NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

CAMEL Question: *Can Applied Math Extend Life?*

by

Qingxia Li, Xinyao Yang, and Lauren S. Gollahon

Part I – Infection Risk

James was a student at Vanderbilt University. On his way back to school after a visit with relatives, James had a layover at the Incheon International Airport Seoul, South Korea. He immediately noticed that most people were wearing a face mask. There were big signs everywhere stating: "Stay Away from Camels and Be Aware of MERS."

James had never heard of this before, so he decided to do some research while he was waiting for his flight. Using his smartphone, he quickly found an article about MERS and started reading:

> South Korea on Sunday reported its fifth death from MERS as the government vowed "all-out" measures to ease growing public fear over the largest outbreak outside Saudi Arabia. The number of infections rose to 64 after 14 new cases, including one death, of Middle East Respiratory Syndrome (MERS) were confirmed on Saturday night, the health ministry said. All of the 14 were among group of 1,820 quarantined after being exposed to those diagnosed earlier, it added. ...
>
> With the number of new cases growing on a daily basis and public fear rising, more than 1,300 schools were closed temporarily and school trips, public events and sports games were cancelled across the country.[1]

James remembered that his friend Samuel, from Africa, told him about Ebola, which was also quite deadly to humans. From times.com James found out that MERS doesn't appear to be able to spread as quickly as Ebola can[2] (Figures 1 and 2, next page). While Ebola spreads through direct contact with the bodily fluids of an infected person, MERS doesn't spread easily from person to person, and though it can spread through the respiratory tract, very close contact is needed.

James also recalled that there had been an outbreak of flu on the campus of Vanderbilt University in the winter of 2013. The campus had to close for three days. And lately Ebola had been in the news. So, he wondered, what was the difference between MERS, Ebola and the flu anyway? He went back to his notes and constructed a table to show the major traits for each virus (Figure 3). He began to wonder whether a college student in the U.S. was at risk for getting Ebola. Since he was just in South Korea, another worry was whether he might have been exposed to MERS. And, come to think of it, what did disease "spreading" really mean?

Back at Vanderbilt University, James went to his virology instructor, Dr. McCarroll, for an explanation. Dr. McCarroll told him that there were no available vaccines to control either Ebola or MERS, but there was a vaccine to control the spread of flu. It was made available after the first reported outbreak of the year. As a result, the prevalence of Ebola and MERS could continue to grow over time, while the flu virus would eventually reach a maximum point and become stable. That was why people who contracted Ebola and MERS needed to be immediately isolated for medical treatment.

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[1] Agence France-Presse. June 7th, 2015. South Korea reports 5th death from MERS, 14 new cases. *Mail Online.* Retrieved from <http://www.dailymail.co.uk/wires/afp/article-3114012/South-Korea-reports-5th-death-MERS-14-new-cases.html>.

[2] Sifferlin, A. June 8th, 2015. Here's the difference between MERS and Ebola. *Time News.* Retrieved from <http://time.com/3910571/mers-ebola/>.

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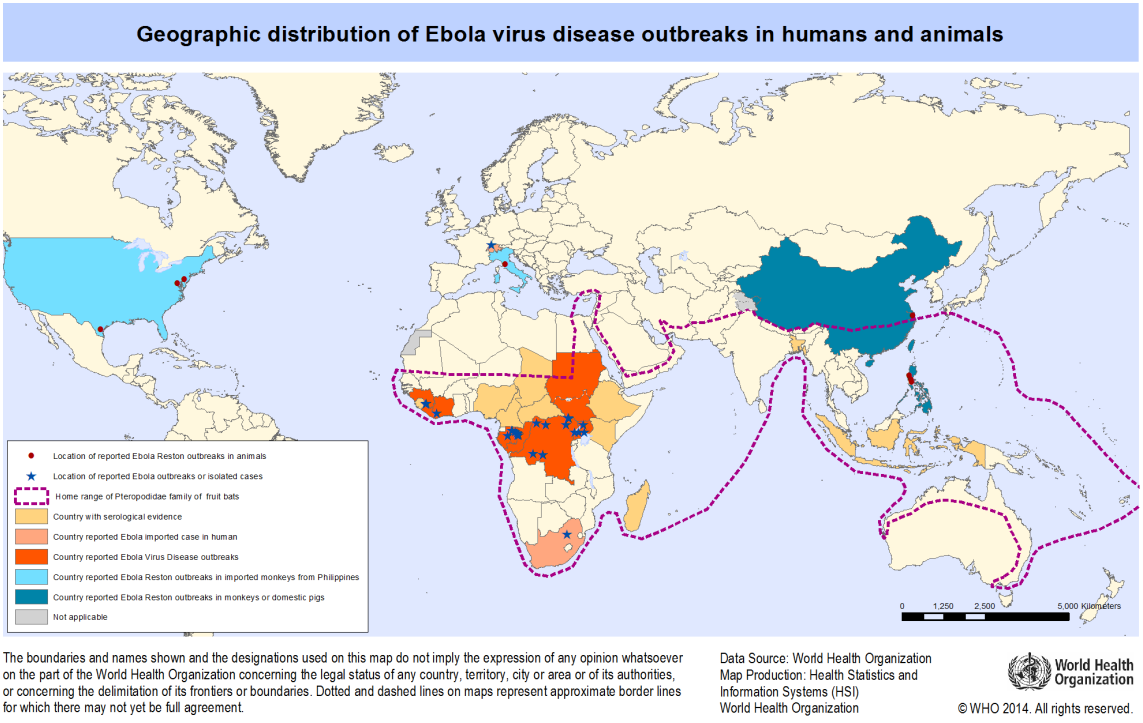


Figure 1. Global outbreak of Ebola. <http://www.who.int/csr/disease/ebola/ebola-map-humans-animals-2014.png?ua=1>

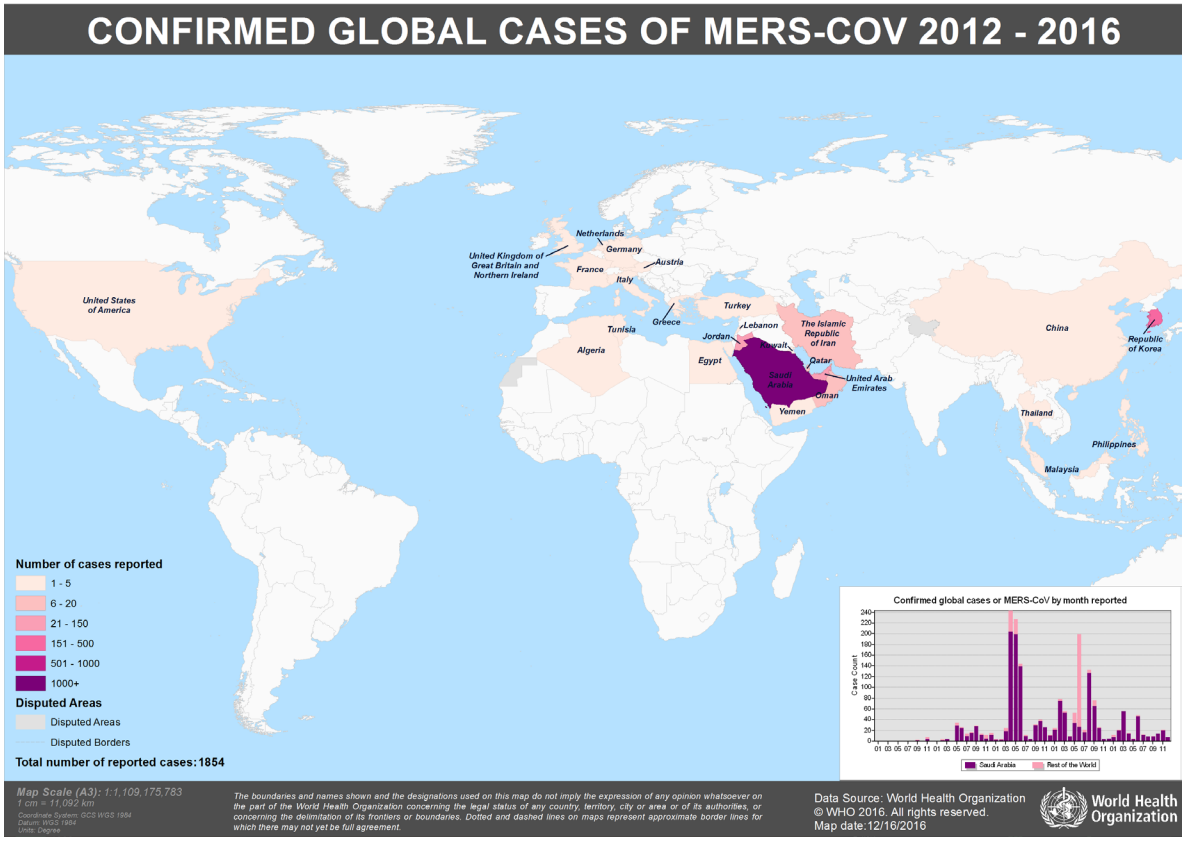


Figure 2. Global outbreak of MERS. <http://www.who.int/csr/disease/coronavirus_infections/maps-epicurves/en/>

MERS, Ebola and H3N2

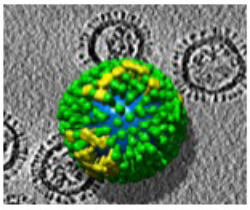
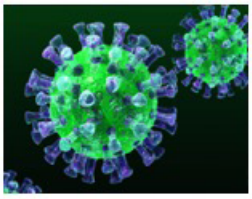
Pathogen	Virus type	Major Traits	Image
Ebola	Filovirus Negative sense, single stranded RNA with lipid coating	-Geographically isolated -Humans are not natural reservoirs - Zoonotic disease -Relatively robust survival time -Produces ebolavirus glycprotein that gloms onto blood vessel cells and causes BV to leak. **No treatment**	
H3N2	Influenzavirus A Negative sense, single stranded, segmented RNA	-Cough, fever, sore throat, chills, fatigue, body aches, runny nose. -Progressing to pneumonia or respiratory failure. Death due to comorbidities. **Treatments:** Tamiflu and Relenza vaccines are available	
MERS	Coronavirus Positive sense ssRNA Helically symmetrical nucleocapsid	-Acute respiratory illness (fever, shortness of breath, cough), GI distress -Progressing to pneumonia and kidney failure. Death due to comorbidities. **-No treatment**	

Figure 3. Summary of key characteristics for MERS, H3N2 and Ebola. *Sources:* Ebola image: <http://phil.cdc.gov/phil/details.asp?pid=10816>, H3N2 image: <https://commons.wikimedia.org/wiki/File:Steven_H3N2_Flu_ET.jpg>, MERS image: <https://en.wikipedia.org/wiki/Middle_East_respiratory_syndrome>.

Dr. McCarroll reminded James that she had discussed two growth models in her virology class that were based on differential equations.

Since James was in Calculus II and getting ready for differential equations in the next section, he decided to do a little reading ahead on the exponential growth and logistics growth models. He learned that these could be used to predict the changes of the number of infected people if the spreading rate of the viruses were provided.

where N is the number of infected people with the virus, r is the per capita infection rate for people who are exposed to this virus, and K is the maximum number of people in the population that could be infected by this virus, (i.e., the carrying capacity of the population in this model). The exponential growth model can be used to measure a population that continues to grow forever and the logistic growth model can be used to measure a population that will reach a maximum (carrying capacity) after some time.

The exponential growth model is defined as $\frac{dN}{dt} = rN$ and the logistic growth model is $\frac{dN}{dt} = rN(1 - \frac{N}{K})$

Questions

1. Explain the difference between infection, transmission and virulence.
2. Using external sources, describe what positive or negative-sense ssRNA means with regard to virus replication. How does having positive or negative ssRNA make a difference with respect to infection, transmission or virulence?
3. Solve and graph the solution of the exponential growth model with the fixed per capita growth rate $r = 0.1$ and the initial number of infected people: $N(0) = 10$.
4. Solve and graph the solution of the logistic growth model with the fixed per capita growth rate $r = 0.4$ and the initial number of infected people: $N(0) = 1$, and the carrying capacity $K = 5000$.

Part II – Ebola

James continued his internet research and found a FAQ on Ebola from *The New York Times.*[1] He was surprised to learn that it is a zoonotic disease, or a disease that can be transmitted across species. His interest grew as he read:

> *How Does the Disease Progress?*
>
> Symptoms usually begin about eight to 10 days after exposure to the virus, but can appear as late as 21 days after exposure, according to the C.D.C. At first, it seems much like the flu: a headache, fever and aches and pains. Sometimes there is also a rash. Diarrhea and vomiting follow. Then, in about half of the cases, Ebola takes a severe turn, causing victims to hemorrhage. They may vomit blood or pass it in urine, or bleed under the skin or from their eyes or mouths. But bleeding is not usually what kills patients. Rather, blood vessels deep in the body begin leaking fluid, causing blood pressure to plummet so low that the heart, kidneys, liver and other organs begin to fail.
>
> *Where Does Ebola Come From?*
>
> Ebola was discovered in 1976 and was once thought to originate in gorillas, because human outbreaks began after people ate gorilla meat. Scientists now believe that bats are the natural reservoir for the virus, and that apes and humans catch it from eating food that bats have drooled or defecated on, or by coming in contact with surfaces covered in infected bat droppings and then touching their eyes or mouths. The current outbreak seems to have started in a village near Guéckédou, Guinea, where bat hunting is common, according to Doctors without Borders.

Questions

1. How can Ebola be transmitted? What makes a virus an "airborne" virus?
2. What kinds of symptoms do flu victims suffer than Ebola victims generally do not?
3. What mathematical principles describe the spread of disease?

[1] How Many Ebola Patients Have Been Treated Outside of Africa? *The New York Times*. <http://www.nytimes.com/interactive/2014/07/31/world/africa/ebola-virus-outbreak-qa.html>.

Part III – H3N2

James remembered that there had been a big flu outbreak across campus in November, 2013 and the school had to close for two days right before the final exam week. He found out that *one* student returned from vacation with a contagious and long lasting flu virus (H3N2 or Hong Kong Flu) and the influenza quickly spread to the whole campus. Unfortunately, he also got the flu and had to visit the Student Health Center a couple times and the line was always very long.

James researched the flu and found out that influenza can be spread in three main ways: by direct transmission (when an infected person sneezes mucus directly into the eyes, nose or mouth of another person); the airborne route (when someone inhales the aerosols produced by an infected person coughing, sneezing or spitting) and through hand-to-eye, hand-to-nose, or hand-to-mouth transmission, either from contaminated surfaces or from direct personal contact such as a hand-shake.

James also read that there were different factors needed to calculate how quickly a disease would spread. Force of infection, r, is the per capita rate at which susceptible individuals contract the infection. The rate at which new infected cases are produced is rX, where X is the number of susceptible individuals. While patient information remains private, Vanderbilt's policy requires them to record the number of student visits to the Student Health Center for a particular indication. James was interested in determining how quickly the virus would spread through the student body such that the school would be closed. So he obtained the number of students (see Table 1) infected with H3N2 who visited Student Health Center from Nov. 5th to Dec. 13th, 2013.

Table 1. The number of student visits to Student Health Center with H3N2 from November 5th to December 13th, 2013.

Date	11/05	11/07	11/09	11/11	11/13	11/15	11/17	11/19	11/21	11/23
# of Flu Cases	1	5	8	17	38	83	177	380	761	1420
Date	11/25	11/27	11/29	12/01	12/03	12/05	12/07	12/09	12/11	12/13
# of Flu Cases	2350	3322	4080	4537	4790	4890	4950	4997	4999	5000

Questions

1. What kinds of symptoms do flu and Ebola victims share?
2. Plot the data that is given for number of student visits to Student Health Center from November 5th to December 13th, 2013. You may choose Nov. 5th to be Day 1, Nov. 7th to be Day 2, and etc. What pattern do you observe? Is the growth exponential or logistic?
3. Based on your results, please find a differential equation such that the graph of the solution best reflects the data given above.

Part IV – MERS

Since James was able to determine the differences between Ebola and H3N2 biologically and he also determined the rate of spread using the exponential and logistic growth models, he felt ready to explore what might be happening with MERS, especially since he was just in a country that reported small outbreaks. On the website for the World Health Organization he found a news update:[1]

> 21 July 2013 — WHO has been informed of two additional laboratory-confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in Saudi Arabia.
>
> Both the cases are currently critically ill and hospitalized in ICUs. The first case is a 41-year-old Saudi male in Riyadh who presented to the hospital with symptoms on 15 July. The second patient is a 59-year-old Saudi female in the Al-Ahsa governorate. She presented with symptoms on 11 July.

He also found a research article with the following figure:[2]

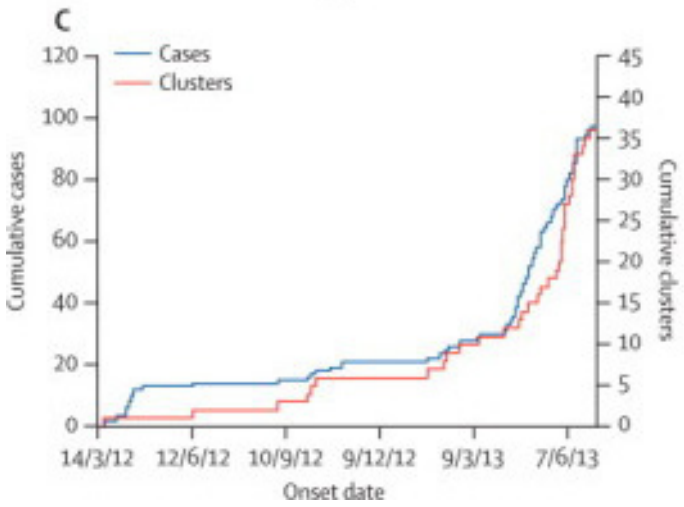


Figure 4. Cumulative number of confirmed cases and clusters detected of MERS-CoV. A cluster is a set of cases with known epidemiological links; a case is viewed as an independent cluster of size one.

The graph presents temporal trends in infection incidence using epidemiological data on reported cases and clusters. The analysis of observed cluster incidence over time indicates a doubling time of 90 (95% CI 65–133) days.

Questions

1. Please state the definition of the Middle East respiratory syndrome coronavirus. How can MERS-CoV be transmitted?
2. What are the current measures to treat MERS-CoV? How could you avoid the infection of MERS-CoV?
3. What mathematical model best represents the data given above, exponential growth model or logistic growth model?
4. Let $N(t)$ be the number of cumulative cases and $N(0)$ be 1 on March 14th, 2012. Please find a function that best matches the data. (*Hint:* Identify several points on the graph, record these points in Excel, and find the trendline of the graph.)

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[1] World Health Organization. 2013. Middle East respiratory syndrome coronavirus (MERS-CoV) — update. <http://www.who.int/csr/don/2013_07_21/en/>. Last accessed 12/23/2016.

[2] Cauchemez, S. 2014. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. *Lancet Infect Dis.* 14(1): 50–56. doi: 10.1016/S1473-3099(13)70304-9.

Part V – Putting It Together in a Biological Context

At this point, James had a better understanding of the differences between the virus replication machinery, virulence, and rates of infection. But one thing he still needed to somehow make sense of was how the mechanism of transmission fit into this picture. So he went back to his virology notes and found some interesting differences.

Influenza (H3N2) is transmitted person-to-person by three main methods: 1) direct transmission (sneezing or coughing in someone's face); 2) An airborne route (when someone inhales the aerosols produced by an infected person coughing or sneezing); 3) Through hand-to-eye, hand-to-nose, or hand-to-mouth transmission, either from contaminated surfaces (e.g., money, doorknobs, handrails) or from direct personal contact (e.g., a hand-shake).

Ebola is also transmitted from person-to-person. But unlike H3N2, it only occurs by direct contact with the blood or body fluids of an infected person. Body fluids include saliva, mucus, vomit, feces, sweat, tears, breast milk, urine and semen. Most people spread the virus through blood, feces and vomit. Entry points for the virus include the nose, mouth, eyes, open wounds, cuts and abrasions.

In contrast, the method of MERS transmission is still unclear, but it seemed that it was somehow related to contact with camels. When James read that, a light bulb went off: so that's where the "Stay Away From Camels" sign came from! He found a figure that explained some of the issues involved (Figure 5). He also followed <http://www.dailymail.co.uk/wires/afp/article-3113223/South-Korea-MERS-virus-cases-reach-50-people.html> for the full report.

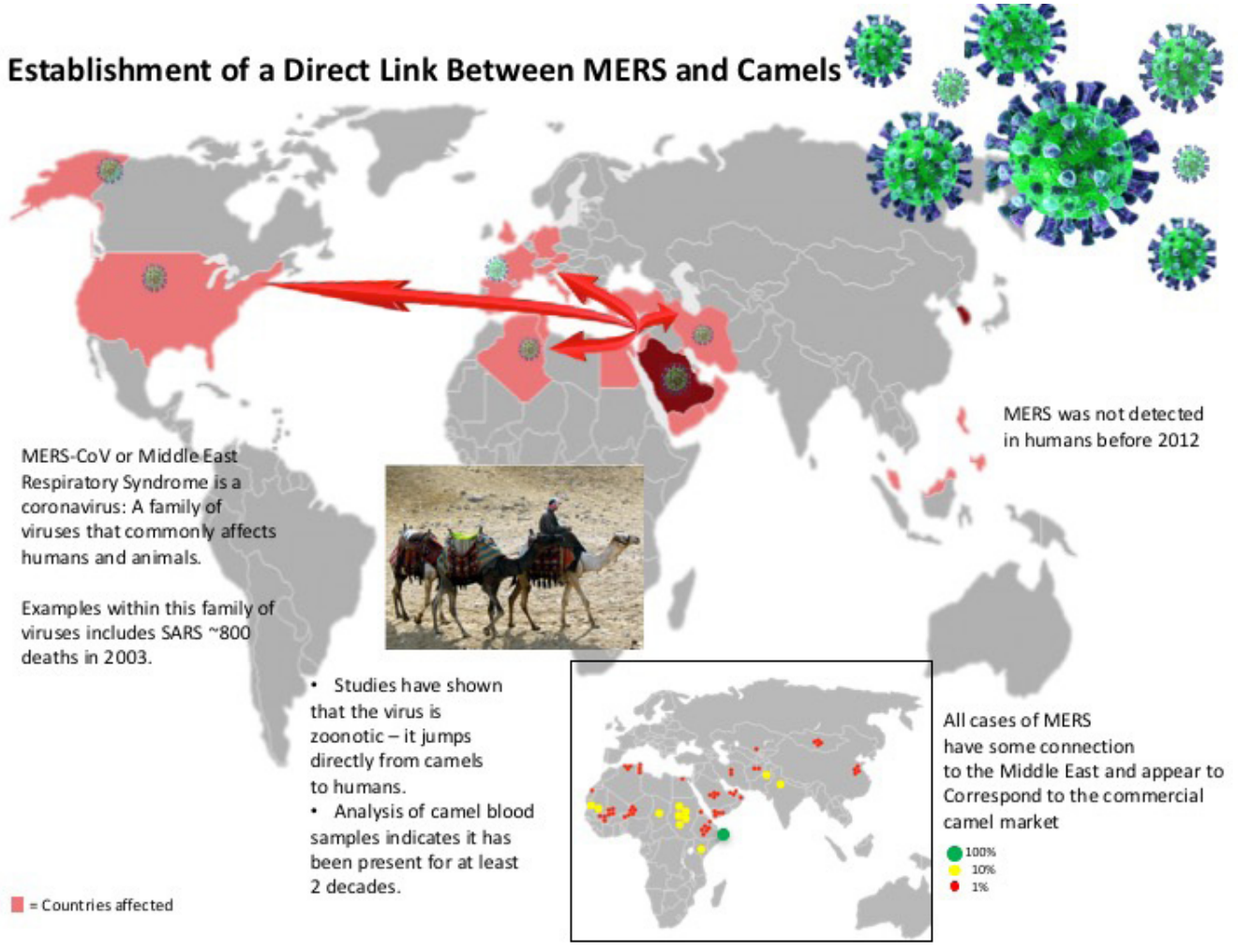

Figure 5. Global map of countries with reported MERS cases.

At this point James wanted to relate mode of transmission to virulence. In order to get a better understanding of the relationship between virulence and transmission route, he found a video clip on domestication of human pathogens.

Instructions: Watch the following clip: <http://youtu.be/BBavDRDlug8>. The important segment runs between minutes 27–32. After watching the five minute segment, answer the following questions.

Questions

1. Which virus is an example of the evolutionary process that led to a decrease in its pathogenicity? And why?
2. Using the example of the cholera outbreak in South America, explain why a poor water supply gave rise to a more virulent strain of cholera than a better water supply.
3. Based on the information presented in this case study, discuss which of the three viruses that James studied carries the greatest impact to society? Explain your reasoning.