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LS120 Final Paper

Effect of SMS Intervention on Transmission Dynamics of the Novel Coronavirus MERS-CoV

On May 7, 2013, a 65-year-old man in Northern France was confirmed to have contracted a novel coronavirus (NCoV), deemed to be named Middle East respiratory syndrome coronavirus (MERS-CoV) (Enserink 2013, WHO 2013, Spencer 2013). He is one of a 31 laboratory confirmed cases since September 2012, out of which 18 deaths arose (WHO 2013). This strain belongs to a family of viruses that can cause a range of illnesses in humans, from the common cold to SARS (WHO 2013). Though in general, little is known about coronaviruses except for the SARS outbreak, a more foundational understanding of this emerging coronavirus is vital to controlling the potential spread (Spencer 2013). This paper looks at the molecular and cellular biology, human biology and patient care, and population health and epidemiology of known coronavirus to postulate for the recently emerging coronavirus, MERS-CoV, to see how short messaging service (SMS) interventions could potentially have an impact on the transmission dynamics of the disease.

Part 1. Background

I, Molecular and Cellular Biology

Named for the crown-like spikes on their surface, coronaviruses are spherical, enveloped viruses (Tyrrell and Myint 1996, CDC 2013). The outer envelope has three main transmembrane

glycoproteins--the envelope (E) and membrane (M) proteins that are involved in maturation and release as well as the spike (S) protein involved in receptor binding, cell fusion, and major antigen interactions (Weiss and Leibowitz 2011, Baric 2007). Another major protein is the basic phosphoprotein, the nucleocapsid (N) protein around which the positively stranded RNA is loosely wound (Baric 2007). This is one of the largest known RNA genomes, of 30-32 kb, arranged from the 5' methylated cap to 3' poly-A tail end with leader (L), reading frames (ORF1a, ORF1b, replicase), structural genes (HE, S, E, M, and N proteins), and accessory genes (Baric 2007, Weiss and Leibowitz 2011). ORF1a and ORF1b create the replication complex and code for the replicase protein (Baric 2007).

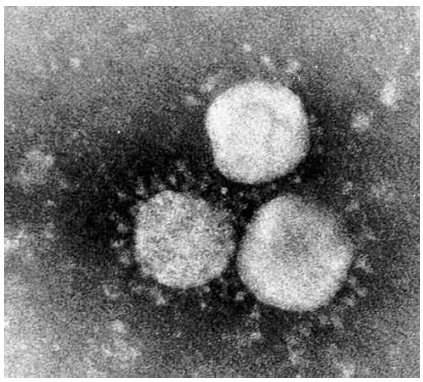
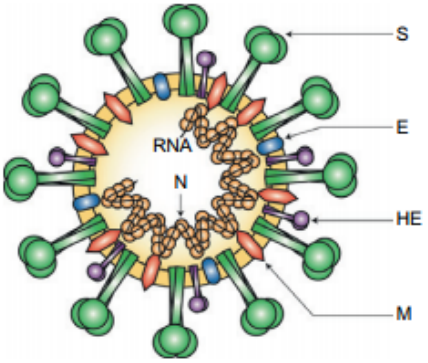
(A)  (B) 

Figure 1. (A) Electron micrograph showing human coronavirus (Tyrrell and Myint 1996) (B) Coronavirus viron structure (Weiss and Leibowitz 2011).

Replication occurs in the cytoplasm with the binding of the replication complex to the 3' end SARS genome, using the positive stranded RNA as a template to create a complementary negative strand, from which more positive strands can later be included in the progeny of the virus (Baric 2007). This way, large numbers of the necessary positive stranded RNAs can be created from few negative stranded RNAs (Baric 2007). These positively stranded RNAs can be made directly into mRNA using discontinuous transcription (Cann 2009). This results in different length sequences that are specific to a gene, allowing for more efficient expression of genes by demand (Baric 2007). The mRNA is

transcribed from the 3’ to 5’ end and result in transcription attenuation of incomplete subgenomic negative strands that dissociated and relocate to the 5’ end. The complementary transcription regulatory sequence (TRS) to transcription align and begin prime transcription of antileader RNA sequences until hitting a repeated intergenic sequence UCUAAAC which interactions with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF (Cann 2009). This results efficient translation of S-proteins and later proteins because each mRNA is protein specific (Baric 2007).

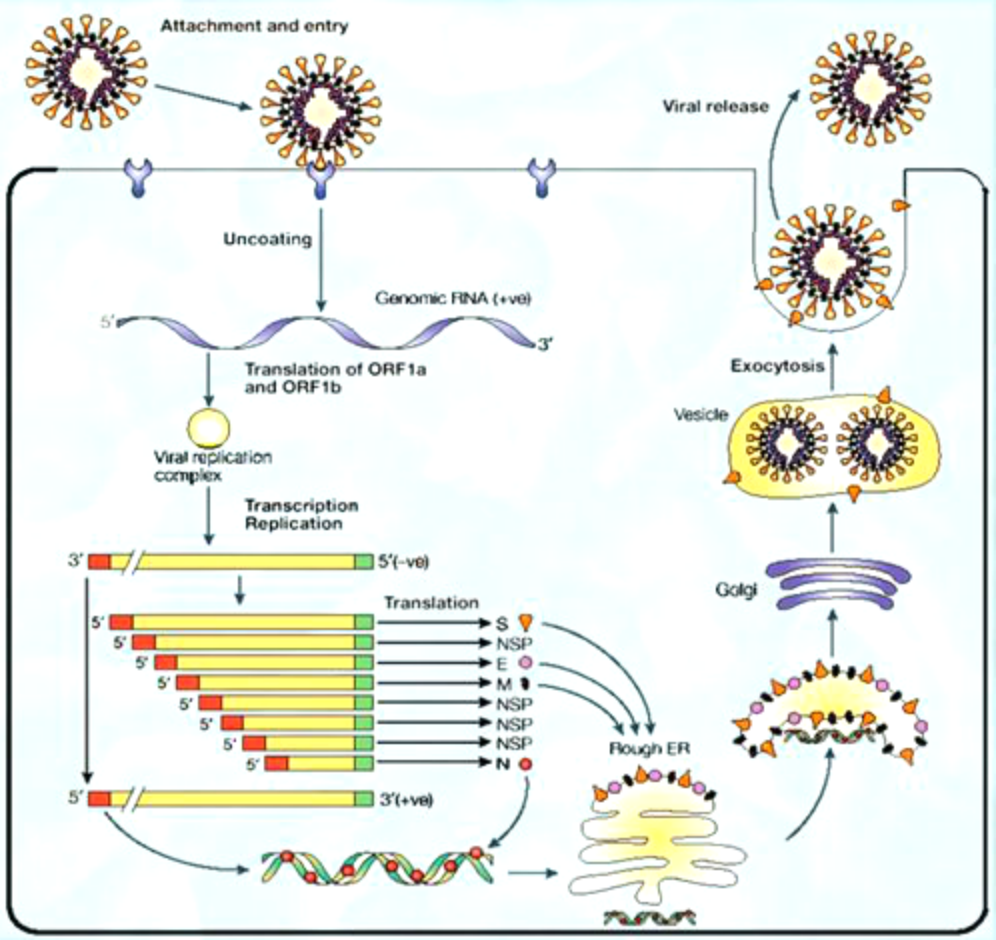


Figure 2. Coronavirus lifecycle including attachment, penetration, uncoating, synthesis, assembly, and release (Baric 2007).

The virus enters the cells by attaching to the host cell with angiotensin 2 (ACE2), which is a wrench-like receptor for docking and entry that is coded with the virus S protein, and penetrating the

host cell via viroplexis (Baric 2007). The virus then uncoats with nucleocapsid disassembly in the cytoplasm. After the genome is accessible, the replication complex is transcribed and genome replication and transcription of subgenomic mRNAs commences. The genome is then encapsidated by the N protein and the nucleocapsid aligns near envelope glycoproteins in the rough endoplasmic reticulum and Golgi sites of assembly. The virus is released as nucleocapsids bud in the rough endoplasmic reticulum and vesicles are secreted via exocytic pathway of the cell resulting in 100-10,000 progeny (Baric 2007).

II, Human Biology and Patient Care

In humans, coronaviruses generally cause respiratory infections, occasional enteric infections for infants less than a year old, or rare neurological syndrome (CDC 2013). Most manifest clinically as mild diseases such as a cold or upset stomach. However, severe acute respiratory syndrome (SARS) is a type of coronavirus that can result in fever, dry cough, dyspnea, headache, hypoaxemia, lymphopenia, and possibly death from progressive respiratory failure due to alveolar damage (CDC 2013). Like the other viruses in its family, MERS-CoV causes respiratory strain, with fever, cough, and breath difficulties, and sometimes kidney failure that is the result of inflammation and, ultimately, death (Spencer 2013).

Laboratory tests can be done to confirm the cause of illness, but are not frequently used because the illness is generally mild and the testing is specialized and less accessible (CDC 2013). One way to diagnose coronaviruses is to use serological testing to detect antibodies against the virus produced in response to infection using indirect fluorescent antibody testing and enzyme-lined immunosorbent assays (ELISA) (Cann 2009). Another is to use molecular testing or reverse

transcriptase-polymerase chain reaction tests specific for the RNA from novel coronavirus (Cann 2009). In the most recent case in France, laboratory confirmation for the novel coronavirus was obtained from a bronchoalveolar lavage specimen after a nasopharyngeal specimen tests were negative (WHO 2013).

Those who develop severe acute lower respiratory illness within 10 days after traveling to from the Arabian Peninsula are at risk and should be evaluated (CDC 2013). Transmission of coronaviruses are mostly from aerosols of respiratory secretions, through faecal-oral, and mechanical transmission (Cann 2009). SARS is highly contagious, transmitted through droplets produced by coughing and sneezing, as well as other routes of infection such as faecal contamination (CDC 2013). Though the current methods of spread are not fully understood, exposure to the regions that experience highly contagious disease puts individuals at higher risk (WHO 2013).

There are no specific treatments for illnesses caused by human coronaviruses, as most will recover on their own similar to common colds (CDC 2013). The best treatment strategy for SARS is still unknown but ribavirin and corticosteroids were used extensively during the SARS outbreak but cause significant side effects, resulting in the use of various combinations of lopinavir/ritonavir or convalescent plasma and immunoglobulin (Lai 2005). Noninvasive positive pressure ventilation can help alleviate symptoms and interferons could be useful as well (Lai 2005). Right now there is testing of a new drug cocktail of ribavirin, an antiviral drug, combined with interferon alpha 2b in macaque monkeys, showing that a combination might be useful for patient management in the event of future nCoV infections (Munster et. al. 2013). This is interesting because it is related drugs used in the treatment for SARS. More research is being done to look at the biology and possible treatments for the novel disease, but will possibly be related to the treatments associated with SARS because of the high

similarities in the strains.

A similar concept could probably be applied to vaccination as well. Adenoviral-based vaccine can induce strong SARS-CoV-specific immune responses in monkeys, giving potential for future vaccinations that can also be adapted to MERS-CoV (Gao et. al. 2003). It would be important to develop drugs that target antigens such as the S glycoprotein that is involved in protective immunity and neutralizing antibodies as well as the N protein that deals with T-cell epitopes and antibody immunity (Baric 2007). Even with the lessons learned from SARS-CoV and other coronaviruses, before developing vaccines, questions must be resolved such as immune pathology, protection against zoonotic or heterologous strains, and determining most vulnerable populations (Baric 2007).

III, Population Health and Epidemiology

Coronaviruses were first isolated from chickens in 1937 but human coronaviruses were first identified in the mid 1960s (CDC 2013). Though viruses can cause a number of animal diseases, most will infect only one animal species or only closely related species (WHO 2013). SARS-CoV can infect people and animals, including monkeys, Himalayan palm civets, raccoon dogs, cats, dogs, and rodents (CDC 2013). It is hypothesized that because of the zoonotic origins of SARS, zoonotic strains could be the source of future outbreaks (Donnelly et. al. 2004). Based on recent sequencing of the MERS genome, it was found that it is most closely related to bat coronaviruses, similar to SARS (van Boheemen et. al. 2012). It is also possible that the virus, like SARS-CoV, has a zoonotic origin from pools circulating in horseshoe bats that attack palm civets and raccoon dogs that then interact and are eventually eaten by humans (Wang et. al. 2006).

There are three main sub-groupings of coronaviruses, known as alpha, beta, and gamma

coronaviruses along with a fourth provisionally-assigned new group called delta coronaviruses (CDC 2013). There were five known coronaviruses that can affect humans, including alpha coronaviruses 229E and NL63 as well as beta coronaviruses OC43, HKU1, and SARS-CoV. The novel coronavirus is most similar to the SARS-CoV and is also a beta coronavirus (WHO 2013). However, the number of coronavirus serotypes and extent of antigenic variation is unknown (Cann 2009). Phylogenetic relationships show that the human isolates are clustered within animal isolates before spreading to the epidemic phase (Baric 2007). The genome of the SARS virus was sequenced within 6 weeks of identification of atypical pneumonia in Hong Kong and suggested that any recombination events are ancient and not implicated in the emergence of SARS (Donnelly et. al. 2004).

The spread and incidence of coronaviruses other than SARS-CoV is not well documented in tropical or subtropical climates, including the low publicity of other emerging coronaviruses such as HCoV-NL63 (Chiu et. al. 2005). It is known that coronaviruses are strongly seasonal, with greatest incidence in children in winter and where adult infections are less common (Cann 2009). However, the story of the spread of SARS can give insight into how coronaviruses can spread quickly given certain settings. Overall, the disease resulted in 8,096 cases, 774 deaths in 32 countries (Baric 2007). The SARS outbreak started in Guangdong in February 2003 where 300 people became ill and at least five died (Cann 2009). From south China, it then spread to Hong Kong, Vietnam, Singapore, and even Canada with humans as the main vehicle of transmission (Leung and Ooi 2003). The story of SARS relies heavily on “super-spread” events, where one infected individual trasmitted the disease to a large population of susceptible individuals, especially in different countries through travel, which should be avoided in for the novel coronavirus (Riley et. al. 2003). The story of MERS-CoV currently includes infections of 24 individuals from Saudi Arabia, 2 from Qatar, 2 from Jordan, 3 from United Kingdom, 3

from United Arab Emirates, and now, one from France as well (CDC 2013).

In the case of SARS-CoV, the differential spread of the disease could be affected by how open the government is about disease rates, the designation of specific centers for treatment and quarantine, the campaign to rally all individuals to mobilize against the disease, and more (Koh et. al. 2003). Means to combat such a respiratory disease are limited to containment--restricting how often individuals may come into contact with the disease. During the SARS epidemic it was found that there was 100% protection of healthcare workers who use proper personal protective equipment such as N95 respirators, gloves, and goggles (Baric 2007). This can help limit spread throughout a hospital. Transmission rates fell during the epidemic due to reductions in population contact rates and improved hospital control as well as rapid hospitalization of symptomatic individuals (Riley et. al. 2003). Additionally, limiting the movement of individuals who may have interfaced with the disease through quarantine or restricted travel could prevent spread through different communities or countries (Koh et. al. 2003). There is currently no travel ban for individuals from these regions, but proper caution should be invoked (WHO 2013).

Part 2. Proposal

I, Background and Purpose

It was a single mobile phone text message that alerted residents in the Guangdong province of the impending epidemic known as SARS (Huang 2004). That text message prompted provincial officials to take a stance and prompted the cascade of events. However, text messaging also helped spread chaos, fear, and disorder spread through networks of individuals in Hong Kong and a $2.6

million dollar loss per day in the Hainan banana market because of a vicious rumor that they contained SARS (Jardin 2003, Jean 2007). As more active efforts with mobile phones have included, with great success, diagnosis, compliance reminders, and more, it would make sense that their role in the spread of information can be leveraged for the better, for the purpose of predicting and controlling the spread of disease (Free et. al. 2013). It is important for technology to be used to give feedback to healthcare institutions to provide better and more efficient care.

It would be interesting to better understand why and how technology impacted the SARS epidemic while at the same time learning more about the current MERS-CoV outbreak. This is especially applicable because of the similar nature of the diseases, not only biologically in classification and phylogeny, but also epidemiologically in its ability to spread and impact lives so quickly and profoundly. This study will compare the transmission dynamics of MERS-CoV without intervention, with basic interventions of quarantine and isolation, and with the utilization of a technological intervention. It is hypothesized that with the application of short-messaging service (SMS) technology as an intervention strategy, tracking and controlling the spread of the novel MERS-CoV will be more efficient.

II, Materials and Methods

The intervention will be an SMS campaign with inbound and outbound information from the individuals using it. The inbound information would include carefully designed and timed internationally relevant information similar to press releases from the WHO or CDC, but more relevant to those without internet connection and more timely. Firstly, it would help share correct information without causing panic, almost like a Harvard Message Me service. Additionally, it would disease-relevant tips,

like mDiabetes or Text4Baby (Saligram 2012, Jordan et. al. 2011). This would follow the idea that the use of SMS technology helped spread information through the SARS epidemic--but this time with correct information.

In addition to these tips and information, designated individuals would have the option of responding to text messages to report and sort cases where symptoms arrive or if outbreaks occur in a specific region. This outbound information would allow for "crowdsourcing," or engaging a large group of people to respond, similar to Outbreaks Near Me, an application that tracks user submitted reports of disease outbreaks. After classifying and assessing validity through cross validation, information from these applications had a significant correlation with official measures from the CDC during the H1N1 outbreak and have potential to be applied to MERS-CoV as well (Freifeld et. al. 2010). This means of reporting information could be more targeted than measures that parse through social media or search queries like Google Flu Trends but can have the same effect of giving more timely information than official measures (Ginsberg et. al. 2009).

Teaming up with cell phone providers in the countries who are most at risk for MERS-CoV would help enlist participants. It is not entirely necessary to have full coverage, but the critical coverage will be determined on a case-by-case basis for each country. It would be best to target those who are more central in their social networks, as they have the most social ties and influence. They can be nominated by other individuals through the "friendship paradox," or that individuals nominated by others are statistically more likely to be more central in their networks (Christakis and Fowler 2010).

This combination of different technological ideas could help inform both the patients as well as officials the current state of the spread of MERS-CoV. It would crowdsource some information, but ultimately, this would give more control over the information that is shared. As the disease is currently

spreading, it would be especially important to receive information that is as accurate as possible. At the same time, it is also especially important to be updating the information through rapid means of communication. To understand the possible effectiveness of this intervention, this proposal discusses the impact it will have on the hypothetical transmission dynamics of MERS-CoV.

III, Results and Conclusions

Modelling a disease can help understand the mechanisms through which infectious diseases spread, how an epidemic could be controlled, and predict the future course of an epidemic (Jia and Tsui 2006). Some important measures include incubation period, infectiousness and disease progression, case fatality, and ultimately, the transmission dynamics and transmission model (Connelly et. al. 2004). The transmission model looks at how the current size of the outbreak, the transmissibility of the disease, and mixing behavior of the population can impact the population-level risk posed by an emerging infectious disease (Connelly et. al. 2004).

One measure is the basic reproduction number, or the average number of secondary infections produced by a single primary infection introduced into a large population of previously unexposed hosts (Woolhouse and Gowtage-Sequeria 2005). In the case of SARS-CoV, the basic reproductive number has estimates from 1.05 to 7.7, but has a baseline of 3 determined by Lipsitch et. al. 2003. If R_0 is greater than 1, which it is for all estimates of the SARS outbreak, an infectious disease outbreak has the potential to infect a substantial portion of the population if there is no significant change in behavior or susceptibility of the population (Donnelly et. al. 2004). Therefore, interventions like vaccination that reduces susceptibility or isolation and quarantine that changes behavior will attempt to reduce R_0 to be less than 1.

When defining the transmission model, states that are often used include susceptible (S) who are healthy but have potential to develop disease, exposed (E) which are in latent period, infected (I) which are capable of transmitting the infection, and removed (R) who have immunity either by recovering or dying (Jia and Tsui 2006). There were many proposed models for SARS, but some of the more compelling are listed below, including the basic model using SEIR states, the SEQIR model including quarantine (Q) states, and the SEQIR model including quarantine (Q) and isolation (D) states based on various papers.

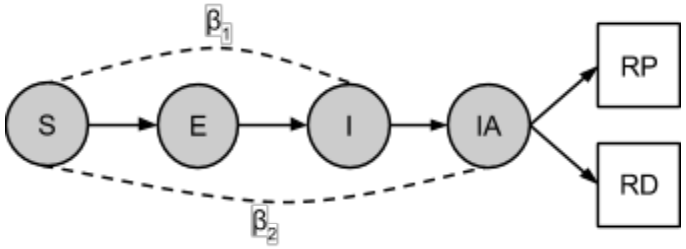


Figure 3. Basic transmission model of MERS-CoV based on SEIR structure. Includes susceptible (S), exposed (E), infected (I) and infected and admitted to a hospital (IA), and removed by immunity (RP) and removed by death (RD) where the transitions β_1 and β_2 represent the the state of secondary infections for each respective path (Jia and Tsui 2006).

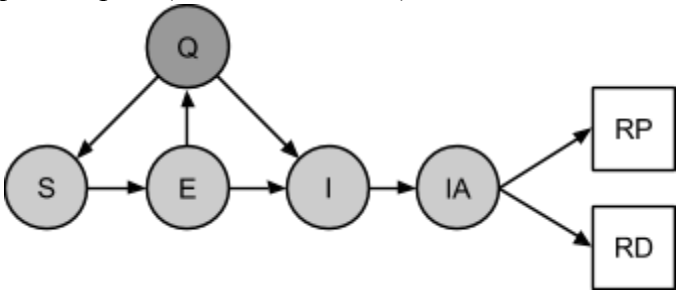


Figure 4. Updated transmission model of MERS-CoV including single quarantine (Q) state (Wang and Ruan 2003).

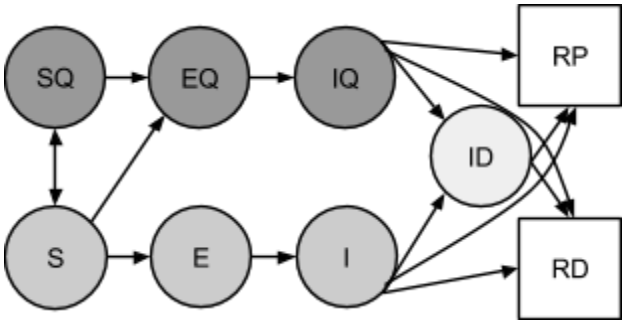


Figure 5. Updated transmission mode of MERS-CoV including states of quarantine for susceptible (SQ), exposed (EQ), and infected (IQ) as well as the state of infected isolation (ID) (Lipsitch et. al. 2003).

Each of the transitions between the states depends on the disease and can be determined by taking measures and looking at software such as SIR Epidemic Dyanmics through Wolfram Demonstrations Project (Wolfram). The basic calculations associated with each model can also be seen in Figure 6. In the big picture, the addition of quarantine and isolation states can help reduce the reproduction number such that it becomes lower than 1. Ultimately, the most effective quarantine is to find the balance between the proportion of contacts quarantined and the proportional reduction in infectious period and days in quarantine per person (Lipsitch et. al. 2003).

$$\frac{dS}{dt} = \mu N - \mu S - \beta \frac{I}{N} S$$
$$\frac{dE}{dt} = \beta \frac{I}{N} S - (\mu + a) E$$
$$\frac{dI}{dt} = aE - (\nu + \mu) I$$
$$\frac{dR}{dt} = \nu I - \mu R.$$

Figure 6. Basic calculations associated with SEIR model, where $S + E + I + R = N$.

Unlike quarantine and isolation, the technological intervention would not necessarily change the model, rather, would change the transitions between the different states of the model. In the basic

models, the aim of the technological intervention would be to reduce the transition between the the susceptible (S) state and the exposed (E) state by reducing the number of people who come in contact with the disease by giving information about where the outbreaks are and promoting better practices. And because R_0 is proportional to β, this would result in a decrease in the basic reproductive number as well, and, therefore, the transmissibility of disease. In the SEQIR model, the technological intervention. Of course, more comprehensive analysis of the statistics presented by the progression of the disease would be needed.

IV, Future and Impact

Some cautions about interpreting the results of this study include some of the assumptions made at the onset of the study. The baseline measurements extrapolated from previous articles about SARS-CoV, and though they are good working assumptions, they should be updated as the outbreak progresses. One of the difficulties of this proposal is the dynamic nature of the information that will change as the disease progresses, which is accounted for in the flexibility of the discussed variables. In terms of the technological intervention itself, it may be difficult to get the critical mass necessary to get crowdsourced information or make a true impact on the behavior in light of more recent developments in the disease. Also, an international, all encompassing solution might be good on a global scale, but is not necessarily as efficient in a given locale.

Practically speaking, using technology to get a better idea of the potential spread of the MERS-CoV virus could help, real time, to adjust policies to help control the spread. This is a case where as the biological solutions take more time to be developed and enacted, interventions that target the social determinants of the spread of disease could be targeted to attempt to stop transmission.

However, this does not mean that biological solutions are not necessary, rather, that a properly timed combination of the two would be a viable means to address MERS-CoV. This intervention would work really well with an attempt to decrease susceptibility, such as vaccination. Such changes, of course would be reflected in the model as well, ideally in the sense of a decreased basic reproductive number. Additionally, having the text-messaging channel in place would be great to inform the public that vaccines are available and are the preferred means of staying safe.

Applying technology to the possible novel coronavirus outbreak not only addresses a health problem that is currently pertinent to many nations and can possibly reach a global scale, but also helps create a framework from which future interventions for similar epidemics or contagions can arise. This is important in the context of global health threats because having such an infrastructure is just one step toward spreading the proper information to incite behavior change in light of a possible outbreak and retrieving the correct information to make epidemiological guesses to the spread of the disease.

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