Yale SCHOOL OF MEDICINE

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CONNECTICUT STATE DEPARTMENT OF EDUCATION

Module 4: Treatment

The Story…

Six days after testing for Covid-19, 16-year-old Tash's results are in, and it's not good news. He has tested positive, and his friends Ray and June urge Tash to seek out whatever care he needs in order to get better as soon as possible. Tash once again calls his pediatrician, who discusses the current treatments being utilized to treat Covid-19. The doctor tells Tash that the only treatment is for him to control the symptoms with medicines like acetaminophen (Tylenol) and ibuprofen. He will need to remain in isolation. In addition, the pediatrician states that new treatments are currently being developed and tested, but will not be available before Tash recovers. For now, all Tash can do is isolate himself and wait. What are the different treatments for Covid-19, and how are they developed?

Performance Expectations: After completing Module 3, students will be able to:

- Understand general approaches to treating infections caused by viruses.
- Identify different phases of clinical trials involved in drug development and approval.
- Consider why treatment recommendations change over time.

Challenges in Module 3

1. **Why don't antibiotics work against COVID-19?**
2. **How are medications developed?**
3. **How are research studies designed?**
4. **What specific treatments are being used for COVID-19?**

Challenge 1: Why don't antibiotics work against COVID-19?

Learning Targets:

•I can recognize the differences between bacteria and viruses.
•I can explain why antibiotics aren't used to treat people with COVID-19.

Estimated Time: 30 minutes

Activity 1: Recognize the differences between bacteria and viruses.

•**Watch [7:58]: "**Viruses and Bacteria: What's the difference and who cares anyway?" https://www.youtube.com/watch?v=O7iaPos8a90
•**Read:** "The coronavirus isn't alive. That's why it's so hard to kill" https://www.washingtonpost.com/health/2020/03/23/coronavirus-isnt-alive-thats-why-its-so-hard-kill/
•**Read:** "Why antibiotics can't be used to treat your cold or flu" https://www.health.qld.gov.au/news-events/news/antibiotics-viruses-cold-flu#:~:text=Viruses%20can't%20reproduce%20on,don't%20work%20on%20viruses.
•**Reflect & Discuss:**
•If viruses aren't alive, how come they can make people so sick?
•What's the downside of simply trying an antibiotic when someone is sick?
•What are some viruses other than coronavirus? What treatments can you think of for these other viruses?
•**Create:** with a partner, using online search tools, draw a diagram of a virus and a bacteria. Label the parts.
•**Share:** your answers and diagram with the class. Be prepared to explain how you chose the websites you used to create your diagram.

Career Spotlight:

Info about a career as a Microbiologist - https://www.bls.gov/ooh/life-physical-and-social-science/microbiologists.htm

Yale Faculty Highlight: Dr. Elijah Paintsil - https://www.ynhh.org/physicians/elijah-e-paintsil.aspx

Challenge 2: How are medications developed?

Learning Targets:

•I can identify different phases of clinical trials involved in drug development and approval.
•I can confront the history of disparities and injustice in drug development.
•I can apply lessons learned to the emergency use of medications for COVID-19.

Estimated Time: 90 minutes

Activity 1: Explain the process of drug development.

•**Read:** "What are Clinical Trials and Studies" https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies
•**Watch** [3:03]: "Robots Speed the Pace of Modern Drug Discovery" https://www.youtube.com/watch?time_continue=106&v=EwzhEAZRX5o&feature=emb_logo
•**Watch** [3:48]: "How a Drug Becomes a Drug" https://www.youtube.com/watch?v=U96He401wj4
•**Watch** 1:48]: "What are Clinical Trial Phases" https://www.youtube.com/watch?time_continue=2&v=dsfPOpE-GEs&feature=emb_logo - this video discusses medications for cancer treatment but the concepts apply to medications for all sorts of diseases
•**Reflect & Discuss:**
1.The process to make a new medication is very detailed. What are the pros and cons to such a complex process?
2.If medications gain approval for use after successfully completing phase III trials, what is the purpose of phase IV trials?
•**Share:** your answers with the class.

Activity 2: Disparities and injustice in drug development.

•**Read:** "Minorities Are Underrepresented in Clinical Trials" https://www.aafp.org/news/blogs/leadervoices/entry/20181204lv-clinicaltrials.html
•**Read:** "Tuskegee Experiment: The Infamous Syphilis Study" https://www.history.com/news/the-infamous-40-year-tuskegee-study
•**Watch: "**The History of Clinical Research Timeline" https://www.youtube.com/watch?time_continue=3&v=civjEGT--1A&feature=emb_logo
•**Reflect & Discuss:**
1.Why might minority populations be underrepresented in clinical trials?

2.How might historical injustices like the Tuskegee Experiments impact research and medical care today?

•**Explore:** with a partner one of the following topics using online resources - The Nuremberg Code or Henrietta Lacks. Share your answers and what you learned with the class.

Activity 3: Emergency use of medications for COVID-19

•**Watch** [1:45]**: "**What is an EUA" https://www.youtube.com/watch?time_continue=4&v=iGkwaESsGBQ&feature=emb_logo

•**Read:** "Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment" https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment

•**Read:** "FDA ends emergency use authorization for hydroxychloroquine to treat COVID" https://www.cbsnews.com/news/hydroxychloroquine-fda-ends-emergency-use-authorization-covid-19/

•**Read:** "Scientists Are Wrong All the Time, and That's Fantastic" https://www.wired.com/2015/02/scientists-wrong-time-thats-fantastic/

•**Reflect & Discuss:**

1.Why does the process of Emergency Use Authorization exist?

2.What are some risks to fast-forwarding the normal process of approving medications?

3.How can we trust scientists (like the researchers who make new medicines) when they are wrong so much of the time?

•**Share:** your answers with the class.

Career Spotlight:

Info about a career as a Pharmaceutical Scientist - https://explorehealthcareers.org/career/pharmacology/pharmaceutical-scientist/

Drug Discovery at Yale - https://medicine.yale.edu/pharm/research/drugdiscovery/

Challenge 3: How are research studies designed?

Learning Targets:

•I can consider different ways that scientists design research studies to see if treatments work.
•I can discuss why treatment recommendations change over time.
•I can explore confusion related to treatments for COVID-19 rooted related to research study design.

Estimated Time: 60 minutes

Activity 1: Different ways that scientists design research studies to see if treatments work.

•**Read:** Clinical Trials Versus Studies: Is There A Difference?" (this article focuses on a disease called cystic fibrosis, but the principles about study design apply more broadly) https://www.cff.org/Research/Developing-New-Treatments/Clinical-Trials/Clinical-Trials-101/Clinical-Trials-Versus-Studies-Is-There-a-Difference/

•**Read:** "Observational vs. experimental studies" https://www.iwh.on.ca/what-researchers-mean-by/observational-vs-experimental-studies

•**Watch:** "Types of statistical studies" (start watching at 2:15) https://www.khanacademy.org/math/ap-statistics/gathering-data-ap/types-of-studies-experimental-vs-observational/v/types-of-statistical-studies

•**Complete:** Answer the following questions and read the explanations to see some differences between observational vs. experimental studies. https://www.khanacademy.org/math/ap-statistics/gathering-data-ap/types-of-studies-experimental-vs-observational/a/observational-studies-and-experiments

•**Read:** Because of the urgency to find effective treatments for patients with COVID-19, many research studies were done simultaneously in the first half of 2020. Next, we will explore conflicting results from studies of one particular drug, hydroxychloroquine, to understand how researchers, doctors, and policy-makers have changed their opinions over time about this medicine.

•**Watch [3:01]:** "Widely cited hydroxychloroquine study is 'flawed', Fauci tells hearing" https://www.youtube.com/watch?v=RkNC5OQD2UE

•**Read:** "Hydroxychloroquine for COVID-19: Scientists say it's time to stop promoting the drug" https://www.today.com/health/scientists-say-it-s-time-stop-promoting-hydroxychloroquine-covid-19-t188262

•**Find out:**

1.How were the studies designed that concluded hydroxychloroquine was effective? How about the studies that found that it didn't help?

2.How has the research cycle of scientific inquiry influenced the medical community's opinion of the drug over time? Use 3 sources to demonstrate the change over time.

•**Reflect & Discuss:** How did policy-makers and government officials add to the confusion surrounding research on hydroxychloroquine for COVID-19? Use 3 sources to support your opinions

•**Design:** Imagine you are a researcher who has an idea for using a medicine to treat a newly discovered disease. Design a research study to test if the medicine works. Use either an observational study or experimental (randomized, placebo controlled) study design. Explain why you've made these choices for your research design.

Career Spotlight:

Yale Faculty Highlight: Dr. Harlan Krumholz - https://www.youtube.com/watch?v=AqkYMAVXdo8

Yale Faculty Highlight: Dr. Sarwat Chaudhry- https://www.youtube.com/watch?v=g-VxrNifBYw

Challenge 4: What specific treatments are being used for COVID-19?

Learning Targets:

•I can consider how bias and confounding can confuse results of scientific studies.
•I can explore information about current and emerging treatments for COVID-19.
•I can describe why treatment recommendations change over time.

Estimated Time: 90 minutes

Activity 1: Apply sound scientific principles.

•**Read:** There has been a rush to develop new medicines. Developing a new medicine that is safe and effective can take years. Since we don't have years to wait, doctors are looking to repurpose many existing medications (i.e., medicines that are already approved for use for other conditions) to see if they may help patients with COVID-19. This way they don't need to start from scratch, which can save years in finding effective treatments. But there can be lots of problems with this approach if we are too quick to act - we risk forgetting sound scientific principles.

•**Read:** "Vitamin D Deficiency and COVID-19: Is There a Connection?" https://www.yalemedicine.org/stories/vitamin-d-covid-19/

•**Read:** Hydroxychloroquine is a medication used for malaria (a parasitic infection) and lupus (a disease of the immune system), that had been shown to work *in vitro* against another type of coronavirus (SARS) in the past, so doctors tried to use it early on against COVID-19 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7108130/pdf/ciaa237.pdf). There was initial promise based on experiences in small groups of patients, but these early studies lacked the scientific rigor needed for approval and wide use of a medicine. Instead, they provided important hypotheses to drive larger studies that could do a more thorough job of seeing if hydroxychloroquine would help patients with COVID-19. Unfortunately, these larger, more scientifically rigorous trials were not encouraging - the science does not currently support using this medicine for treatment or prevention of COVID-19 unless the medicine is being used as part of a research study (https://www.acpjournals.org/doi/10.7326/M20-1998).

•**Reflect & Discuss:**

1.Why might vitamin D levels be lower in populations with higher rates of COVID-19?
2.How could a scientist test if taking vitamin D helps treat COVID-19?
3.Should doctors be allowed to prescribe medications that are not approved? Should patients be able to get an unapproved medicine without a prescription?

•**Share:** your answers with the class.

Activity 2: Explore current treatments for COVID-19.

•**Read:** "Coronavirus Drug and Treatment Tracker" https://www.nytimes.com/interactive/2020/science/coronavirus-drugs-treatments.html

•**Read:** "Treatments for COVID-19" https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19

•**Read:**

Anti-inflammatory medicines

We know that many people exposed to SARS-CoV-2 get mild or no symptoms at all. Others get so sick that they end up in the hospital or die. The differences in how sick people get may be because some people's immune system overreacts to the infection. Our immune systems are designed to fight off infection. When the immune system reacts properly, we can get over an infection quickly, but if the system overreacts, it can cause us to get really sick. A lot of the medicines that are being studied and used for COVID-19 block the overactive response of the immune system. Dexamethasone is an example. However, the immune system is really important to fight infections including COVID-19 - we don't want to block it in most people with COVID-19! So medicines like dexamethasone should only be used for people who get severely ill from COVID-19.
We can measure levels of a patient's immune response with some specialized blood tests called "inflammatory markers." In some of the sickest patients with COVID-19, inflammatory markers are very elevated. There are some medicines that lower levels of inflammatory markers in COVID-19. Tocilizumab is one such medicine; it blocks the function of a specific molecule in the immune system called IL-6 (interleukin 6, which is in a family of compounds called cytokines). By blocking the function of IL-6, the thought is that an overreacting immune system won't cause as much damage to the patient. Tocilizumab has been used in other immune disorders where the patient's immune system is overreacting. In COVID-19 it has been shown to improve levels of inflammatory markers on blood tests in sick hospitalized patients, but the effect on the patient's health directly is not so clear.

Anti-virals

Many antiviral medications that have been developed for other diseases are being tried for COVID-19. One that has been used to treat COVID-19 is remdesivir, which was originally developed as a possible treatment for other viruses (hepatitis C, Ebola, Marburg) but was never approved for use for any of these. "Remdesivir is a molecule that is similar to the nucleotide building blocks the virus uses to copy its RNA genome. By imitating those building blocks, remdesivir blocks the enzyme that the coronavirus uses to replicate itself." (https://www.nature.com/articles/d41586-020-01367-9).

A research study demonstrated that remdesivir reduced the time to recovery for hospitalized patients with severe COVID-19 infection, and it was granted FDA approval in October 2020. However, since it requires many doses through an IV, it is impractical for anyone other than the sickest patients.

New treatments

Many new treatments are being developed and studied. One group of medicines that shows promise is monoclonal antibodies. Antibodies are proteins the body makes to fight off specific infections. When someone is exposed to a virus, the body should make natural antibodies to fight the virus and help the person recover from illness. However, it can take time for natural antibodies to form, and during that time some people can get really sick. "Monoclonal antibodies" are medicines that work like natural antibodies but can be given right away, before natural antibodies have time to work. In COVID-19 infection, a patient can receive monoclonal antibodies through an injection or an IV as soon as possible after the infection starts. They help prevent patients from developing serious symptoms from their COVID-19 infection. There are many different types of monoclonal antibodies for COVID-19 being developed but all of them are reserved for people who are at high risk of getting seriously ill from COVID-19.

Other strategies

Sick patients with COVID-19 are doing better even though we don't have effective medications yet because we are getting better at preventing and treating life-threatening complications of the disease. For example, prone positioning (having sick patients lie on their stomachs) of patients with COVID-19 in the hospital can help with oxygenation. Aggressive use of medications to prevent blood clots in hospitalized patients has also helped prevent life threatening complications.

•**Reflect & Discuss:**

1.Which treatments currently show the most promise for COVID-19?
2.What is the role of the immune system in COVID-19?
3.What are antibodies? What is the role of antibodies in recovering from COVID-19?
4.Where can people get reliable and trustworthy information about medical treatments? Who should people ask if they have questions or confusion about medical treatments?

•**Share:** your answers with the class.

Activity 3: Find out!

•**Explore:** Using resources in the readings from this Challenge or other online sources, find out if there is any evidence to support the statements below. Find out by citing at least one source for each of these statements, either refuting or supporting the claims. Be prepared to present your answers and sources to class, including an explanation about why you thought your sources were trustworthy.

1.Sick patients with COVID-19 are doing better even though we don't have effective medications yet because we are getting better at preventing and treating life-threatening complications of the disease.

2.Even though azithromycin is an antibiotic, some scientific studies have shown it may help treat COVID-19 because it reduces inflammation.

3.When there was a rush of excitement about using hydroxychloroquine to treat COVID-19, some patients who needed it for other reasons had difficulty getting it.

4.Medications that are used to treat HIV infection are being used to treat COVID-19.

5.Some people are taking advantage of the uncertainty around COVID-19 treatments to make money selling unproven (and sometimes dangerous) treatments.

•**Share:** your answers with the class.

Career Spotlight:

Yale Faculty Highlight: Dr. Jeremy Schwartz - https://medicine.yale.edu/news-article/25220/

Info about a career as a Hospitalist doctor - https://www.careeronestop.org/site-search.aspx?keyword=hospitalist

Info about a career as a Critical Care Medicine doctor - https://www.acponline.org/about-acp/about-internal-medicine/subspecialties/additional-training-options/critical-care

Info about a career as an ICU Nurse - https://www.registerednursing.org/specialty/icu-nurse/

Info about a career as a Respiratory Therapist - https://www.respiratorytherapistlicense.com/what-is-a-respiratory-therapist/

Info about a career as a Pharmacist - https://explorehealthcareers.org/career/pharmacy/pharmacist/

Module 4: Treatment (Teacher notes)

Teacher Note:
Module 3 contains four different challenges, each which contains a number of stand-alone activities that can be done in any order based on the interests and needs in individual classrooms.

In This Lesson (NGSS standards):

Science and Engineering Practices:

- Constructing Explanations and Designing Solutions
- Engaging in Argument from Evidence
- Obtaining, Evaluating, and Communicating Information

Disciplinary Core Ideas:

- **LS1.A:** Structure and Function
- **ETS1.A**: Defining and Delimiting Engineering Problems
- **ETS1.B:** Developing Possible Solutions
- **ETS1.C:** Optimizing the Design Solution

Crosscutting Concepts:

- Systems and System Models
- Structure and Function

NGSS Performance Expectations

- **HS-ETS1-1:** Analyze a major global challenge to specify qualitative and quantitative criteria and constraints for solutions that account for societal needs and wants.
- **HS-ETS1-2:** Design a solution to a complex real-world problem by breaking it down into smaller, more manageable problems that can be solved through engineering.
- **HS-ETS1-3:** Evaluate a solution to a complex real-world problem based on prioritized criteria and trade-offs that account for a range of constraints, including cost, safety, reliability, and aesthetics as well as possible social, cultural, and environmental impacts.
- **HS-ETS-4:** Use a computer simulation to model the impact of proposed solutions to a complex real-world problem with numerous criteria and constraints on interactions within and between systems relevant to the problem.
- **HS-LS1-1:** Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.
- **HS-LS1-2:** Develop and use a model to illustrate the hierarchical organization of interacting systems that provide specific functions within multicellular organisms.

HS-LS1-3: Plan and conduct an investigations to provide evidence that feedback mechanisms maintain homeostasis.

Key Terms:

- Virus
- Bacteria
- Antibiotic
- Antiviral
- Drug trial (phase I, II, III, and IV)
- Randomized, placebo-controlled trial (also called experimental study)
- Observational study
- Pharmacology
- Repurpose
- In vitro and in vivo
- Emergency authorization
- SARS-CoV-2, COVID19, Coronavirus
- Confounding