer) been affected?

The diversion of healthcare resources to manage the COVID-19 crisis has significantly affected the ability of many health systems to maintain standards of care for patients with other medical conditions. Hospitals in the worst-affected countries are struggling to keep pace with the number of admissions from the coronavirus alone, and have almost zero capacity to cope with other conditions. Even in countries that are not as badly affected, many hospitals have now deferred elective surgeries, redirected any upper respiratory tract infection or pneumonia cases to isolation wards, and cancelled or postponed non-critical outpatient clinic visits.

This also means that people are deferring their health checks, including screening tests to pick up cancer incidence. The latter in particular means there will be patients who would otherwise have been identified through routine screening as being in need of urgent medical attention, and these are now missed or delayed – which means the window of opportunity for seeking early or effective treatment may be closed, resulting in morbidity or mortality that could have been avoided. The situation may be compounded when the supply chains for essential medicines are disrupted, a reality that is starting to happen in several countries which are key producers of medical supplies.

- **Professor Yik-Ying TEO**, Dean, Saw Swee Hock School of Public Health, National University of Singapore

Is it possible that one day this will happen again?

Over the past 30 years, the number of annual epidemics has nearly tripled. In the past 15 years alone, outbreaks of Zika, MERS-CoV, SARS, cholera, tuberculosis, HIV/AIDS, influenza and Ebola have killed hundreds of thousands of people.

We know why this is happening. We live in a world where humans are increasingly connected — not only to each other but also to animals, which are responsible for about three-quarters of new infectious diseases.

What’s more, human beings are moving around the planet faster than at any other time in history, giving pathogens endless opportunities to find new hosts, cross borders and evolve into stronger strains than we’ve seen in the past.

**Climate change** is also fuelling the spread of disease, as warmer temperatures disrupt our ecological balance and expand the habitats of mosquitoes and other disease-carrying species. Meanwhile, antimicrobial resistance is undermining some of the gains we have made in controlling outbreaks, as infections become more difficult — and even impossible — to kill.

The next pandemic is only a matter of time. And as has become painfully obvious over these past few weeks, we remain dangerously underprepared.
The next pandemic is a matter of when, not if
Image: New England Journal of Medicine / Milken Institute

- **Michelle A. Williams**, Dean of the Harvard T.H. Chan School of Public Health, US

**Is there any vaccine for this virus?**

There are currently no specific vaccines for COVID-19 that are immediately available; however, there are many potential vaccines currently being researched and developed.

For a vaccine to be developed, we have to identify and understand the structure and behaviour of the virus, then conduct extensive laboratory and human testing. Fortunately, we have been able to identify the virus and sequence its DNA quickly, and we now understand that it is very similar to two previous viruses that we know a lot about: SARS and MERS. However, a certain amount of time is required to understand how safe and effective the vaccines are in preventing disease. We have to ensure that any vaccines are not harmful and offer effective protection against the coronavirus. Based on the timeline required for this, there is unlikely to be a vaccine offered to the general public within the next 12 months.

- **Dr David Walcott**

There is currently no approved vaccine for COVID-19. Vaccines usually take at least a year from first human trials to regulatory approval - however, due to the urgency of the need for this vaccine, it may be made available to health workers and high-risk individuals in six to nine months.

- **Dr Kate Tulenko**
Things to do for Coronavirus Prevention

as of: 03/29/20

Here are some suggestions that may help you, and can’t hurt:

*STAY HOME when mildly sick*
- If symptoms are mild, DON’T go to a hospital, clinic or doctor office.
- If you need medical help, GET HELP. If not sure, PHONE first.
- Avoid unnecessary visits to protect yourself and others, including the nurses, doctors, techs, and clerks who care for you.

WASH YOUR HANDS frequently with soap for 20 seconds. Do the palms, backs of hands, between your fingers, and rub fingertips/nails in your palms. If you can’t wash, use a hand sanitizer. It doesn’t replace washing, so wash when you can and when you return home.

HAND SANITIZER for use after touching contaminated objects. Use one that is more than 60% alcohol. Carry a travel bottle. USE it when out and when you return home. Keep one in your car.

Cough or sneeze into a disposable tissue. Throw it out after using it. Use your elbow (or hand) only if you have no tissue. Use a hand sanitizer afterwards.

NO HANDSHAKING, kiss or hug. No fist or elbow bump, as the virus may be there from previous coughing. A slight bow or hand to your heart is safer.

DONT touch your face if possible, especially your mouth, nose and eyes.

Watch what you TOUCH when not home- doors, light switches, handles, elevator buttons, etc.:
- Use PROTECTION: Touch things with a paper towel, napkin, disposable glove or a wipe.
- Gas pumps: touch pumps and touch screen/buttons with protection.
- Doors: Open or hold with a fist, hip or foot. Don’t grab the handle with your hand if possible.
- Bathroom doors and faucets: Use protection when touching them. Use sanitizer after leaving.
- Salad bar avoid salad bars, self-serve and food carts.
- Store carts, baskets, child seats, refrigerators: Use disinfectant wipes at stores to wipe them.
- Packages, mail. Wipe them off, throw out packaging, wipe off the counter, wash your hands.

Masks? If have access to a mask definitely wear it when out & about.
- Wear one if you’re coughing, sneezing, symptomatic.
- Wear one if you are high risk for medical reasons or caring for a high-risk person.
- DON’T touch the mask, especially the front; clean your hands if you do.
- Remove from the back. Slide fingers underneath ties or loops. Remove from back to front.
- Wash hands after removing mask.
- If you must reuse the same mask then follow *mask reuse guidelines.*

Social Distancing. This means distance from each other to stop the spread.
- You may do well, but others may not.
- If you get it, you can spread it.
- Others may not be as lucky as you, even if they are young.
- Young adults are not immune and can spread it!
- Your touch and breath can spread the virus.
- Simply not touching is **not** enough. So, here are a few rules:
  - Avoid social visits for now.
  - No restaurants or food carts. Drive through, pick up or delivery may be okay - it’s not the food, it’s people. When home, empty containers, throw them out, wipe counter, wash your hands.
  - No shared drinks.
  - No time for bars, cafes.
  - No **visiting** nursing homes, retirement centers, long-term care facilities.
  - No play dates, sleep overs. Daycare is a grey zone. Don’t put your kids in someone’s house.
  - Kids get colds. If they need medical attention, and need to go to the ER, then what?
  - Someone who comes over may look well but transmit the virus.

**Mask reuse guidelines:**

Doctors scramble for best practices on reusing medical masks during shortage

Broadly, there are three different types of masks usable for infection control:
- N95 Type Respirator Masks
- Surgical Masks
- Elastomeric Respirators

Of these three types, only Elastomeric Respirators are suitable for sterilization in an autoclave – neither Surgical Masks nor N95 respirators may be steam sterilized for re-use.

**N95 Mask Decontamination Procedures:**

**Hydrogen Peroxide Vapor:** Final Report for the Bioquell Hydrogen Peroxide Vapor (HPV) Decontamination for Reuse of N95 Respirators (PDF, 1.14 MB), provided by Battelle see: [https://www.fda.gov/media/136386/download](https://www.fda.gov/media/136386/download)

**UVGI Irradiation:** “N95 Filtering Facepiece Respirator Ultraviolet Germicidal Irradiation (UVGI) Process for Decontamination and Reuse” see: [https://www.nebraskamed.com/sites/default/files/documents/covid-19/n-95-decon-process.pdf](https://www.nebraskamed.com/sites/default/files/documents/covid-19/n-95-decon-process.pdf)
Grocery Shopping Procedure

This is obviously a high risk but essential trip that requires some degree of well thought out handling procedures to minimize virus exposure. You will be entering an enclosed well-trafficked public space to acquire a wide variety of items that have been touched by many, many people along the way to the store shelves. Practicing sterile logistics and handling will go a long way to keeping any potential virus particles from making their way into your house or apartment.

Safety tips at the grocery store

Try to limit your trips and definitely stay home if you are sick. Use the store’s home delivery service if possible. If you do go to the store, try following as many of these preventive measures as practicable:

- Pre-prepare your food reception area into dirty & clean zones
- Have disinfection cleaner, rubber gloves and paper towels pre-positioned
- Have a plastic garbage bag to put your street clothes in (shower & change clothes)
- Arrange your method of payment for easy access at the store
- Wear a mask & latex surgical gloves during your trip
- Use disinfecting wipes to wipe down your grocery cart.
- Practice social distancing by staying 6 feet apart from other shoppers.
- Avoid touching your eyes, nose, or mouth during your shopping trip.
- Try to avoid buying leafy vegetables not in a plastic bag or a container, UNLESS it can be cooked.
- Avoid salad bars, food carts and self-serve. Stick with pre-packaged if possible.
- Upon returning home, non-perishable packages & deliveries can be stored in garage
- Place your shopping bags in your dirty zone
- Bag your street clothes and take a shower immediately
- Change into clean clothes and prepare to disinfect & store your purchases
- Wipe down all packaged items with disinfectant and/or store in garage for a week
- Soak fresh produce with peelable skin in warm soapy water, rinse, dry and store
- When all items have be stored, disinfect your dirty & clean staging zones
- Finally, tend to your PPE (mask, gloves, street clothes)

IMPORTANT: The virus attaches itself to hair and clothes any detergent or soap kills it but you should take a shower when you get in from the street. Avoid sitting down anywhere - go straight to the bathroom or shower. If you cannot wash your street clothes immediately, then hang them in direct sunlight which also neutralizes the virus.

Video demonstration of safe shopping procedures:

How to Safely Grocery Shop During Coronavirus
https://www.youtube.com/watch?v=TKx-F4AKteE
Preventing the Spread of Coronavirus Disease 2019 in Homes and Residential Communities


Recommended precautions for household members, intimate partners, and caregivers in a nonhealthcare setting of

A patient with symptomatic laboratory-confirmed COVID-19

OR

A patient under investigation

Household members, intimate partners, and caregivers in a nonhealthcare setting may have close contact with a person with symptomatic, laboratory-confirmed COVID-19 or a person under investigation. Close contacts should monitor their health; they should call their healthcare provider right away if they develop symptoms suggestive of COVID-19 (e.g., fever, cough, shortness of breath) (see Interim US Guidance for Risk Assessment and Public Health Management of Persons with Potential Coronavirus Disease 2019 (COVID-19) Exposure in Travel-associated or Community Settings.)

Close contacts should also follow these recommendations:

- Make sure that you understand and can help the patient follow their healthcare provider’s instructions for medication(s) and care. You should help the patient with basic needs in the home and provide support for getting groceries, prescriptions, and other personal needs.

- Monitor the patient’s symptoms. If the patient is getting sicker, call his or her healthcare provider and tell them that the patient has laboratory-confirmed COVID-19. This will help the healthcare provider’s office take steps to keep other people in the office or waiting room from getting infected. Ask the healthcare provider to call the local or state health department for additional guidance. If the patient has a medical emergency and you need to call 911, notify the dispatch personnel that the patient has, or is being evaluated for COVID-19.

- Household members should stay in another room or be separated from the patient as much as possible. Household members should use a separate bedroom and bathroom, if available.

- Prohibit visitors who do not have an essential need to be in the home.

- Household members should care for any pets in the home. Do not handle pets or other animals while sick. For more information, see COVID-19 and Animals.

- Make sure that shared spaces in the home have good air flow, such as by an air conditioner or an opened window, weather permitting.

- Perform hand hygiene frequently. Wash your hands often with soap and water for at least 20 seconds or use an alcohol-based hand sanitizer that contains 60 to 95% alcohol, covering all surfaces of your hands and rubbing them together until they feel dry. Soap and water should be used preferentially if hands are visibly dirty.
• Avoid touching your eyes, nose, and mouth with unwashed hands.

• The patient should wear a facemask when you are around other people. If the patient is not able to wear a facemask (for example, because it causes trouble breathing), you, as the caregiver, should wear a mask when you are in the same room as the patient.

• Wear a disposable facemask and gloves when you touch or have contact with the patient’s blood, stool, or body fluids, such as saliva, sputum, nasal mucus, vomit, urine.
  o Throw out disposable facemasks and gloves after using them. Do not reuse.
  o When removing personal protective equipment, first remove and dispose of gloves. Then, immediately clean your hands with soap and water or alcohol-based hand sanitizer. Next, remove and dispose of facemask, and immediately clean your hands again with soap and water or alcohol-based hand sanitizer.

• Avoid sharing household items with the patient. You should not share dishes, drinking glasses, cups, eating utensils, towels, bedding, or other items. After the patient uses these items, you should wash them thoroughly (see below “Wash laundry thoroughly”).

• Clean all “high-touch” surfaces, such as counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, and bedside tables, every day. Also, clean any surfaces that may have blood, stool, or body fluids on them.
  o Use a household cleaning spray or wipe, according to the label instructions. Labels contain instructions for safe and effective use of the cleaning product including precautions you should take when applying the product, such as wearing gloves and making sure you have good ventilation during use of the product.

• Wash laundry thoroughly.
  o Immediately remove and wash clothes or bedding that have blood, stool, or body fluids on them.
  o Wear disposable gloves while handling soiled items and keep soiled items away from your body. Clean your hands (with soap and water or an alcohol-based hand sanitizer) immediately after removing your gloves.
  o Read and follow directions on labels of laundry or clothing items and detergent. In general, using a normal laundry detergent according to washing machine instructions and dry thoroughly using the warmest temperatures recommended on the clothing label.

• Place all used disposable gloves, facemasks, and other contaminated items in a lined container before disposing of them with other household waste. Clean your hands (with soap and water or an alcohol-based hand sanitizer) immediately after handling these items. Soap and water should be used preferentially if hands are visibly dirty.

• Discuss any additional questions with your state or local health department or healthcare provider. Check available hours when contacting your local health department.
Footnotes

1 Home healthcare personnel should refer to Interim Infection Prevention and Control Recommendations for Patients with Known or Patients Under Investigation for Coronavirus Disease 2019 (COVID-19) in a Healthcare Setting.

2 Close contact is defined as—
   a) being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time; close contact can occur while caring for, living with, visiting, or sharing a health care waiting area or room with a COVID-19 case
   — or —
   b) having direct contact with infectious secretions of a COVID-19 case (e.g., being coughed on).

MORE COVID-19 FAQ’s

Get Your Home Ready

Detailed Planning Guidance

COVID-19 Readiness Resources

- Visit cdc.gov/COVID19 for the latest information and resources
- COVID 2019 Situation Summary
- Prevention and Treatment
- What to Do If You Are Sick

CDC Communication Resources

- Communication Resources
- Print Resources

Cases & Latest Updates
Disinfection Procedures

How to Clean and Disinfect Surfaces

- If surfaces are dirty, they should be cleaned using a detergent or soap and water prior to disinfection.
- For disinfection, diluted household bleach solutions, alcohol solutions with at least 70% alcohol, and most common EPA-registered household disinfectants should be effective.
  - Diluted household bleach solutions can be used if appropriate for the surface. Follow manufacturer’s instructions for application and proper ventilation. Check to ensure the product is not past its expiration date. Never mix household bleach with ammonia or any other cleanser. Unexpired household bleach will be effective against coronaviruses when properly diluted.
- Prepare a bleach solution by mixing:
  - 5 tablespoons (1/3rd cup) bleach per gallon of water or
  - 4 teaspoons bleach per quart of water
  - Products with EPA-approved emerging viral pathogens claims are expected to be effective against COVID-19 based on data for harder to kill viruses. Follow the manufacturer’s instructions for all cleaning and disinfection products (e.g., concentration, application method and contact time, etc.).
  - For soft (porous) surfaces such as carpeted floor, rugs, and drapes, remove visible contamination if present and clean with appropriate cleaners indicated for use on these surfaces. After cleaning:
    - If the items can be laundered, launder items in accordance with the manufacturer’s instructions using the warmest appropriate water setting for the items and then dry items completely.
    - Otherwise, use products with the EPA-approved emerging viral pathogens claims (examples at this link) that are suitable for porous surfaces

Linens, Clothing, and Other Items That Go in the Laundry

- Do not shake dirty laundry; this minimize the possibility of dispersing virus through the air.
- Wash items as appropriate in accordance with the manufacturer’s instructions. If possible, launder items using the warmest appropriate water setting for the items
and dry items completely. Dirty laundry that has been in contact with an ill person can be washed with other people’s items.

- Clean and disinfect hampers or other carts for transporting laundry according to guidance above for hard or soft surfaces.

**Personal Protective Equipment (PPE) and Hand Hygiene:**

**Cleaning staff should wear disposable gloves and gowns for all tasks in the cleaning process, including handling trash.**

- Gloves and gowns should be compatible with the disinfectant products being used.
- Additional PPE might be required based on the cleaning/disinfectant products being used and whether there is a risk of splash.
- Gloves and gowns should be removed carefully to avoid contamination of the wearer and the surrounding area. Be sure to clean hands after removing gloves.
- Gloves should be removed after cleaning a room or area occupied by ill persons. Clean hands immediately after gloves are removed.
- Cleaning staff should immediately report breaches in PPE (e.g., tear in gloves) or any potential exposures to their supervisor.

**Cleaning staff and others should clean hands often,** including immediately after removing gloves and after contact with an ill person, by washing hands with soap and water for 20 seconds. If soap and water are not available and hands are not visibly dirty, an alcohol-based hand sanitizer that contains 60%-95% alcohol may be used. However, if hands are visibly dirty, always wash hands with soap and water.

- Follow normal preventive actions while at work and home, including cleaning hands and avoiding touching eyes, nose, or mouth with unwashed hands.
  - Additional key times to clean hands include:
    - After blowing one’s nose, coughing, or sneezing
    - After using the restroom
    - Before eating or preparing food
    - After contact with animals or pets
    - Before and after providing routine care for another person who needs assistance (e.g., a child)
To Keep Your Home Virus-Free

Clean and Disinfect

The first thing you'll want to know is that cleaning and disinfecting are two very different things. The CDC recommends we all do a bit of both, even if nobody in your home is sick.

- Cleaning is about removing contaminants from a surface.
- Disinfecting is about killing pathogens.
- Do both daily if anything or anyone has entered or exited your home.

Transmission from person-to-person is a much greater risk than transmission via surfaces, but the CDC recommends we clean and disinfect high-touch surfaces in our homes at least once daily just to be safe, assuming we have had contact with the outside world in some way, either a person leaving and returning or goods coming in.

Target Your Home's High-Touch Surfaces

Researchers have found that the novel coronavirus is capable of living on surfaces such as cardboard for 24 hours, but up to two or three days on plastic and stainless steel. So cleaning and disinfecting high-touch surfaces is a step we should all take.

High-Touch Surfaces to Clean and Disinfect Daily:

- Doorknobs
- Table surfaces
- Hard dining chairs (seat, back, and arms)
- Kitchen counters
- Bathroom counters
- Faucets and faucet knobs
- Toilets (seat and handle)
- Light switches
- TV remote controls
- Game controllers

Everyone’s home is a little different, so just think about the surfaces you interact with most. For me, that includes the above, plus desk surfaces and mousepads (we'll get to gadgets in a bit). Now that you know what you're cleaning, here's how you should do it.

First Clean, Then Disinfect:

1. First, clean the surfaces, removing any contaminants, dust, or debris. You can do this by wiping them with soapy water (or a cleaning spray) and a hand towel.
2. Then apply a surface-appropriate disinfectant. The quickest and easiest way to do this is with disinfecting wipes or disinfectant spray.
The EPA has a full list of disinfectants that will kill the novel coronavirus, but here are a few essentials to keep an eye out for. You can find most of these disinfectants online at Amazon or Walmart if your local grocery store is out of stock. Most disinfectants should have a label that lists the viruses they’re effective against, and that’s what you’ll want to look out for more than any particular active ingredient.

"If [a disinfectant product] has an indication for killing influenza, RSB, SARS virus, or other coronaviruses, then it should work against this one also," Townes said.

**Disinfectants:**
- Disinfecting wipes (Clorox, Lysol, or store brand will do)
- Disinfectant spray (Purell, Clorox, Lysol, all make sprays that will work)
- Isopropyl alcohol
- Hydrogen peroxide

**If You Cannot Find Store-Bought Disinfectants**

Store shelves are bare in a lot of places, especially in the cleaning section, but you still have plenty of options. First off, please do use more soap, water, and scrubbing. That can make a huge difference.

The CDC also has a recommended recipe for a homemade cleaning solution using household bleach.

**How to Make Homemade Bleach Disinfectant Spray:**
- 4 teaspoons household bleach
- 1 quart water
- Pour both into one quart spray bottle, shake vigorously
- Spray on surface to disinfect, let sit for 10 minutes, wipe away with wet cloth

Bleach is excessive in most cases. You should never ever mix bleach solution with any other cleaning chemical, and it’s likely to damage or discolor sensitive surfaces. Use it as a last resort if you can’t source or acquire any other kind of disinfectant. With bleach, remember to wear gloves, open your windows (ventilation is your friend), and be careful.

Alternatively you can make your own bleach-free sanitizer spray with a few ingredients you can order online.

**Does the Laundry Machine Work on Clothes?**

Yes, mostly. Just washing your clothing with regular laundry soap and drying it at a slightly higher temperature than you might have otherwise is all you have to do to disinfect your clothes.

Be sure to disinfect surfaces the dirty laundry comes in contact with, including the hamper and your hands—especially if you have a sick person in the house.
Clean and disinfect the hamper like you would any other surface, and wash your hands thoroughly after handling dirty laundry from someone who is ill. The CDC recommends using a liner in your hamper.

*Don’t forget to clean your coat and backpack.* Wiping the inside off with a disinfectant wipe should do the trick unless your jacket is machine washable.

## Should You Disinfect Food and Snacks?

No, not without reason. According to the FDA, there is no evidence to suggest that food or food packaging can transmit the novel coronavirus, so there is currently no need to disinfect food or food packaging any more than you usually would. Just observe standard food safety.

## Should You Disinfect Packages and Mail?

![PHOTOGRAPH: JULIE CLOPPER/GETTY IMAGES](https://via.placeholder.com/150)

Yes, lightly. According to the USPS, mail and packages are relatively low-risk for transmitting the novel coronavirus, and packages from China pose no special risk compared to packages from anywhere else. That said, researchers have found that *it can live on cardboard for around 24 hours*, so giving packages a once over with a disinfecting wipe isn’t a bad idea.

## How to Disinfect Your Devices

Here’s where cleaning and disinfecting can get tricky. Your devices might be all that’s keeping you sane during your self-isolation but, as we all know, they’re magnets for germs. They’re high-touch surfaces you carry with you everywhere, so you need to clean and disinfect them, too. To avoid repeating myself, let’s just say it here: Disinfecting wipes are the best way to clean your devices, hands down. But some devices have special considerations.

### How to Disinfect Your Phone or Tablet

If you have them, disinfect an iPhone or Android phone with a disinfecting wipe or alcohol solution (at least 70 percent). Make sure you pay special attention to the screen, the buttons, and anywhere dust and pocket lint tend to get trapped. Also make sure you remove any case that’s on your phone or tablet, clean underneath, put it back on, and clean the outside. Following the CDC recommendations for other high-touch surfaces in the home, a once-daily disinfecting isn’t going to hurt your devices.

(Read our full guide to disinfecting your phone.)

### How to Disinfect Your Computer

Laptop displays aren’t always made of glass (matte displays are plastic) so avoid using a disinfecting wipe on the screen, just in case. The display should be cleaned with isopropyl
alcohol (70 percent) solution and a soft towel. Make sure you wipe down the keyboard, the trackpad, the exterior, and where your wrists rest on the laptop.

Most desktop computers are already in sore need for a cleaning. The best way to do that is with a disinfecting wipe or isopropyl alcohol solution and a soft towel. Again, avoid disinfecting wipes on the monitor, just in case—stick to isopropyl alcohol there. But otherwise, just make sure you wipe down the mouse (top, sides, and bottom), the keys on your keyboard, the exterior of the keyboard, and any mousepad you might have.

**Don't Forget Accessories**

For any other electronic device, if the exterior is largely plastic (gaming mice, gamepads, TV remotes) it’s safe to give them a once-over with a disinfecting wipe or isopropyl alcohol solution.

**Stay Home, Stay Safe**

There’s a lot going on right now. It’s stressful. It’s scary. It can be hard to know what you should do or what’s going on. If you have more questions, and who doesn’t right now, we have a lot of thoughtful, thoroughly researched news and articles about the novel coronavirus. You can read more here. Stay safe out there, and please, if you can, stay home.

*Updated March 21: We clarified that if you’re unable to obtain disinfectants, using soap and water on surfaces is still important and can be effective.*

**Sanitize Your Smartphone**

When it comes to cleaning a smartphone, gentleness is key. These are expensive and delicate bits of electronics, so you don’t want to dive in with abrasive cleaning solutions and materials. Clorox wipes and the like aren’t just excessive; they can eat away at the oleophobic coating that keeps fingerprints from smudging your display. Simple, common cleaning materials are all you need to get your handset germ-free—although as of Monday, you also have Apple’s blessing to use 70 percent isopropyl alcohol wipe or Clorox disinfecting wipes on hard surfaces if you insist.

Before you start, power down the device, remove any cases, and unplug any accessories so you’ve got full access to the phone. Your main cleaning tool should be a microfiber cloth. Anything that’s soft and that won't scratch your phone will do, though Apple specifically recommends a camera lens cloth, if you want to follow its advice.

It’s a good idea to start without any fluids at all, just a little pressure, but if needed then you can add warm and soapy water to the mix. Use it sparingly, applying it with your cloth, and drying off the device carefully with another cloth. Be sure to avoid getting excess moisture around ports and buttons.
Generally speaking, cans of compressed air aren't recommended on phones, though you can use them on your keyboard. The powered jet of air might interfere with the inner workings of your handset, and you don't want to take the chance. If you find your phone's ports have been cluttered with debris, try using cotton swabs or toothpicks to tease it out, again taking care not to cause any damage.

If your phone is fully IP68 rated for waterproofing—and triple-check the specs before you attempt this—then you can place the phone in a bowl of clean water for a few minutes, then leave it to dry on a paper towel or dab the moisture off with a cloth.

We'd recommend looking online for device-specific instructions, too. Google says it's OK to use cleaning wipes on Pixel handsets, but use them sparingly, well away from the ports and buttons. If possible buy ones that have been specifically approved for use on electronics.

Another option is an ultraviolet light sanitizer. The science behind UV germ blitzing is robust enough, but they aren't guaranteed to kill every type of bacteria out there, in every single crevice on your phone. These devices are something you want to use alongside the other methods that we've described above.

**Clean Your Keyboards and Mouse**

When it comes to cleaning your other gadgets, similar rules apply. Think about the gear that you're in contact with most often, like your keyboard and mouse. These peripherals are a little bit more hardy than your smartphone, so you can take more aggressive measures, like that can of compressed air we mentioned.

Start with a shake to knock loose any debris and move on to disinfectant wipes. Avoid using harsh cleaning chemicals or any type of bleach, as you might damage the finish of your gadgets. Keyboards and mice aren't usually waterproofed in the same way that phones are, so keep moisture to a minimum and make sure you properly dry everything off.

One interesting trend we've seen in recent years is keyboard cleaning gel. You simply roll the gel across your keyboard and it soaks up all the dirt and germs as it makes its way across, oozing between cracks and crevices to pick up debris and leaving your keyboard as good as new. Important caveat: We haven't tried this ourselves and can't vouch for it. But it seems like a relatively inexpensive solution to take a flier on.

If you're cleaning a whole laptop, then your tools of choice should be a can of compressed air, a microfiber cloth, and a very small amount of water where necessary. According to Dell, a 50:50 isopropyl alcohol and water mixture can be used on the screens attached to its computers, applied from a damp cloth, but go carefully. Once again, don't use sprays or any harsher chemicals, no matter how rough the mess.

Keeping your gadgets clean is just one part of a broader plan you should implement to help prevent the spread of the novel coronavirus. You should shake hands less, wash them more, and work from home if possible. But while you can force yourself not to touch your face, it's going to be pretty impractical to avoid touching your smartphone for the next few months. Might as well sanitize it before you do.
According to the Centers for Disease Control and Prevention, diluted bleach, hydrogen peroxide or 70% isopropyl alcohol effectively kill coronavirus. You can make your own solution and use paper towels, or if you don’t like spraying product, you can buy commercial wipes or sanitizers. The CDC suggests mixing 4 teaspoons of bleach per quart of water. Let it sit for one minute on the surface until you dry it off.

**The good news? Coronavirus is vulnerable to disinfectants and soap.** The virus has a lipid (fatty) outer membrane surrounding it that is easily disrupted by soap and water, and by many disinfectants. It appears to survive for days on a surface, at most, not for weeks like norovirus, the virus responsible for some stomach flus. 

**Vinegar is great, but it’s not a bonafide disinfectant.** You can use it to clean, but not to sanitize. Vinegar is ineffective against most bacteria and viruses, including coronavirus. Vodka, which is only 40% alcohol, won’t work, either. 

**Wipes and solutions that you spray on a surface are equally effective,** Carroll said. However, there has been a stampede to buy products like wipes, so it’s a good idea to have solutions stocked and ready to go under the sink.

**Be aware of the time a disinfectant needs to stay on a surface while air-drying.** Sansoni notes that you should “read the product label on all disinfectants and wipes, because they have instructions on letting the surface stay wet or air dry for a certain amount of time, which varies by product.”

Some products may require 30 seconds to dry, others may need as long as a few minutes. You can find product guidelines [here](https://www.huffpost.com/entry/clean-disinfect-food-kitchen-coronavirus_l_5e78bc8bc5b6f5b7c54804ca), along with a link to sanitizing products approved by the Environmental Protection Agency for coronavirus.

**Disposable gloves are fine.** If you have gloves and want to wear them, that’s fine, Carroll said. If you don’t wear gloves, then wash your hands thoroughly when done (see below).

**Consider disinfecting nonporous containers.** Because of the research mentioned above, there’s always the chance a nonporous (glass and metal) container could have been handled by someone with the virus — including a stocking person at the store. You can use the same disinfectant wipes or solution to clean cans, bottles and jars.

**Transfer some foods to clean containers.** For foods like whole grains, dried beans, pasta, cereals and other similar items, you may want to transfer them to clean containers. That way you don’t have to worry about the small chance of a virus lurking on the container the food came in.

**Run your dishwasher on the sanitizer setting if you have it.** Machines with a sanitizer setting reach an internal temperature of 155 degrees Fahrenheit, which is tough for a virus to survive.

**You can just leave containers and packages** in a designated corner of the kitchen or inside a cabinet for three days if you don’t have time to disinfect them, Gordon said. Cardboard is not a great host for the virus: “We know that concentration of live virus decreases relatively rapidly on cardboard.”

**For produce, just rinse it as usual.** “You do not need to soak your produce in a sanitizing solution,” Gordon said. There are no known instances of produce or food itself transferring the virus, according to the European Food Safety Authority. Respiratory viruses do not tend to reproduce via the digestive tract, according to this study.

**Wash your hands thoroughly.** Once you’ve finished cleaning, wash your hands thoroughly with soap and water for at least 20 seconds, following these CDC recommendations.
Dry your clean hands on a clean towel. “Remember not to wipe dirty hands on a clean towel,” Carroll reminds us, “and make sure all the other family members do the same.” If you have kids or a spouse who forgets this rule, keep your own stock of clean towels for use after kitchen cleanup.

Show Me the Science - Why Wash Your Hands?

https://www.cdc.gov/handwashing/why-handwashing.html

Español (Spanish)

Keeping hands clean is one of the most important steps we can take to avoid getting sick and spreading germs to others. Many diseases and conditions are spread by not washing hands with soap and clean, running water.

How germs get onto hands and make people sick

Feces (poop) from people or animals is an important source of germs like *Salmonella*, *E. coli* O157, and *norovirus* that cause diarrhea, and it can spread some respiratory infections like *adenovirus* and *hand-foot-mouth disease*. These kinds of germs can get onto hands after people use the toilet or change a diaper, but also in less obvious ways, like after handling raw meats that have invisible amounts of animal poop on them. A single gram of human feces—which is about the weight of a paper clip—can contain one trillion germs¹. Germs can also get onto hands if people touch any object that has germs on it because someone coughed or sneezed on it or was touched by some other contaminated object. When these germs get onto hands and are not washed off, they can be passed from person to person and make people sick.

Washing hands prevents illnesses and spread of infections to others

Handwashing with soap removes germs from hands. This helps prevent infections because:

- People frequently touch their eyes, nose, and mouth without even realizing it. Germs can get into the body through the eyes, nose and mouth and make us sick.
- Germs from unwashed hands can get into foods and drinks while people prepare or consume them. Germs can multiply in some types of foods or drinks, under certain conditions, and make people sick.
- Germs from unwashed hands can be transferred to other objects, like handrails, table tops, or toys, and then transferred to another person’s hands.
- Removing germs through handwashing therefore helps prevent diarrhea and respiratory infections and may even help prevent skin and eye infections.

Teaching people about handwashing helps them and their communities stay healthy.

Handwashing education in the community:

- Reduces the number of people who get sick with diarrhea by 23-40% ²³⁶
- Reduces diarrheal illness in people with weakened immune systems by 58% ⁴
- Reduces respiratory illnesses, like colds, in the general population by 16-21% ³⁵
- Reduces absenteeism due to gastrointestinal illness in schoolchildren by 29-57% ⁷
Not washing hands harms children around the world

About 1.8 million children under the age of 5 die each year from diarrheal diseases and pneumonia, the top two killers of young children around the world.

- Handwashing with soap could protect about 1 out of every 3 young children who get sick with diarrhea and almost 1 out of 5 young children with respiratory infections like pneumonia.
- Although people around the world clean their hands with water, very few use soap to wash their hands. Washing hands with soap removes germs much more effectively.
- Handwashing education and access to soap in schools can help improve attendance.
- Good handwashing early in life may help improve child development in some settings.
- Estimated global rates of handwashing after using the toilet are only 19%.

Handwashing helps battle the rise in antibiotic resistance

Preventing sickness reduces the amount of antibiotics people use and the likelihood that antibiotic resistance will develop. Handwashing can prevent about 30% of diarrhea-related sicknesses and about 20% of respiratory infections (e.g., colds). Antibiotics often are prescribed unnecessarily for these health issues. Reducing the number of these infections by washing hands frequently helps prevent the overuse of antibiotics—the single most important factor leading to antibiotic resistance around the world. Handwashing can also prevent people from getting sick with germs that are already resistant to antibiotics and that can be difficult to treat.

References
Show Me the Science - How to Wash Your Hands

https://www.cdc.gov/handwashing/show-me-the-science-handwashing.html

Español (Spanish)

Keeping hands clean is one of the most important steps we can take to avoid getting sick and spreading germs to others. Many diseases and conditions are spread by not washing hands with soap and clean, running water. CDC recommends cleaning hands in a specific way to avoid getting sick and spreading germs to others. The guidance for effective handwashing and use of hand sanitizer was developed based on data from a number of studies.

Microbes are all tiny living organisms that may or may not cause disease.

Germs, or pathogens, are types of microbes that can cause disease.

Wet your hands with clean, running water (warm or cold), turn off the tap, and apply soap.

Why? Because hands could become recontaminated if placed in a basin of standing water that has been contaminated through previous use, clean running water should be used. However, washing with non-potable water when necessary may still improve health. The temperature of the water does not appear to affect microbe removal; however, warmer water may cause more skin irritation and is more environmentally costly.

Turning off the faucet after wetting hands saves water, and there are few data to prove whether significant numbers of germs are transferred between hands and the faucet.

Using soap to wash hands is more effective than using water alone because the surfactants in soap lift soil and microbes from skin, and people tend to scrub hands more thoroughly when using soap, which further removes germs.

To date, studies have shown that there is no added health benefit for consumers (this does not include professionals in the healthcare setting) using soaps containing antibacterial ingredients compared with using plain soap. As a result, FDA issued a final rule in September 2016 that 19 ingredients in common “antibacterial” soaps, including triclosan, were no more effective than non-antibacterial soap and water and thus these products are no longer able to be marketed to the general public. This rule does not affect hand sanitizers, wipes, or antibacterial products used in healthcare settings.

Lather your hands by rubbing them together with the soap. Be sure to lather the backs of your hands, between your fingers, and under your nails.

Why? Lathering and scrubbing hands creates friction, which helps lift dirt, grease, and microbes from skin. Microbes are present on all surfaces of the hand, often in particularly high concentration under the nails, so the entire hand should be scrubbed.

Scrub your hands for at least 20 seconds. Need a timer? Hum the "Happy Birthday" song from beginning to end twice.
**Why?** Determining the optimal length of time for handwashing is difficult because few studies about the health impacts of altering handwashing times have been done. Of those that exist, nearly all have measured reductions in overall numbers of microbes, only a small proportion of which can cause illness, and have not measured impacts on health. Solely reducing numbers of microbes on hands is not necessarily linked to better health. The optimal length of time for handwashing is also likely to depend on many factors, including the type and amount of soil on the hands and the setting of the person washing hands. For example, surgeons are likely to come into contact with disease-causing germs and risk spreading serious infections to vulnerable patients, so they may need to wash hands longer than a woman before she prepares her own lunch at home. Nonetheless, evidence suggests that washing hands for about 15-30 seconds removes more germs from hands than washing for shorter periods.

Accordingly, many countries and global organizations have adopted recommendations to wash hands for about 20 seconds (some recommend an additional 20-30 seconds for drying):

- The Benefits of Hand Washing
- New Zealand. Step-by-Step Guide to Hand Washing
- The Global Public-Private Partnership for Handwashing. Why Handwashing?
- World Health Organization. Guidelines on Hygiene in Health Care: A Summary

Rinse your hands well under clean, running water.

**Why?** Soap and friction help lift dirt, grease, and microbes—including disease-causing germs—from skin so they can then be rinsed off of hands. Rinsing the soap away also minimizes skin irritation. Because hands could become recontaminated if rinsed in a basin of standing water that has been contaminated through previous use, clean running water should be used. While some recommendations include using a paper towel to turn off the faucet after hands have been rinsed, this practice leads to increased use of water and paper towels, and there are no studies to show that it improves health.

Dry your hands using a clean towel or air dry them.

**Why?** Germs can be transferred more easily to and from wet hands; therefore, hands should be dried after washing. However, the best way to dry hands remains unclear because few studies about hand drying exist, and the results of these studies conflict. Additionally, most of these studies compare overall concentrations of microbes, not just disease-causing germs, on hands following different hand-drying methods. It has not been shown that removing microbes from hands is linked to better health. Nonetheless, studies suggest that using a clean towel or air drying hands are best.

References
Show Me the Science – When & How to Use Hand Sanitizer in Community Settings

https://www.cdc.gov/handwashing/show-me-the-science-hand-sanitizer.html

Español (Spanish)

Note: For hand hygiene guidance in healthcare settings, please visit the Clean Hands Count webpage.

CDC recommends washing hands with soap and water whenever possible because handwashing reduces the amounts of all types of germs and chemicals on hands. But if soap and water are not available, using a hand sanitizer with at least 60% alcohol can help you avoid getting sick and spreading germs to others. The guidance for effective handwashing and use of hand sanitizer in community settings was developed based on data from a number of studies.

Alcohol-based hand sanitizers can quickly reduce the number of microbes on hands in some situations, but sanitizers do not eliminate all types of germs.

Why? Soap and water are more effective than hand sanitizers at removing certain kinds of germs, like Cryptosporidium, norovirus, and Clostridium difficile\(^1\)\(^-\)\(^5\). Although alcohol-based hand sanitizers can inactivate many types of microbes very effectively when used correctly\(^1\)\(^-\)\(^15\), people may not use a large enough volume of the sanitizers or may wipe it off before it has dried\(^14\).

Hand sanitizers may not be as effective when hands are visibly dirty or greasy.

Why? Many studies show that hand sanitizers work well in clinical settings like hospitals, where hands come into contact with germs but generally are not heavily soiled or greasy\(^16\). Some data also show that hand sanitizers may work well against certain types of germs on slightly soiled hands\(^17\)\(^-\)\(^18\). However, hands may become very greasy or soiled in community settings, such as after people handle food, play sports, work in the garden, or go camping or fishing. When hands are heavily soiled or greasy, hand sanitizers may not work well\(^3\)\(^-\)\(^7\)\(^,\)\(^16\). Handwashing with soap and water is recommended in such circumstances.

Hand sanitizers might not remove harmful chemicals, like pesticides and heavy metals, from hands.

Why? Although few studies have been conducted, hand sanitizers probably cannot remove or inactivate many types of harmful chemicals. In one study, people who reported using hand sanitizer to clean hands had increased levels of pesticides in their bodies\(^19\). If hands have touched harmful chemicals, wash carefully with soap and water (or as directed by a poison control center).

If soap and water are not available, use an alcohol-based hand sanitizer that contains at least 60% alcohol.

Why? Many studies have found that sanitizers with an alcohol concentration between 60–95% are more effective at killing germs than those with a lower alcohol concentration or non-alcohol-based hand sanitizers\(^20\)\(^-\)\(^26\). Hand sanitizers without 60-95% alcohol 1) may not work equally well for many types of germs; and 2) merely reduce the growth of germs rather than kill them outright.

When using hand sanitizer, apply the product to the palm of one hand (read the label to learn the correct amount) and rub the product all over the surfaces of your hands until your hands are dry.

Why? The steps for hand sanitizer use are based on a simplified procedure recommended by
CDC. Instructing people to cover all surfaces of both hands with hand sanitizer has been found to provide similar disinfection effectiveness as providing detailed steps for rubbing-in hand sanitizer.

Swallowing alcohol-based hand sanitizers can cause alcohol poisoning.

Why? Ethyl alcohol (ethanol)-based hand sanitizers are safe when used as directed, but they can cause alcohol poisoning if a person swallows more than a couple of mouthfuls.

From 2011 – 2015, U.S. poison control centers received nearly 85,000 calls about hand sanitizer exposures among children. Children may be particularly likely to swallow hand sanitizers that are scented, brightly colored, or attractively packaged. Hand sanitizers should be stored out of the reach of young children and should be used with adult supervision. Child-resistant caps could also help reduce hand sanitizer-related poisonings among young children. Older children and adults might purposefully swallow hand sanitizers to become drunk.

References

Antibacterial soaps don't kill viruses
Consumer Reports News: May 01, 2009 04:18 PM

Washing your hands frequently with regular soap and water is important to help prevent the spread of germs. But while antibacterial products may seem like a stronger cleaning option, they are no more effective in cleaning your hands than regular soap and water—and they do not kill viruses like H1N1 (swine) flu. In fact, the routine use of antibacterial cleaning products has been seriously questioned by scientists and studies have shown that triclosan, the active ingredient in many antibacterial products, may make matters worse by creating harmful drug-resistant bacteria.

Stick with simple soap and water and if you can't wash your hands, use an alcohol-based sanitizer with at least 60% alcohol content.

—Urvashi Rangan, Technical Policy Director, Consumers Union
Does Soap Really Kill 99.9 Percent of Germs?

Does soap really kill germs like it's supposed to?

- By Everyday Einstein Sabrina Stierwalt on July 11, 2016


Eighty million. That’s the number of germs exchanged in a kiss. Ten to two hundred million. That’s the number of germs that are found on an average cell phone.

What is a clean freak to do? How can we possibly combat all of those germs? This question comes from listener Geraldo in Brazil and I think it’s a great one. Does soap really kill 99.9% of germs?

**HOW DOES SOAP CLEAN?**

Remember that a germ is what we call any microscopic particle or organism that can make us sick, so this includes viruses and bacteria. Most of the gunk we want to wash off of our hands, whether it be dirt or germs, adheres to us thanks to the oils on our skin. Destroying the oil with a solvent like alcohol or kerosene will thus remove the associated germs.

However, although soaps used in hospitals are often strong, alcohol based versions, alcohol and kerosene are themselves toxic to varying degrees and thus not ideal for frequent in-home use. Imagine smelling like kerosene all day? Luckily, we have soap.

**Informed Opinions**

James Emerson, "I know that I know nothing." –Socrates

✉️ M.S. Organic Chemistry & Biophysical Chemistry

Updated Sep 16


Soap destroys the integrity of cell membranes, which consist of a lipid bilayer of polarized molecules.

Regular soap kills bacteria, fungi, protists (such as single-celled amoeba).

Regular soap is not expected to kill viruses because a virus is not a cell with cell membrane instead, they are obligate intracellular parasites which must infect a host which is a cell, or has cells.
Viruses have their RNA or DNA encapsulated in a protein coat. Some viruses can persist in their virulence (contagiousness) even on dry surfaces, for weeks or longer. Soap helps wash viruses off the hands.

The common cold is a virus, flu is a virus. The importance of hand washing for preventing viral infections is to wash the viruses off the hands, and down into the drain. Hand washing and bathing are top methods of preventing viral infection, by not eating food that dirty hands have touched, or preventing transfer of the virus from the hands to the eyes, nose, mouth, etc when touching them with the hands.

Antibacterial soap is a marketing trick which is not more effective than plain old Ivory soap.

- Antiseptic agents and disinfectants are over-used and contribute to increased bacterial resistance.
- Improper use of antibiotics (such as when people don’t finish all the pills simply because they feel better) allows for subtle genetic variations, mutations as resistant bacteria are allowed to reproduce. This sort of thing is considered as the main reason for the emergence of antibiotic resistance among pathogens, such as MRSA (methicillin resistant *Staphylococcus aureus*) and the growing antibiotic resistance of enterococcal bacteria.
  - These bacteria are not immune to soap killing them outside the body but are very difficult to treat once they’ve gained a foothold, as a person is infected.
- Sterile or disinfected environments have increasingly contributed to increases in the incidence of allergies in children, with the good intention of keeping their kids germ-free. The normal immune system, however, must be *primed* by gradual exposure to pathogens over time. Playing in the dirt is OK, mud is OK (in most places), and is necessary. Hookworm is a nasty parasitic infection and is endemic (common) in the US South but easily diagnosed (simple test) and easily cured (1-pill treatment). Please get tested if you go barefoot or without tall socks, ever.
- Living [constantly] in a sterile environment from infancy is *not* OK.

Soap is for external use. It is not intended to clean bacterially infected wounds because soap is not meant for internal use. One can use it to clean surface wounds like cuts or scrapes, shortly after the skin is damaged. Application of hydrogen peroxide, and covering the wound also work well, in preventing the wound from becoming infected.

The idea of putting antibacterial chemicals into soap is 1) unnecessary 2) falsely or misleadingly appealing while 3) providing little benefit and 4) is actually helping germs to develop resistance to the particular chemical which does not work better than soap, but only strengthens the bacteria who are merely exposed as low concentration.

The bacteria take a face punch, pause then ask with a crazy smile, “*is that all you got?*” and walk off only to pass their increasing immunity to their offspring.

“Antibacterial soap” marketing is a farce unless maybe such soaps were meant to clean garbage cans, toilet bowls. Yet most household cleaners already contain bleach or Lysol and kill bacteria dead, and unrelentingly, just like normal soap already does.

It is common to find that most soaps for sale contain benzalkonium chloride, soaps that do not contain this chemical (despite a lack of good reasoning for its presence) are less common.
Benzalkonium chloride, when used in concentration as a directed antiseptic agent, works well. In low concentrations, the reasoning for the production of benzene derived compounds on such massive scales, is specious.

This disinfectant at low concentration commonly found in antibacterial soaps is not necessary, is not worth the extra price, and not taking antibiotics as directed makes the problem of increasingly resistant bacteria more serious, more quickly, as rapidly reproducing bacterial generations evolve immunity.

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edit, 2/16/2019:

I was listening to NPR’s Science Friday on Feb 15, 2019 and the guest was Material Scientist and New York Times bestselling author of Stuff Matters, Mark Miodownik.


At the end of the interview, the author discussed the property of wetting, or how liquids interact with solids and he was then asked about his view of soap.

He mentioned that he didn’t see the benefits of using liquid soap as opposed to what used to be mostly bar-soap. To paraphrase, instead of using the manual movement of the hands to create lather with bar soap, liquid soap is so easily dispensed that too much, or twice as much volume is pumped out and which is also easily washed down the drain. (The link above is to the Feb. 15th show; it is a good interview).

Just as liquid pumped soap has become more inescapable as with soap with antibacterial disinfectant added, the takeaway for me:

- wet the hands with running water
- use half a pump which should be of sufficient volume while a full pump every time would lead to purchasing more soap sooner (I see what they did there -.- )
- wash the hands, generating lather (the more bubbles and manual motion, the better) with the same mechanical motions we’re used to with bar soap
- finally, rinse the hands under the running water, washing the bad down the drain

Thanks for reading
Containment

Dr. Julie Silver, Physician at Harvard Medical School quoting Dr. Reem Ghalib.

Dear Friends,

So much confusion, misinformation and denial is bouncing around on social media about the coronavirus that I thought I would try to explain, in plain language, why the experts see this as such an emergency.

You will see the claim online that this virus is a lot like the viruses that cause colds, and that if you get it, it will probably just seem like a bad cold and you are very unlikely to die. Depending on who you are, these statements are probably true. But they are incomplete, and the missing information is the key to understanding the problem.

This is a coronavirus that is new to the human population, jumping into people late last year from some kind of animal, probably at a wildlife market in Wuhan, China. It is related to the viruses that cause colds, and acts a lot like them in many ways. It is very easy to transmit through the respiratory droplets that all of us give off. But nobody has ever been exposed to this before, which means nobody has any immunity to it.

The virus is now moving explosively through the human population. While most people will recover, about 20 percent of the people who catch it will wind up with a serious disease. They will get pneumonia that causes shortness of breath, and they may need hospitalization.

Some of those people will get so sick that they cannot be saved and will die of the pneumonia. The overall death rate for people who develop symptoms seems to be 2 or 3 percent. Once we have enough testing to find out how many people caught the virus but did not develop symptoms, that might come down to about 1 percent, optimistically.

This is a large number. It is at least 10 times higher than the mortality rate for the seasonal flu, for instance, which in some years kills 60,000 or 70,000 Americans. So just on that math, we could be looking at 600,000 or 700,000 dead in the United States. But it gets worse.

Older people with existing health problems are much more vulnerable, on average. The mortality rate of coronavirus among people over age 80 may be 15 or 20 percent. It appears to have 7 or 8 percent mortality for people aged 70 to 79. Here is the terrible part: If you are a healthy younger person, you can catch the virus and, without developing serious symptoms yourself, you can pass it along to older people. In other words, as the virus spreads, it is going to be very easy to go out and catch it, give it to your grandmother and kill her, even though you will not die yourself. You can catch it by touching a door knob or an elevator button.

Scientists measure the spread of an epidemic by a number called R0, or “R naught.” That number is calculated this way: for every person who develops the illness, how many other people do they give it to before they are cured (or dead) and no longer infectious? The R0 for coronavirus, in the absence of a control strategy, appears to be a number close to 3 – maybe a bit higher or lower, but in that ballpark. This is an extremely frightening number for such a deadly disease.

Suppose you catch the virus. You will give it to 3 other people, and they will each give it to three others, and so forth. Here is how the math works, where you, the “index case,” are the first line:

1
3
9
27
81
243
729
2,187
6,561
19,683
59,046
177,147
531,441
1,594,323
4,782,969
14,348,907

So, in just 15 steps of transmission, the virus has gone from just one index case to 14.3 million other people. Those 15 steps might take only a few weeks. The index person may be young and healthy, but many of those 14 million people will be old and sick, and they will likely die because they got a virus that started in one person's throat.

The United States is not at this point yet, with millions infected, as best we can tell. We don't really know, because our government has failed us. We are many, many weeks behind other countries in rolling out widespread testing, so we don't really have a clue how far the thing has spread. We do know that cases are starting to pop up all over the place, with many of the people having no known exposure to travelers from China, so that means this virus has escaped into our communities.

We do not have approved treatments, yet. We do not have a vaccine. The only tool we really have now is to try to slow down the chain of transmission.

This can be done. In other words, R0 is not fixed – it can be lowered by control measures. If we can get the number below 1, the epidemic will die out. This is the point of the quarantines and the contact-tracing that you are hearing so much about in the news. But the virus is exploding so fast that we will not have the labor available to trace contacts for much longer, so we have to shift strategies. This has already begun, but we are not doing it fast enough.

It is now likely that the majority of Americans will get this virus. But slowing it down is still crucial. Why? Because the healthcare system has limited resources. We only have about a million hospital beds in America. We have well under a million ventilators. If millions of Americans get sick enough to need treatment, we will have a calamity on our hands. What will happen is a form of battlefield triage, where the doctors focus on trying to treat the young and allow the older people to die.

This is not theoretical. It is already happening in Italy, where people over 65 are being left alone on hospital gurneys to suffocate to death from pneumonia. They basically drown in their own sputum. There is simply not enough medical capacity to take care of them. The United States appears to be about two weeks behind Italy on the epidemic growth curve.

What do we need to do now? We need to cancel all large gatherings – all of them. You have probably seen that the N.B.A. has postponed the rest of its season. Other sporting events, concerts, plays and everything else involving large audiences in a small space – all of it needs to be canceled. Even if these events take place, do not go to them. No lectures, no plays, no movies, no cruises – nothing.

Stay at home as much as possible. Stay out of restaurants. I would cancel any travel that is not absolutely essential. Work from home if you possibly can. You may have to go buy groceries and medicine, of course, but make the trips quick and purposeful. Wash your hands assiduously.
after you have been in public places, for a full 20 seconds, soaping up thoroughly and being sure to get between the fingers. Sunlight and alcohol will kill the virus.

And please stop passing around statements on social media claiming that the situation is not serious or is being exaggerated. This is a national crisis, and conveying misinformation to your friends and family may put their lives in danger”
Why lockdowns can halt the spread of COVID-19


21 Mar 2020

Samantha Sault Writer, Washington DC and Geneva

The UK, US, EU and many other countries are currently in some degree of “lockdown,” with restaurants and bars, shops, schools and gyms closed, and citizens required, or at least strongly encouraged, to stay home to avoid catching or spreading COVID-19, the respiratory illness caused by the novel coronavirus.

Researchers are well on their way to discovering vaccines and treatments for the virus, but even in a best-case scenario, these are likely to be 12-18 months away.

Have you read?

- The whole of Italy is now in lockdown to battle COVID-19
- 3 perspectives on life after lockdown in Shanghai

Until then, extreme social distancing is pretty much the only intervention available to help individuals stay healthy, and to break the chain of transmission - giving more vulnerable populations a fighting chance of surviving this pandemic.

But how exactly does a lockdown work? And why is it important for even younger and healthier people, who face a lower risk of severe illness, to remain in their homes as much as possible?

The goal: R<1

The purpose of a lockdown, explains a new study from the Imperial College London COVID-19 Response Team, is to reduce reproduction – in other words, to reduce the number of people each confirmed case infects.

The goal is to keep reproduction, or “R,” below one (R<1) – with each case infecting fewer than one other person, on average.

The authors of the study say there are two routes to try to get there:

- Mitigation, “slowing but not necessarily stopping epidemic spread – reducing peak healthcare demand while protecting those most at risk of severe disease from infection.” This is done by isolating suspected cases and their households, and social distancing the elderly and people at highest risk of serious illness.
• **Suppression**, or basically, lockdown, which “aims to reverse epidemic growth, reducing case numbers to low levels” by social distancing the entire population “indefinitely” and closing schools and universities.

The study’s models show that, painful as lockdown may be for many of us, it works.

Without any lockdown or social distancing measures, we can expect peak mortality in approximately three months. In this scenario, 81% of the UK and US populations would be infected, with 510,000 dying in the UK and 2.2 million dying in the US.

![Figure 1: Unmitigated epidemic scenarios for GB and the US. (A) Projected deaths per day per 100,000 population in GB and US. (B) Case epidemic trajectories across the US by state.](image)

Projected COVID-19-related deaths in the UK and US without any interventions
Image: Imperial College London

In contrast, isolating confirmed and suspected cases and social distancing the elderly and vulnerable would “reduce peak critical care demand by two-thirds and halve the number of deaths.”
To get closer to the goal of R<1, they say, “a combination of case isolation, social distancing of the entire population and either household quarantine or school and university closure are required.”

The study finds this “intensive policy is predicted to result in a reduction in critical care requirements from a peak approximately three weeks after the interventions are introduced and a decline thereafter while the intervention policies remain in place.”

![Figure 2: Mitigation strategy scenarios for GB showing critical care (ICU) bed requirements. The black line shows the unmitigated epidemic. The green line shows a mitigation strategy incorporating closure of schools and universities; orange line shows case isolation; yellow line shows case isolation and household quarantine; and the blue line shows case isolation, home quarantine and social distancing of those aged over 70. The blue shading shows the 3-month period in which these interventions are assumed to remain in place.](Image: Imperial College London)

While the word “indefinitely” isn’t one we want to hear, it’s possible long-term suppression could be the best way to reduce infections and deaths – at least until a vaccine is available.

**What is the World Economic Forum doing about the coronavirus outbreak?**

**So, have the lockdowns worked?**

Starting 23 January 2020, the Chinese government locked down Hubei Province, including Wuhan, the city of 11 million where the outbreak started. They halted transportation in and out and barred tens of millions of people from working or going to school and closed all shops.
except those selling food or medicine. In some areas, residents were even forced to limit trips to
the store, or order supplies for delivery.

This unprecedented lockdown of tens of millions of people was considered a “vast experiment”
– but it may have worked. Following the lockdown, cases began to slow. On 19 March, China’s
National Health Commission [reported no new confirmed infections in Hubei].

**New cases in China have slowed**

Total confirmed cases of coronavirus in the country

![Graph showing the number of COVID-19 cases in China](image)

*Source: China National Health Commission, WHO, Updated: 10 Mar 06:00 GMT*  
*Following the lockdown, new COVID-19 cases in China slowed.*  
*Image: BBC*

Italy and Spain have been under similarly intense nationwide lockdowns, from 9 March
and 15 March, respectively, with citizens required to stay in their homes except for work,
food shopping or medical appointments.

In parts of Italy where lockdowns started earlier, however, we’re already seeing a
"flattening of the curve". Lodi, for example, locked down on 23 February, but Bergamo
did not lock down until 8 March. Now, cases seem to be leveling off in Lodi.
This week, both Italy and Spain reported their largest daily increases in COVID-19-related deaths. But if the lockdown models, hypothetical and real, are correct, the peaks could be approaching.
Visualizing the History of Pandemics

Published March 14, 2020 By Nicholas LePan
Source [https://www.visualcapitalist.com/history-of-pandemics-deadliest/](https://www.visualcapitalist.com/history-of-pandemics-deadliest/)

The History of Pandemics

Pan-dem-ic /panˈdemɪk/ (of a disease) prevalent over a whole country or the world.

As humans have spread across the world, so have infectious diseases. Even in this modern era, outbreaks are nearly constant, though not every outbreak reaches pandemic level as the Novel Coronavirus (COVID-19) has.

Today’s visualization outlines some of history’s most deadly pandemics, from the Antonine Plague to the current COVID-19 event.

A Timeline of Historical Pandemics

Disease and illnesses have plagued humanity since the earliest days, our mortal flaw. However, it was not until the marked shift to agrarian communities that the scale and spread of these diseases increased dramatically.

Widespread trade created new opportunities for human and animal interactions that sped up such epidemics. Malaria, tuberculosis, leprosy, influenza, smallpox, and others first appeared during these early years.

The more civilized humans became – with larger cities, more exotic trade routes, and increased contact with different populations of people, animals, and ecosystems – the more likely pandemics would occur.

Here are some of the major pandemics that have occurred over time:

<table>
<thead>
<tr>
<th>Name</th>
<th>Time period</th>
<th>Type / Pre-human host</th>
<th>Death toll</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonine Plague</td>
<td>165-180</td>
<td>Believed to be either smallpox or measles</td>
<td>5M</td>
</tr>
<tr>
<td>Japanese smallpox</td>
<td>735-737</td>
<td>Variola major virus</td>
<td>1M</td>
</tr>
<tr>
<td>epidemic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plague of Justinian</td>
<td>541-542</td>
<td>Yersinia pestis bacteria / Rats, fleas</td>
<td>30-50M</td>
</tr>
<tr>
<td>Black Death</td>
<td>1347-1351</td>
<td>Yersinia pestis bacteria / Rats, fleas</td>
<td>200M</td>
</tr>
<tr>
<td>New World Smallpox</td>
<td>1520 –</td>
<td>Variola major virus</td>
<td>56M</td>
</tr>
<tr>
<td>Name</td>
<td>Time period</td>
<td>Type / Pre-human host</td>
<td>Death toll</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>------------------------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Outbreak</td>
<td>onwards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Great Plague of London</td>
<td>1665</td>
<td>Yersinia pestis bacteria / Rats, fleas</td>
<td>100,000</td>
</tr>
<tr>
<td>Italian plague</td>
<td>1629-1631</td>
<td>Yersinia pestis bacteria / Rats, fleas</td>
<td>1M</td>
</tr>
<tr>
<td>Cholera Pandemics 1-6</td>
<td>1817-1923</td>
<td>V. cholerae bacteria</td>
<td>1M+</td>
</tr>
<tr>
<td>Third Plague</td>
<td>1885</td>
<td>Yersinia pestis bacteria / Rats, fleas</td>
<td>12M (China and India)</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Late 1800s</td>
<td>Virus / Mosquitoes</td>
<td>100,000-150,000 (U.S.)</td>
</tr>
<tr>
<td>Russian Flu</td>
<td>1889-1890</td>
<td>Believed to be H2N2 (avian origin)</td>
<td>1M</td>
</tr>
<tr>
<td>Spanish Flu</td>
<td>1918-1919</td>
<td>H1N1 virus / Pigs</td>
<td>40-50M</td>
</tr>
<tr>
<td>Asian Flu</td>
<td>1957-1958</td>
<td>H2N2 virus</td>
<td>1.1M</td>
</tr>
<tr>
<td>Hong Kong Flu</td>
<td>1968-1970</td>
<td>H3N2 virus</td>
<td>1M</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1981-present</td>
<td>Virus / Chimpanzees</td>
<td>25-35M</td>
</tr>
<tr>
<td>Swine Flu</td>
<td>2009-2010</td>
<td>H1N1 virus / Pigs</td>
<td>200,000</td>
</tr>
<tr>
<td>SARS</td>
<td>2002-2003</td>
<td>Coronavirus / Bats, Civets</td>
<td>770</td>
</tr>
<tr>
<td>Ebola</td>
<td>2014-2016</td>
<td>Ebolavirus / Wild animals</td>
<td>11,000</td>
</tr>
<tr>
<td>MERS</td>
<td>2015-Present</td>
<td>Coronavirus / Bats, camels</td>
<td>850</td>
</tr>
<tr>
<td>COVID-19</td>
<td>2019-Present</td>
<td>Coronavirus – Unknown (possibly pangolins)</td>
<td>9,800 (as of Mar 19, 2020)</td>
</tr>
</tbody>
</table>

*Note: Many of the death toll numbers listed above are best estimates based on available research. Some, such as the Plague of Justinian, are subject to debate based on new evidence.*

But the lesson is clear: pandemics will happen again in the near future, so we might as well learn as much as we can from the current one and prepare ourselves to be better prepared for the next one.
HISTORY OF PANDEMICS

Throughout history, as humans spread across the world, infectious diseases have been a constant companion. Even in this modern era, outbreaks are nearly constant.

Here are some of history’s most deadly pandemics, from the Antonine Plague to COVID-19.

200M
Black Death (Bubonic Plague)

The plague originated in rats and spread to humans via infected fleas.

The outbreak wiped out 30-50% of Europe’s population. It took more than 200 years for the continent’s population to recover.

Smallpox killed an estimated 90% of Native Americans. In Europe during the 1600s, an estimated 400,000,000 people were being killed by smallpox annually. The first ever vaccine was created to ward off smallpox.

The death toll of this plague is still under debate as new evidence is uncovered, but many think it may have helped hasten the fall of the Roman Empire.

A series of Cholera outbreaks spread around the world in the 1800s killing millions of people. There is no solid consensus on death tolls.

COVID-19
2020

Sources:
CDC, WHO, NIAID, Wikipedia, Historical accounts, Encyclopedia Britannica

VISUAL CAPITALIST
www.visualcapitalist.com

THROUGHOUT HISTORY,

Antonine Plague
165 - 180

Plague of Justinian
150 - 162

Japanese Smallpox Epidemic
155 - 157

Bubonic Plague
1300 - 1500

Black Death
1347 - 1351

Smallpox
1565 - 1620

17th Century Great Plagues
1665 - 1666

18th Century Great Plagues
1701 - 1700

Cholera 1 outbreak
1801 - 1825

The Third Plague
1850 - 1860

Yellow Fever
1900 - 1900

HIV/AIDS
1981 - PRESENT

SARS
2003 - 2004

Swine Flu
2009 - 2010

Ebola
2014 - 2015

Asian Flu
1918 - 1919

Spanish Flu
1918 - 1919

Russian Flu
1918 - 1924

Hong Kong Flu
1968 - 1969

COVID-19
2020 - 2021

[High to Lowest]

DEATH TOLL

THE OUTBREAKS

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COVID-19
2020 - 2021

[High to Lowest]
For those who aced Biology

This next section is your scientific deep dive into this totally simple but deadly lifeform…
Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus

Susan R. Weiss¹ and Sonia Navas-Martin²

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1306801/

FIG. 1.

Coronavirus virion. (A) Electron micrograph of MHV particles. (B) Schematic of virion. Viral particles contain an internal helical RNA-protein nucleocapsid surrounded by an envelope containing viral glycoproteins. Nucleocapsid (N) protein is a phosphoprotein that is complexed with genome RNA to form the nucleocapsid. Spike glycoprotein (S) forms the large glycosylated peplomers that are characteristic of coronaviruses. M, the transmembrane protein, is highly hydrophobic and spans the membrane three times. E, a membrane-spanning protein, is a minor component of the membrane. Some group II viruses express another glycoprotein, hemagglutinin-esterase (HE), which forms smaller spikes on virions.

VIRAL LIFE CYCLE

We will briefly summarize the coronavirus life cycle (Fig. 1); this is not designed to be a comprehensive review, but rather to provide a context for discussion (below) of the functions of various viral proteins. Coronaviruses attach to specific cellular receptors via the spike protein (Table 1); this triggers a conformational change in spike which then mediates fusion between the viral and cell membranes which results in the release of the nucleocapsid into the cell (Fig. 3). Upon entry into the cell, the 5′ end of the genome RNA, ORFs 1a and 1b, are translated into pp1a and pp1ab; pp1ab is translated via a frameshift mechanism, which occurs at high frequency (25 to 30%) (25, 27). ORF 1a encodes one or two papain-like proteases (PLpro or PLP) and a picornavirus 3C-like protease (3CLpro), which function to process pp1a and pp1ab into the mature replicase proteins (178, 379; reviewed in reference 378). Also, encoded in
the X domain of ORF 1a is a (putative) ADP-ribose 1'-phosphatase activity (287, 378). Encoded in ORF 1b and processed from pp1ab are an RNA-dependent RNA polymerase (RdRp) and a helicase (116), as well as other enzymatic activities, including a (putative) 3'-to-5' exonuclease (ExoN), poly(U)-specific endoribonuclease (XendoU), and (putative) S-adenosylmethionine-dependent ribose 2'-O-methyltransferase (144, 287, 378). An additional putative enzymatic activity, cyclic phosphodiesterase, is encoded downstream in ORF 2a. These multiple enzymatic activities are speculated to play roles in metabolism of coronavirus RNA and/or in interfering with host cell processes (378).

FIG. 3.

Model of coronavirus replication. After receptor interaction and fusion of viral and plasma membranes, virus-specific RNA and proteins are synthesized, probably entirely in the cytoplasm. Expression of coronaviruses starts with translation of two polyproteins, pp1a and pp1ab, which undergo cotranslational proteolytic processing into the proteins that form the replicase complex. This complex is used to transcribe a 3′-coterminal set of nested subgenomic mRNAs, as well as genomic RNA, that have a common 5′ “leader” sequence derived from the 5′ end of the genome. Proteins are translated from the 5′ end of each mRNA. New virions are assembled by budding into intracellular membranes and released through vesicles by the cell secretory mechanisms. RER, rough endoplasmic reticulum; ER/GIC, endoplasmic reticulum/Golgi intermediate compartment.

During infection with coronaviruses, as with all other RNA viruses, replication of genome and transcription of mRNAs must occur. Replication of the genome involves the synthesis of a full-length negative-strand RNA that is present at a low concentration and serves as template for full-length genomic RNA. Multiple (six in the case of MHV) overlapping 3′-coterminal subgenomic
RNAs serve as mRNAs, as does full-length genomic RNA. Each mRNA has a common (75- to 78-nucleotide) leader sequence at its 5′ end; this leader is derived from the 5′ end of genome RNA (170, 283). In addition, negative-strand RNAs corresponding in length to each of the mRNAs as well as the full genomic length are present at low concentrations (26). The mechanism by which the group of positive- and negative-strand RNAs are synthesized involves a unique discontinuous transcription mechanism that is not completely understood. However, subgenomic mRNA synthesis is believed to be regulated by transcription-regulating sequences, present in the genome RNA, at the transcriptional start sites for each mRNA (171). The current model is that discontinuous transcription occurs during the synthesis of subgenomic negative-strand RNAs, with the antileader sequences being added onto the 3′ ends of negative-strand RNAs which then serve as templates for synthesis of mRNAs (90). Viral proteins are translated from individual mRNAs, generally from the 5′ ORF only (Fig. 3). The replicase, for example, is translated from the 5′ end of the genomic RNA. In some cases there may be two ORFs carried on and translated from one mRNA. An example of this is the E protein of MHV, which is translated from a downstream ORF (ORF 5b) on mRNA 5; it is believed that the translation of ORF 5b is mediated by an internal ribosome internal entry site (146). After translation, the M and E membrane proteins are localized to the Golgi intracellular membranes near, but just beyond, the endoplasmic reticulum Golgi intermediate compartment, which is believed to be the actual site of budding (154). Thus, in addition to M, other viral and/or cellular factors are probably required to determine the site of budding. M and E proteins, expressed in the absence of other viral proteins and viral RNA, are sufficient to produce virus-like particles (62, 63, 154, 160). The spike protein is distributed on intracellular membranes as well as the plasma membrane. The spike protein interacts with the transmembrane region of the M protein during assembly (74). For some viruses, spike-mediated cell-to-cell fusion occurs, thus promoting syncytium formation and viral spread. Nucleocapsid protein complexes with genome RNA, forming helical structures. The N protein interacts with the M protein (167), and budding into vesicles occurs. Virus is then transported to the cell surface, where it leaves the cell. Interestingly, TGEV and MHV appeared to exit epithelial cells from opposite sides. When the two viruses are used to experimentally infect the same cells, porcine epithelial cells (expressing MHV receptor), TGEV is released preferentially at the apical membrane, while MHV is released preferentially at the basolateral surface, suggesting that vesicles containing the two coronaviruses are targeted differently (266). This suggests that the two viruses are sorted at the Golgi into different transport vesicles carrying information directing them to different surfaces. Thus, the difference in site of release may contribute to the difference in virus spread found between TGEV and MHV. TGEV causes a localized enteric infection, while MHV spreads to multiple organs.
Coronaviruses: An Overview of Their Replication and Pathogenesis

Anthony R. Fehr and Stanley Perlman

Abstract

Classification

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, and Roniviridae families. The Coronavirinae comprise one of two subfamilies in the Coronaviridae family, with the other being the Torovirinae. The Coronavirinae are further subdivided into four groups, the alpha, beta, gamma and delta coronaviruses. The viruses were initially sorted into these groups based on serology but are now divided by phylogenetic clustering.

All viruses in the Nidovirales order are enveloped, non-segmented positive-sense RNA viruses. They all contain very large genomes for RNA viruses, with Coronavirinae having the largest identified RNA genomes, containing approximately 30 kilobase (kb) genomes. Other common features within the Nidovirales order include: i) a highly conserved genomic organization, with a large replicase gene preceding structural and accessory genes; ii) expression of many nonstructural genes by ribosomal frameshifting; iii) several unique or unusual enzymatic activities encoded within the large replicase-transcriptase polyprotein; and iv) expression of downstream genes by synthesis of 3′ nested sub-genomic mRNAs. In fact, the Nidovirales order name is derived from these nested 3′ mRNAs as nido is Latin for “nest”. The major differences within the Nidovirus families are in the number, type, and sizes of the structural proteins. These differences cause significant alterations in the structure and morphology of the nucleocapsids and virions.
Genomic Organization

As previously mentioned, coronaviruses contain a non-segmented, positive-sense RNA genome of ~30 kb. The genome contains a 5′ cap structure along with a 3′ poly (A) tail, allowing it to act as a mRNA for translation of the replicase polyproteins. The replicase gene encoding the nonstructural proteins (Nsps) occupies two-thirds of the genome, about 20 kb, as opposed to the structural and accessory proteins, which make up only about 10 kb of the viral genome. The 5′ end of the genome contains a leader sequence and untranslated region (UTR) that contains multiple stem loop structures required for RNA replication and transcription. Additionally, at the beginning of each structural or accessory gene are transcriptional regulatory sequences (TRSSs) that are required for expression of each of these genes (see section on RNA replication). The 3′UTR also contains RNA structures required for replication and synthesis of viral RNA. The organization of the coronavirus genome is 5′-leader-UTR-replicase-S (Spike)—E (Envelope)-M (Membrane)-N (Nucleocapsid)-3′UTR-poly (A) tail with accessory genes interspersed within the structural genes at the 3′ end of the genome (Fig. 1). The accessory proteins are almost exclusively non-essential for replication in tissue culture; however some have been shown to have important roles in viral pathogenesis [1].

**Figure 1**
Genomic Orientation of Representative α, β, and γ CoVs

An illustration of the MHV genome is depicted on top. The expanded regions below show the structural and accessory proteins in the 3′ regions of the MHV, SARS-CoV, and MERS-CoV. Size of the genome and individual genes are approximated using the legend at the top of the diagram but are not drawn to scale. HCoV-229E, human coronavirus 229E; MHV, mouse hepatitis virus; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; IBV, infectious bronchitis virus.
Virion Structure

Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy [2,3]. The most prominent feature of coronaviruses is the club-shape spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the virion is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses.

Coronavirus virus particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome. The S protein (~150 kDa), utilizes an N-terminal signal sequence to gain access to the ER, and is heavily N-linked glycosylated. Homotrimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus [4,5]. The trimeric S glycoprotein is a class I fusion protein [6] and mediates attachment to the host receptor [7]. In most, but not all, coronaviruses, S is cleaved by a host cell furin-like protease into two separate polypeptides noted S1 and S2 [8,9]. S1 makes up the large receptor-binding domain of the S protein while S2 forms the stalk of the spike molecule [10].

The M protein is the most abundant structural protein in the virion. It is a small (~25–30 kDa) protein with 3 transmembrane domains [11] and is thought to give the virion its shape. It has a small N-terminal glycosylated ectodomain and a much larger C-terminal endodomain that extends 6–8 nm into the viral particle [12]. Despite being co-translationally inserted in the ER membrane, most M proteins do not contain a signal sequence. Recent studies suggest the M protein exists as a dimer in the virion, and may adopt two different conformations allowing it to promote membrane curvature as well as bind to the nucleocapsid [13].

The E protein (~8–12 kDa) is found in small quantities within the virion. E protein from coronaviruses are highly divergent but have a common architecture [14]. The membrane topology of E protein is not completely resolved but most data suggest that it is a transmembrane protein. The E protein has a N-terminal ectodomain and a C-terminal endodomain and has ion channel activity. As opposed to other structural proteins, recombinant viruses lacking the E protein are not always lethal although this is virus type dependent [15]. The E protein facilitates assembly and release of the virus (see section on Assembly and Release of Coronaviruses), but also has other functions. For instance, the ion channel activity in SARS-CoV E protein is not required for viral replication but is required for pathogenesis [16].

The N protein constitutes the only protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA in vitro, but each domain uses different mechanisms to bind RNA. It has been suggested that optimal RNA binding requires contributions from both domains [17,18]. N protein is also heavily phosphorylated [19], and phosphorylation has been suggested to trigger a structural change enhancing the affinity for viral versus non-viral RNA. N protein binds the viral genome in a beads-on-a-string type conformation. Two specific RNA substrates have been identified for N protein; the TRSs [20] and the genomic packaging signal [21]. The genomic packaging signal has been found to bind specifically to the second, or C-terminal RNA binding domain [22]. N protein also binds nsp3 [18,23], a key component of the replicase complex, and
the M protein [24]. These protein interactions likely help tether the viral genome to the replicase-transcriptase complex (RTC), and subsequently package the encapsidated genome into viral particles.

A fifth structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coronaviruses. The protein acts as a hemagglutinin, binds sialic acids on surface glycoproteins and contains acetyl-esterase activity [25]. These activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa [26]. Interestingly, HE enhances murine hepatitis virus (MHV) neurovirulence [27]; however, it is selected against in tissue culture for unknown reasons [28].

**Coronavirus Life Cycle**

**Attachment and Entry**

The initial attachment of the virion to the host cell is initiated by interactions between the S protein and its receptor. The sites of receptor binding domains (RBD) within the S1 region of a coronavirus S protein vary depending on the virus, with some having the RBD at the N-terminus of S1 (MHV) while others (SARS-CoV) have the RBD at the C-terminus of S1 [29,30]. The S-protein/receptor interaction is the primary determinant for a coronavirus to infect a host species and also governs the tissue tropism of the virus. Many coronaviruses utilize peptidases as their cellular receptor. It is unclear why peptidases are used, as entry occurs even in the absence of the enzymatic domain of these proteins. Many α-coronaviruses utilize aminopeptidase N (APN) as their receptor, SARS-CoV and HCoV-NL63 use angiotensin-converting enzyme 2 (ACE2) as their receptor, MHV enters through CEACAM1, and the recently identified MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) to gain entry into human cells (See Table 1 for a list of known CoV receptors).

**Table 1**

Coronavirus Receptors

<table>
<thead>
<tr>
<th>Virus</th>
<th>Receptor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphacoronaviruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCoV-229E</td>
<td>APN</td>
<td>[115]</td>
</tr>
<tr>
<td>HCoV-NL63</td>
<td>ACE2</td>
<td>[116]</td>
</tr>
<tr>
<td>Virus</td>
<td>Receptor</td>
<td>References</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>TGEV</td>
<td>APN</td>
<td>[117]</td>
</tr>
<tr>
<td>PEDV</td>
<td>APN</td>
<td>[118]</td>
</tr>
<tr>
<td>FIPV</td>
<td>APN</td>
<td>[119]</td>
</tr>
<tr>
<td>CCoV</td>
<td>APN</td>
<td>[120]</td>
</tr>
<tr>
<td>Betacoronaviruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MHV</td>
<td>mCEACAM</td>
<td>[121,122]</td>
</tr>
<tr>
<td>BCoV</td>
<td>N-acetyl-9-O-acetyleneuraminic acid</td>
<td>[123]</td>
</tr>
<tr>
<td>SARS-CoV</td>
<td>ACE2</td>
<td>[124]</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>DPP4</td>
<td>[100]</td>
</tr>
</tbody>
</table>

APN, aminopeptidase N; ACE2, angiotensin-converting enzyme 2; mCEACAM, murine carcinoembryonic antigen-related adhesion molecule 1; DPP4, dipeptidyl peptidase 4; HCoV, human coronavirus; TGEV, transmissible gastroenteritis virus; PEDV, porcine epidemic diarrhea virus; FIPV, feline infectious peritonitis virus; CCoV, canine coronavirus; MHV, murine hepatitis virus; BCoV, bovine coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus.
Following receptor binding, the virus must next gain access to the host cell cytosol. This is generally accomplished by acid-dependent proteolytic cleavage of S protein by a cathepsin, TMPRSS2 or another protease, followed by fusion of the viral and cellular membranes. S protein cleavage occurs at two sites within the S2 portion of the protein, with the first cleavage important for separating the RBD and fusion domains of the S protein and the second for exposing the fusion peptide (cleavage at S2'). Fusion generally occurs within acidified endosomes, but some coronaviruses, such as MHV, can fuse at the plasma membrane. Cleavage at S2' exposes a fusion peptide that inserts into the membrane, which is followed by joining of two heptad repeats in S2 forming an antiparallel six-helix bundle. The formation of this bundle allows for the mixing of viral and cellular membranes, resulting in fusion and ultimately release of the viral genome into the cytoplasm.

**Replicase Protein Expression**

The next step in the coronavirus lifecycle is the translation of the replicase gene from the virion genomic RNA. The replicase gene encodes two large ORFs, rep1a and rep1b, which express two co-terminal polyproteins, pp1a and pp1ab. In order to express both polyproteins, the virus utilizes a slippery sequence (5’-UUUAAAC-3’) and an RNA pseudoknot that cause ribosomal frameshifting from the rep1a reading frame into the rep1b ORF. In most cases, the ribosome unwinds the pseudoknot structure, and continues translation until it encounters the rep1a stop codon. Occasionally the pseudoknot blocks the ribosome from continuing elongation, causing it to pause on the slippery sequence, changing the reading frame by moving back one nucleotide, −1 frameshift, before the ribosome is able to melt the pseudoknot structure and extend translation into rep1b, resulting in the translation of pp1ab. *In vitro* studies predict the incidence of ribosomal frameshifting to be as high as 25%, but this has not been determined in the context of virus infection. It is unknown exactly why these viruses utilize frameshifting to control protein expression, but it is hypothesized to either control the precise ratio of rep1b:rep1a proteins or delay the production of rep1b products until the products of rep1a have created a suitable environment for RNA replication.

Polyproteins pp1a and pp1ab contain the nsps 1–11 and 1–16, respectively. In pp1ab, nsp11 from pp1a becomes nsp12 following extension of pp1a into pp1b. However γ-coronaviruses do not contain a comparable nsp1. These polyproteins are subsequently cleaved into the individual nsps. Coronaviruses encode either two or three proteases that cleave the replicase polyproteins. They are the papain-like proteases (PLpro), encoded within nsp3, and a serine type protease, the main protease, or Mpro, encoded by nsp5. Most coronaviruses encode two PLpros within nsp3, except the γ-coronaviruses, SARS-CoV and MERS-CoV, which only express one PLpro. The PLpros cleave the nsp1/2, nsp2/3, and nsp3/4 boundaries while the Mpro is responsible for the remaining 11 cleavage events.

Next, many of the nsps assemble into the replicase-transcriptase complex (RTC) to create an environment suitable for RNA synthesis, and ultimately are responsible for RNA replication and transcription of the sub-genomic RNAs. The nsps also contain other enzyme domains and functions, including those important for RNA replication, for example nsp12 encodes the RNA-dependent RNA polymerase (RdRp) domain; nsp13 encodes the RNA helicase domain and RNA 5’-triphosphatase activity; nsp14 encodes the exoribonuclease (ExoN) involved in replication fidelity and N7-methyltransferase activity; and nsp16 encodes 2′-O-methyltransferase activity. In
addition to the replication functions other activities, such as blocking innate immune responses (nsp1; nsp16-2′-O-methyl transferase; nsp3-deubiquitinase) have been identified for some of the nsps, with other largely unknown functions (nsp3-ADP-ribose-1″-phosphatase; nsp15-endoribonuclease (NendoU)) also identified. For a list of non-structural proteins and their proposed functions, see Table 2. Interestingly, ribonucleases nsp15-NendoU and nsp14-ExoN activities are unique to the Nidovirales order and are considered genetic markers for these viruses [37].

Table 2

Functions of coronavirus non-structural proteins (nsps)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>nsp1</td>
<td>Promotes cellular mRNA degradation and blocks host cell translation, results in blocking innate immune response</td>
<td>[125–128]</td>
</tr>
<tr>
<td>nsp2</td>
<td>No known function, binds to prohibitin proteins</td>
<td>[129,130]</td>
</tr>
<tr>
<td>nsp3</td>
<td>Large, multi-domain transmembrane protein, activities include: • Ubl1 and Ac domains, interact with N protein • ADRP activity, promotes cytokine expression • PLPro/Deubiquitinase domain, cleaves viral polyprotein and blocks host innate immune response • Ubl2, NAB, G2M, SUD, Y domains, unknown functions</td>
<td>[131–138]</td>
</tr>
<tr>
<td>nsp4</td>
<td>Potential transmembrane scaffold protein, important for proper structure of DMVs</td>
<td>[139,140]</td>
</tr>
<tr>
<td>nsp5</td>
<td>Mpro, cleaves viral polyprotein</td>
<td>[141]</td>
</tr>
<tr>
<td>Protein</td>
<td>Function</td>
<td>Reference</td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>nsp6</td>
<td>Potential transmembrane scaffold protein</td>
<td>[142]</td>
</tr>
<tr>
<td>nsp7</td>
<td>Forms hexadecameric complex with nsp8, may act as processivity clamp for RNA polymerase</td>
<td>[143]</td>
</tr>
<tr>
<td>nsp8</td>
<td>Forms hexadecameric complex with nsp7, may act as processivity clamp for RNA polymerase; may act as primase</td>
<td>[143,144]</td>
</tr>
<tr>
<td>nsp9</td>
<td>RNA binding protein</td>
<td>[145]</td>
</tr>
<tr>
<td>nsp10</td>
<td>Cofactor for nsp16 and nsp14, forms heterodimer with both and stimulates ExoN and 2-O-MT activity</td>
<td>[146,147]</td>
</tr>
<tr>
<td>nsp12</td>
<td>RdRp</td>
<td>[148]</td>
</tr>
<tr>
<td>nsp13</td>
<td>RNA helicase, 5′ triphosphatase</td>
<td>[149,150]</td>
</tr>
<tr>
<td>nsp14</td>
<td>N7 MTase) and 3′-5′ exoribonuclease, ExoN; N7 MTase adds 5′ cap to viral RNAs, ExoN activity is important for proofreading of viral genome</td>
<td>[151–154]</td>
</tr>
<tr>
<td>nsp15</td>
<td>Viral endoribonuclease, NendoU</td>
<td>[155,156]</td>
</tr>
<tr>
<td>nsp16</td>
<td>2′-O-MT; shields viral RNA from MDA5 recognition</td>
<td>[157,158]</td>
</tr>
</tbody>
</table>

Replication and Transcription

Viral RNA synthesis follows the translation and assembly of the viral replicase complexes. Viral RNA synthesis produces both genomic and sub-genomic RNAs. Sub-genomic RNAs serve as mRNAs for the structural and accessory genes which reside downstream of the replicase polyproteins. All positive-sense sub-genomic RNAs are 3′ co-terminal with the full-length viral genome and thus form a set of nested RNAs, a distinctive property of the order Nidovirales. Both genomic and sub-genomic RNAs are produced through negative-strand intermediates. These negative-strand intermediates are only about 1% as abundant as their positive-sense counterparts and contain both poly-uridylate and anti-leader sequences [38].
Many cis-acting sequences are important for the replication of viral RNAs. Within the 5′ UTR of the genome are seven stem-loop structures that may extend into the replicase 1a gene [39–42]. The 3′ UTR contains a bulged stem-loop, a pseudoknot, and a hypervariable region [43–46]. Interestingly, the stem-loop and the pseudoknot at the 3′ end overlap, and thus cannot form simultaneously [44,47]. Therefore, these different structures are proposed to regulate alternate stages of RNA synthesis, although exactly which stages are regulated and their precise mechanism of action are still unknown.

Perhaps the most novel aspect of coronavirus replication is how the leader and body TRS segments fuse during production of sub-genomic RNAs. This was originally thought to occur during positive-strand synthesis, but now it is largely believed to occur during the discontinuous extension of negative-strand RNA [48]. The current model proposes that the RdRp pauses at any one of the body TRS sequences (TRS-B); following this pause the RdRp either continues elongation to the next TRS or it switches to amplifying the leader sequence at the 5′ end of the genome guided by complementarity of the TRS-B to the leader TRS (TRS-L). Many pieces of evidence currently support this model, including the presence of anti-leader sequence at the 3′ end of the negative-strand sub-genomic RNAs [38]. However, many questions remain to fully define the model. For instance, how does the RdRp bypass all of the TRS-B sequences to produce full-length negative-strand genomic RNA? Also, how are the TRS-B sequences directed to the TRS-L and how much complementarity is necessary [49]? Answers to these questions and others will be necessary to gain a full perspective of how RNA replication occurs in coronaviruses.

Finally, coronaviruses are also known for their ability to recombine using both homologous and non-homologous recombination [50,51]. The ability of these viruses to recombine is tied to the strand switching ability of the RdRp. Recombination likely plays a prominent role in viral evolution and is the basis for targeted RNA recombination, a reverse genetics tool used to engineer viral recombinants at the 3′ end of the genome.

Assembly and Release

Following replication and subgenomic RNA synthesis, the viral structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum (ER). These proteins move along the secretory pathway into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [52,53]. There, viral genomes encapsidated by N protein bud into membranes of the ERGIC containing viral structural proteins, forming mature virions [54].

The M protein directs most protein-protein interactions required for assembly of coronaviruses. However, M protein is not sufficient for virion formation, as virus-like particles (VLPs) cannot be formed by M protein expression alone. However, when M protein is expressed along with E protein VLPs are formed, suggesting these two proteins function together to produce coronavirus envelopes [55]. N protein enhances VLP formation, suggesting that fusion of encapsidated genomes into the ERGIC enhances viral envelopment [56]. The S protein is incorporated into virions at this step, but is not required for assembly. The ability of the S protein to traffic to the ERGIC and interact with the M protein is critical for its incorporation into virions.

While the M protein is relatively abundant, the E protein is only present in small quantities in the virion. Thus, it is likely that M protein interactions provide the impetus for envelope maturation.
It is unknown how E protein assists M protein in assembly of the virion, and several possibilities have been suggested. Some work has indicated a role for the E protein in inducing membrane curvature [57–59], although others have suggested that E protein prevents the aggregation of M protein [60]. The E protein may also have a separate role in promoting viral release by altering the host secretory pathway [61].

The M protein also binds to the nucleocapsid, and this interaction promotes the completion of virion assembly. These interactions have been mapped to the C-terminus of the endodomain of M with CTD 3 of the N-protein [62]. However, it is unclear exactly how the nucleocapsid complexed with virion RNA traffics to the ERGIC to interact with M protein and become incorporated into the viral envelope. Another outstanding question is how the N protein selectively packages only positive-sense full-length genomes among the many different RNA species produced during infection. A packaging signal for MHV has been identified in the nsp15 coding sequence, but mutation of this signal does not appear to affect virus production, and a mechanism for how this packaging signal works has not been determined [22]. Furthermore, most coronaviruses do not contain similar sequences at this locus, indicating that packaging may be virus specific.

Following assembly, virions are transported to the cell surface in vesicles and released by exocytosis. It is not known if the virions use the traditional pathway for transport of large cargo from the Golgi or if the virus has diverted a separate, unique pathway for its own exit. In several coronaviruses, S protein that does not get assembled into virions transits to the cell surface where it mediates cell-cell fusion between infected cells and adjacent, uninfected cells. This leads to the formation of giant, multinucleated cells, which allows the virus to spread within an infected organism without being detected or neutralized by virus-specific antibodies.

Go to: Pathogenesis

Animal Coronaviruses

Coronaviruses cause a large variety of diseases in animals, and their ability to cause severe disease in livestock and companion animals such as pigs, cows, chickens, dogs and cats led to significant research on these viruses in the last half of the 20th century. For instance, Transmissible Gastroenteritis Virus (TGEV) and Porcine Epidemic Diarrhea Virus (PEDV) cause severe gastroenteritis in young piglets, leading to significant morbidity, mortality, and ultimately economic losses. PEDV recently emerged in North America for the first time, causing significant losses of young piglets. Porcine hemagglutinating encephalomyelitis virus (PHEV) mostly leads to enteric infection but has the ability to infect the nervous system, causing encephalitis, vomiting and wasting in pigs. Feline enteric coronavirus (FCoV) causes a mild or asymptomatic infection in domestic cats, but during persistent infection, mutation transforms the virus into a highly virulent strain of FCoV (Feline Infectious Peritonitis Virus, FIPV), that leads to development of a lethal disease called feline infectious peritonitis (FIP). FIP has wet and dry forms, with similarities to the human disease, sarcoidosis. FIPV is macrophage tropic and it is believed that it causes aberrant cytokine and/or chemokine expression and lymphocyte depletion, resulting in lethal disease [63]. However additional research is needed to confirm this hypothesis. Bovine CoV, Rat CoV, and Infectious Bronchitis Virus (IBV) cause mild to severe respiratory
tract infections in cattle, rats, and chickens, respectively. Bovine CoV causes significant losses in the cattle industry and also has spread to infect a variety of ruminants, including elk, deer and camels. In addition to severe respiratory disease, the virus causes diarrhoea (‘winter dysentery’ and ‘shipping fever’), all leading to weight loss, dehydration, decreased milk production, and depression [63]. Some strains of IBV, a γ-coronavirus, also affect the uro-genital tract of chickens causing renal disease. IBV significantly diminishes egg production and weight gain, causing substantial losses in the chicken industry each year [63]. More recently, a novel coronavirus named SW1 was identified in a deceased Beluga whale [64]. Large numbers of virus particles were identified in the liver of the deceased whale with respiratory disease and acute liver failure. Although, electron microscopic images were not sufficient to identify the virus as a coronavirus, sequencing of the liver tissue clearly identified the virus as a coronavirus. It was subsequently determined to be a γ-coronavirus based on phylogenetic analysis but it has not yet been verified experimentally that this virus is actually a causative agent of disease in whales. In addition, there has been intense interest in identifying novel bat CoVs, since these are the likely ultimate source for SARS-CoV and MERS-CoV, and hundreds of novel bat coronaviruses have been identified over the past decade [65]. Finally, another novel group of nidoviruses, *Mesoniviridae*, were recently identified as the first nidoviruses to exclusively infect insect hosts [66,67]. These viruses are highly divergent from other nidoviruses but are most closely related to the roniviruses. In size, they are ~20 kb, falling in between large and small nidoviruses. Interestingly, these viruses do not encode for an endoribonuclease, which is present in all other nidoviruses. These attributes suggest these viruses are the prototype of a new nidovirus family and may be a missing link in the transition from small to large nidoviruses.

The most heavily studied animal coronavirus is murine hepatitis virus (MHV), which causes a variety of outcomes in mice, including respiratory, enteric, hepatic, and neurologic infections. These infections often serve as highly useful models of disease. For instance, MHV-1 causes severe respiratory disease in susceptible A/J and C3H/HeJ mice, A59 and MHV-3 induce severe hepatitis, while JHMV causes severe encephalitis. Interestingly, MHV-3 induces cellular injury through the activation of the coagulation cascade [68]. Most notably, A59 and attenuated versions of JHMV cause a chronic demyelinating disease that bears similarities to multiple sclerosis (MS), making MHV infection one of the best models for this debilitating human disease. Early studies suggested that demyelination was dependent on viral replication in oligodendrocytes in the brain and spinal cord [69,70]; however, more recent reports clearly demonstrate that the disease is immune-mediated. Irradiated mice or immunodeficient (lacking T and B cells) mice do not develop demyelination, but addition of virus-specific T cells restores the development of demyelination [71,72]. Additionally, demyelination is accompanied by a large influx of macrophages and microglia that can phagocytose infected myelin [73], although it is unknown what the signals are that direct immune cells to destroy myelin. Finally, MHV can be studied under BSL2 laboratory conditions, unlike SARS-CoV or MERS-CoV, which require a BSL3 laboratory, and provides a large number of suitable animal models. These factors make MHV an ideal model for studying the basics of viral replication in tissue culture cells as well as for studying the pathogenesis and immune response to coronaviruses.

Human Coronaviruses

Prior to the SARS-CoV outbreak, coronaviruses were only thought to cause mild, self-limiting respiratory infections in humans. Two of these human coronaviruses are α-coronaviruses
(HCoV-229E and HCoV-NL63) while the other two are β-coronaviruses (HCoV-OC43 and HCoV-HKU1). HCoV-229E and HCoV-OC43 were isolated nearly 50 years ago [74,75] [76] while HCoV-NL63 and HCoV-HKU1 were only recently identified following the SARS-CoV outbreak [77,78]. These viruses are endemic in the human populations, causing 15–30% of respiratory tract infections each year. They cause more severe disease in neonates, the elderly, and in individuals with underlying illnesses, with a greater incidence of lower respiratory tract infection in these populations. HCoV-NL63 is also associated with acute laryngotracheitis (croup) [79]. One interesting aspect of these viruses is their differences in tolerance to genetic variability. HCoV-229E isolates from around the world have only minimal sequence divergence [80] while HCoV-OC43 isolates from the same location but isolated in different years show significant genetic variability [81]. This likely explains the inability of HCoV-229E to cross the species barrier to infect mice while HCoV-OC43 and the closely related bovine coronavirus, BCoV, are capable of infecting mice and several ruminant species. Based on the ability of MHV to cause demyelinating disease, it has been suggested that human CoVs may be involved in the development of multiple sclerosis (MS). However, no evidence to date suggests that human CoVs play a significant role in MS.

SARS-CoV, a group 2b β-coronavirus, was identified as the causative agent of the Severe Acute Respiratory Syndrome (SARS) outbreak that occurred in 2002–2003 in the Guangdong Province of China. It is the most severe disease caused by any coronavirus. During the 2002–2003 outbreak approximately 8098 cases occurred with 774 deaths, resulting in a mortality rate of 9%. This rate was much higher in elderly individuals, with mortality rates approaching 50% in individuals over 60 years of age. Furthermore, the outbreak resulted in the loss of nearly $40 billion dollars in economic activity, as the virus nearly shut down many activities in Southeast Asia and Toronto, Canada for several months. The outbreak began in a hotel in Hong Kong and ultimately spread to more than two dozen countries. During the epidemic, closely related viruses were isolated from several exotic animals including Himalayan palm civets and raccoon dogs [82]. However, it is widely accepted that SARS-CoV originated in bats as a large number of Chinese horseshoe bats contain sequences of SARS-related CoVs and contain serologic evidence for a prior infection with a related CoV [83,84]. In fact, two novel bat SARS-related CoVs were recently identified that are more similar to SARS-CoV than any other virus identified to date [85]. They were also found to use the same receptor as the human virus, angiotensin converting enzyme 2 (ACE2), providing further evidence that SARS-CoV originated in bats. Although some human individuals within wet animal markets, had serologic evidence of SARS-CoV infection prior to the outbreak, these individuals had no apparent symptoms [82]. Thus, it is likely that a closely related virus circulated in the wet animal markets for several years before a series of factors facilitated its spread into the larger population.

Transmission of SARS-CoV was relatively inefficient, as it only spread through direct contact with infected individuals after the onset of illness. Thus, the outbreak was largely contained within households and healthcare settings [86], except in a few cases of superspreading events where one individual was able to infect multiple contacts due to an enhanced development of high viral burdens or ability to aerosolize virus. As a result of the relatively inefficient transmission of SARS-CoV, the outbreak was controllable through the use of quarantining. Only a small number of SARS cases occurred after the outbreak was controlled in June 2003.

SARS-CoV primarily infects epithelial cells within the lung. The virus is capable of entering macrophages and dendritic cells but only leads to an abortive infection [87,88]. Despite this,
infection of these cell types may be important in inducing pro-inflammatory cytokines that may contribute to disease [89]. In fact, many cytokines and chemokines are produced by these cell types and are elevated in the serum of SARS-CoV infected patients [90]. The exact mechanism of lung injury and cause of severe disease in humans remains undetermined. Viral titers seem to diminish when severe disease develops in both humans and in several animal models of the disease. Furthermore, animals infected with rodent-adapted SARS-CoV strains show similar clinical features to the human disease, including an age-dependent increase in disease severity [91]. These animals also show increased levels proinflammatory cytokines and reduced T-cell responses, suggesting a possible immunopathological mechanism of disease [92,93].

While the SARS-CoV epidemic was controlled in 2003 and the virus has not since returned, a novel human CoV emerged in the Middle East in 2012. This virus, named Middle East Respiratory Syndrome-CoV (MERS-CoV), was found to be the causative agent in a series of highly pathogenic respiratory tract infections in Saudi Arabia and other countries in the Middle East [94]. Based on the high mortality rate of ~50% in the early stages of the outbreak, it was feared the virus would lead to a very serious outbreak. However, the outbreak did not accelerate in 2013, although sporadic cases continued throughout the rest of the year. In April 2014, a spike of over 200 cases and almost 40 deaths occurred, prompting fears that the virus had mutated and was more capable of human-to-human transmission. More likely, the increased number of cases resulted from improved detection and reporting methods combined with a seasonal increase in birthing camels. As of August 27th, 2014 there have been a total of 855 cases of MERS-CoV, with 333 deaths and a case fatality rate of nearly 40%, according to the European Center for Disease Prevention and Control.

MERS-CoV is a group 2c β-coronavirus highly related to two previously identified bat coronaviruses, HKU4 and HKU5 [95]. It is believed that the virus originated from bats, but likely had an intermediate host as humans rarely come in contact with bat secretions. Serological studies have identified MERS-CoV antibodies in dromedary camels in the Middle East [96], and cell lines from camels have been found to be permissive for MERS-CoV replication [97] providing evidence that dromedary camels may be the natural host. More convincing evidence for this comes from recent studies identifying nearly identical MERS-CoVs in both camels and human cases in nearby proximities in Saudi Arabia [98,99]. In one of these studies the human case had direct contact with an infected camel and the virus isolated from this patient was identical to the virus isolated from the camel [99]. At the present time it remains to be determined how many MERS-CoV cases can be attributed to an intermediate host as opposed to human-to-human transmission. It has also been postulated that human-to-camel spread contributed to the outbreak.

MERS-CoV utilizes Dipeptidyl peptidase 4 (DPP4) as its receptor [100]. The virus is only able to use the receptor from certain species such as bats, humans, camels, rabbits, and horses to establish infection. Unfortunately for researchers, the virus is unable to infect mouse cells due to differences in the structure of DPP4, making it difficult to evaluate potential vaccines or antivirals. Recently, a small animal model for MERS-CoV was developed using an Adenoviral vector to introduce the human DPP4 gene into mouse lungs [101]. This unique system makes it possible to test therapeutic interventions and novel vaccines for MERS-CoV in any animal sensitive to adenoviral transductions.
Diagnosis, Treatment, and Prevention

In most cases of self-limited infection, diagnosis of coronaviruses is unnecessary, as the disease will naturally run its course. However, it may be important in certain clinical and veterinary settings or in epidemiological studies to identify an etiological agent. Diagnosis is also important in locations where a severe CoV outbreak is occurring, such as, at present, in the Middle East, where MERS-CoV continues to circulate. The identification of cases will guide the development of public health measures to control outbreaks. It is also important to diagnose cases of severe veterinary CoV-induced disease, such as PEDV and IBV, to control these pathogens and protect food supplies. RT-PCR has become the method of choice for diagnosis of human CoV, as multiplex real-time RT-PCR assays have been developed, are able to detect all four respiratory HCoVs and could be further adapted to novel CoVs [102,103]. Serologic assays are important in cases where RNA may be difficult to isolate, is no longer present, and for epidemiological studies.

To date, there are no anti-viral therapeutics that specifically target human coronaviruses, so treatments are only supportive. In vitro, interferons (IFNs) are only partially effective against coronaviruses [104]. IFNs in combination with ribavirin may have increased activity in vitro when compared to IFNs alone against some coronaviruses; however, the effectiveness of this combination in vivo requires further evaluation [105]. The SARS and MERS outbreaks have stimulated research on these viruses and this research has identified a large number of suitable anti-viral targets, such as viral proteases, polymerases, and entry proteins. Significant work remains, however, to develop drugs that target these processes and are able to inhibit viral replication.

Only limited options are available to prevent coronavirus infections. Vaccines have only been approved for IBV, TGEV, and Canine CoV, but these vaccines are not always used because they are either not very effective, or in some cases have been reported to be involved in the selection of novel pathogenic CoVs via recombination of circulating strains. Vaccines for veterinary pathogens, such as PEDV, may be useful in such cases where spread of the virus to a new location could lead to severe losses of veterinary animals. In the case of SARS-CoV, several potential vaccines have been developed but none are yet approved for use. These vaccines include recombinant attenuated viruses, live virus vectors, or individual viral proteins expressed from DNA plasmids. Therapeutic SARS-CoV neutralizing antibodies have been generated and could be retrieved and used again in the event of another SARS-CoV outbreak. Such antibodies would be most useful for protecting healthcare workers. In general, it is thought that live attenuated vaccines would be the most efficacious in targeting coronaviruses. This was illustrated in the case of TGEV, where an attenuated variant, PRCV, appeared in Europe in the 1980s. This variant only caused mild disease and completely protected swine from TGEV. Thus, this attenuated virus has naturally prevented the reoccurrence of severe TGEV in Europe and the U.S. over the past 30 years [106]. Despite this success, vaccine development for coronaviruses faces many challenges [107]. First, for mucosal infections, natural infection does not prevent subsequent infection, and so vaccines must either induce better immunity than the original virus or must at least lessen the disease incurred during a secondary infection. Second, the propensity of the viruses to recombine may pose a problem by rendering the vaccine useless and potentially increasing the evolution and diversity of the virus in the wild [108]. Finally, it has been shown in FIPV that vaccination with S protein leads to enhanced disease [109]. Despite this, several
strategies are being developed for vaccine development to reduce the likelihood of recombination, for instance by making large deletions in the nsp1 [110] or E proteins [111], rearranging the 3’ end of the genome [112], modifying the TRS sequences [113], or using mutant viruses with abnormally high mutation rates that significantly attenuate the virus [114].

Owing to the lack of effective therapeutics or vaccines, the best measures to control human coronaviruses remain a strong public health surveillance system coupled with rapid diagnostic testing and quarantine when necessary. For international outbreaks, cooperation of governmental entities, public health authorities and health care providers is critical. During veterinary outbreaks that are readily transmitted, such as PEDV, more drastic measures such as destruction of entire herds of pigs may be necessary to prevent transmission of these deadly viruses.

**Conclusion**

Over the past 50 years the emergence of many different coronaviruses that cause a wide variety of human and veterinary diseases has occurred. It is likely that these viruses will continue to emerge and to evolve and cause both human and veterinary outbreaks owing to their ability to recombine, mutate, and infect multiple species and cell types.

Future research on coronaviruses will continue to investigate many aspects of viral replication and pathogenesis. First, understanding the propensity of these viruses to jump between species, to establish infection in a new host, and to identify significant reservoirs of coronaviruses will dramatically aid in our ability to predict when and where potential epidemics may occur. As bats seem to be a significant reservoir for these viruses, it will be interesting to determine how they seem to avoid clinically evident disease and become persistently infected. Second, many of the non-structural and accessory proteins encoded by these viruses remain uncharacterized with no known function, and it will be important to identify mechanisms of action for these proteins as well as defining their role in viral replication and pathogenesis. These studies should lead to a large increase in the number of suitable therapeutic targets to combat infections. Furthermore, many of the unique enzymes encoded by coronaviruses, such as ADP-ribose-1’-phosphatase, are also present in higher eukaryotes, making their study relevant to understanding general aspects of molecular biology and biochemistry. Third, gaining a complete picture of the intricacies of the RTC will provide a framework for understanding the unique RNA replication process used by these viruses. Finally, defining the mechanism of how coronaviruses cause disease and understanding the host immunopathological response will significantly improve our ability to design vaccines and reduce disease burden.

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