MERS, SARS, and Ebola: The Role of Super-Spreaders in Infectious Disease

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Super-spreading occurs when a single patient infects a disproportionate number of contacts. The 2015 MERS-CoV, 2003 SARS-CoV, and to a lesser extent 2014–15 Ebola virus outbreaks were driven by super-spreaders. We summarize documented super-spreading in these outbreaks, explore contributing factors, and suggest studies to better understand super-spreading.

Introduction

A number of recent virus outbreaks have resulted in rapid virus spread, placing demands on the affected health infrastructures and sparking global concern. In September 2012, Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged as a novel virus that can result in severe respiratory disease with renal failure, with a case fatality rate of up to 38%. Primary infections typically occur in countries located in the Middle East, where dromedary camels have been identified as one of the species harboring the virus. However, travel has contributed to several cases in other countries. Notably, between May and July 2015, an outbreak of MERS-CoV centered in South Korea killed 36 people out of 186 confirmed cases (Promedmail.org, 2015), with thousands quarantined as health authorities attempted to control virus spread.

Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), a close relative of MERS-CoV, was the etiological agent responsible for an outbreak centered around Guangdong Province in the southeast of China. The SARS-CoV outbreak killed 774 and infected 8,096 people between November 2002 and July 2003, for a case fatality rate of 9.6%, in which the virus was first traced to palm civets, and then bats. Over 80% of the total cases and deaths were from mainland China and Hong Kong.

More recently, a devastating Ebola virus (EBOV) outbreak has swept through Western Africa. EBOV is a filovirus that causes severe hemorrhagic fever in humans with up to a 90% case fatality rate if untreated. Outbreaks of EBOV are sporadic, unpredictable, and localized to sub-Saharan Africa. Prior to the 2014–15 outbreak, a total of 1,093 deaths out of 1,393 infections were documented dating back to 1976, when EBOV first emerged. The natural reservoir of EBOV is currently unknown, but fruit bats are suspected to be the animal species harboring the virus.

In addition to their significant impact, these outbreaks were all perpetuated by super-spreaders who disproportionately infect a high number of contacts and likely contribute to the speed and degree of the outbreak. As discussed in detail below, these outbreaks can be traced to one or more individuals who largely contributed to subsequent infections.

Super-Spreaders in the MERS-CoV Outbreak in South Korea

The 2015 MERS-CoV outbreak in South Korea began from an imported case, a 68-year-old male with a recent travel history to several Middle Eastern countries, including Bahrain, the United Arab Emirates, Saudi Arabia, and Qatar. The latter three countries also had reported human cases of MERS-CoV during the same period of time. After the patient started exhibiting disease symptoms, he sought medical assistance at several clinics before being admitted to a hospital, where he was confirmed to be infected with MERS-CoV (WHO, 2015a). Twenty-nine secondary infections have since been directly traced to this index patient. Additionally, two of these secondary cases were shown to be responsible for 106 subsequent infections, out of 166 known cases at the time (Cowling et al., 2015). Transmission was mostly within nosocomial settings, and fourth generation infections have been documented for the first time since the virus was identified in 2012. Thus, the MERS-CoV outbreak in South Korea was driven primarily by three infected individuals, and approximately 75% of cases can be traced back to three super-spreaders who have each infected a disproportionately high number of contacts (Figure 1A). This MERS-CoV outbreak is the second largest on record and the largest outside of the Middle East. The MERS-CoV outbreak currently appears to be under control, with no additional infections reported in South Korea since July 4, 2015.

The SARS-CoV Outbreak

Retrospectively, several super-spreading events were also documented during the SARS-CoV outbreak in 2003. The index patient of the Hong Kong epidemic was treated at Prince of Wales Hospital and was associated with at least 125 secondary cases (Riley et al., 2003). Subsequent super-spreader events occurred at the Hotel Metropole (13 cases) and the Amoy Gardens housing complex (over 180 cases) in Hong Kong and aboard an Air China flight traveling from Hong Kong to Beijing (22 cases) (Braden et al., 2013). Notably, cases from Hotel Metropole were responsible for the spread of SARS-CoV to Canada, Vietnam, and Singapore through travel (Figure 1B),

and the imported case to Canada resulted in 128 SARS-CoV cases at a Toronto hospital (Braden et al., 2013).

Have Super-Spreaders Played a Role in Other Outbreaks?

To a lesser extent, similar events were observed with the 2014-15 EBOV outbreak, centered in the Western African countries of Guinea, Sierra Leone, and Liberia. Epidemiological work has linked five infections with a 2-year-old toddler in the remote village of Meliandou, Guinea. One of the contacts, a midwife, infected at least three others, including a hospital worker at Guéckédou hospital. This worker then infected several family members in the Guéckédou Farako district, as well as 15 others at Macenta hospital (Baize et al., 2014). One of the subsequent cases, a doctor, was known to have infected several others who traveled to Kissidougou and Nzérékoré, further propagating virus transmission (Baize et al., 2014). The outbreak eventually spilled over to neighboring Liberia and Sierra Leone. In Sierra Leone, the funeral of a traditional healer that died from EBOV was shown to have directly infected 13 others (Gire et al., 2014) and was eventually linked to more than 300 cases (WHO, 2015b). The EBOV outbreak has killed 11,284 people, with 27,741 infected as of July 19 2015, en route to becoming the largest filovirus outbreak ever documented. In addition to EBOV, super-spreading has also been documented in outbreaks with other pathogens, including measles (Paunio et al., 1998) and *Mycobacterium tuberculosis* (Kline et al., 1995).

Why Is the Super-Spreader Phenomenon Important?

The initial stages of the outbreaks mentioned above involved at least one super-spreading event. The ability of the pathogen to infect subsequent super-spreaders who may export the disease through travel is likely the difference between an infection cluster and an outbreak or epidemic (Figure 1C). Differences in the initial response to MERS-CoV is why South Korea reported clusters of infections before bringing the virus under control and why China, Thailand, and the Philippines have not reported any additional cases despite imported MERS-CoV infections. It was why SARS-CoV was so devastating in mainland China and Hong Kong from 2002 to 2003. It was also why the 2014–15 EBOV outbreak spiraled out of control in Western Africa, with hundreds of new cases reported weekly, before a coordinated international effort (including contact tracing, isolation, diagnosis, and treatment of infected patients, as well as community education) brought the number down to a more manageable 20–30 weekly infections, with most of the cases diagnosed in Guinea and Sierra Leone. Early discovery, diagnosis, intervention, and quarantine of confirmed cases is crucial for preventing further disease transmission in humans, especially via super-spreaders. As evidenced by the decreased numbers of new cases in the MERS-CoV and EBOV outbreaks, current responses are effective, provided that the measures are implemented properly and followed strictly. Vigilance and patience will be necessary until the ongoing MERS-CoV and EBOV outbreaks are officially at an end.

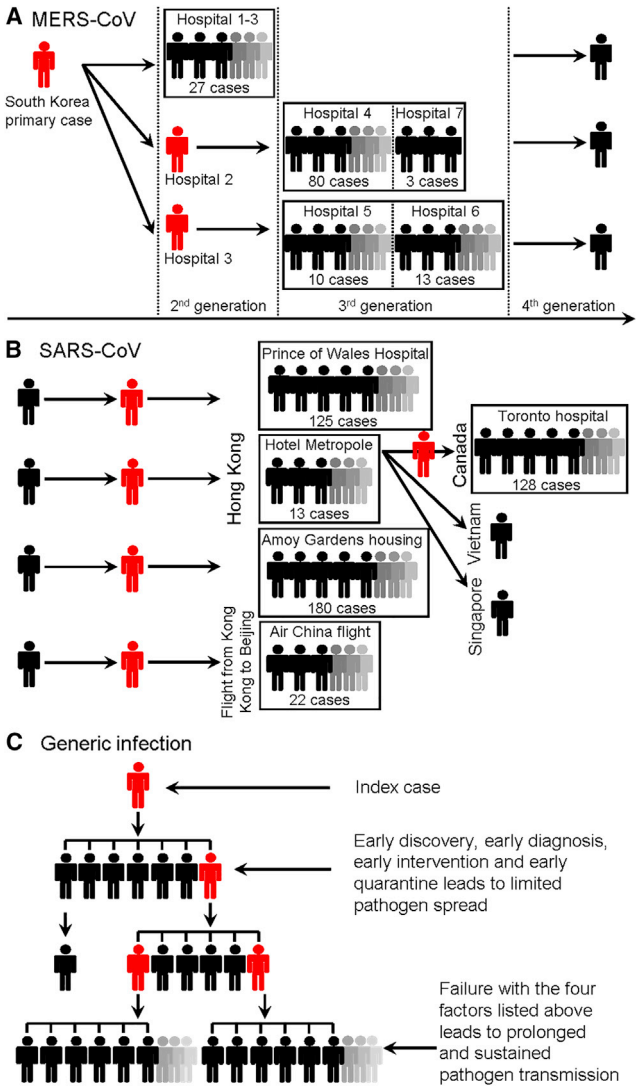

Figure 1. Dynamics and the Role of Super-Spreaders in MERS-CoV and SARS-CoV Transmission

(A and B) Simplified diagrams of super-spreading events driving the 2015 MERS-CoV (A) and 2003 SARS-CoV (B) outbreaks. Super-spreaders are shown in red.

(C) The effect of super-spreaders during infection with a generic pathogen. Most infected cases have limited transmission levels, but infection of super-spreaders can rapidly increase the number of cases in the absence of early intervention, resulting in a (prolonged) outbreak or epidemic.

Approaches or Guidelines that Can Proactively Identify Super-Spreaders

Currently, super-spreaders are only retrospectively categorized after epidemiological tracing. Given their high propensity to spread infection, super-spreaders should be able to shed higher levels of pathogen and/or for a longer period of time after infection. This would increase the probability that the pathogen contacts and subsequently infects a naive host.

To address whether there are factors or parameters that promote or indicate enhanced virus shedding in a laboratory setting, an animal species that closely recapitulates symptoms of the human disease is required, such that any findings can be translated to humans. Animals

Table 1. Factors that May Influence Infectious Diseases Transmission

Factors that Influence Transmission	Examples from MERS-CoV, SARS-CoV, and EBOV
Virus and Host	Virus mutation: the virus may acquire mutations to replicate more efficiently and become highly pathogenic, which may result in higher levels of virus shedding for a longer period of time.
	Duration of contact with an infectious host and route of infection: in a guinea pig model of EBOV infection, animals that were infected mucosally were more infectious than those that were infected systemically. Additionally, prolonged contact with a contagious animal resulted in a higher rate of virus transmission.
	Genetic susceptibility: EBOV is known to be more pathogenic in cynomolgus macaques compared to other nonhuman primate species, such as rhesus macaques. Different nonhuman primate species also demonstrate variable susceptibility to SARS-CoV infection. Hosts that are more susceptible to disease may exhibit higher levels of virus shedding.
	Underlying medical conditions: certain conditions may decrease immunity and increase susceptibility to pathogens, leading to enhanced virus shedding. Many fatal MERS-CoV patients in the recent outbreak in South Korea had other pre-existing medical conditions, including pneumonia and kidney disease.
Environment	Air re-circulation in enclosed spaces: this would increase chances of pathogen encounter, especially those that are airborne. During the SARS-CoV outbreak, this was shown to be a factor behind super-spreading events at the Hotel Metropole, Amoy Gardens housing complex, and a flight between China and Canada. It is likely a contributing factor to the MERS-CoV outbreak since super-spreading events occurred at a hospital or medical clinic.
	Population density: increased numbers of people equally increases the chances to infect a naive host through inadvertent direct or indirect contact.
Behavior	Traditional customs and beliefs conducive to infectious disease spread: the culture of "doctor shopping," in which patients seek medical attention from multiple doctors at different clinics/hospitals allowed MERS-CoV to spread rapidly in South Korea. Unsafe burials and traditional funerals, which involve touching and washing infectious bodies, played a role in EBOV spread in Western Africa.
	Travel and trade: the global nature of today's world allows infectious diseases to easily bypass geographical barriers. For instance, MERS-CoV originated from the Middle East, but imported cases were reported in North America, Europe, and Asia. SARS-CoV originated in Asia, and imported cases were reported in North America, Europe, and other parts of Asia. EBOV originated from Africa, and imported cases were reported in North America and Europe.
	Knowledge and adherence to public health advice: during the MERS-CoV outbreak, a case was imported to China because a South Korean patient did not follow the recommendations of health authorities and traveled despite being a symptomatic, high-risk contact. However, China handled the imported case properly, and the imported Korean patient did not become a super-spreader. During the EBOV outbreak, some patients were able to escape quarantine, thereby increasing the likelihood of infecting others.

could be experimentally infected with different virus strains/variants at varying doses via different challenge routes, in which virus shedding from the oral, nasal, and rectal cavities should be correlated with different parameters, including viremia or virus titers in the organs. However, these studies are currently challenging for SARS-CoV as there is currently not an appropriate animal model that replicates the severe disease seen in humans; infected nonhuman primates exhibit variable, but at most mild to moderate, respiratory disease (McAuliffe et al., 2004) (Lawler et al., 2006). Nonetheless, these types of studies are feasible for MERS-CoV. A model of this infection was developed in the common marmoset that results in severe respiratory disease and partial lethality, in which live virus can be detected in nasal and throat swabs of infected animals (Falzarano et al., 2014). Thus, the studies proposed above can be investigated with MERS-CoV in this animal model.

For EBOV, the cynomolgus and rhesus macaque animal models are well characterized and have been used over the past 20+ years. EBOV shedding is known to occur from the oral, nasal, and/or rectal cavities of nonhuman primates during the advanced stages of disease, but factors that influence virus shedding from these animals have not yet been investigated. Interestingly, using a guinea pig model, it was shown that animals infected intranasally (i.n.) with guinea pig-adapted EBOV were more contagious to naive contact animals than those that were infected intraperitoneally (i.p.) with the same dose (Wong et al., 2015). I.n. infected animals shed virus from their nasal cavity earlier than their i.p. counterparts, and i.p. challenged animals died earlier (and thus were removed from contact with naive animals) compared to i.n. inoculated guinea pigs. It was therefore concluded that the route of infection in addition to the duration of contact time with an infectious host may be factors that influence the efficiency of virus transmission. It will take time to elucidate all possible host and viral factors that contribute to virus shedding, which remains an understudied topic to date. Therefore, it is not currently possible to predict with any level of confidence or statistical significance whether a person will become a super-spreader of a certain disease. Large-scale genome-wide association studies (GWAS) of super-spreaders might provide some clues about the genetic backgrounds of super-spreaders, but the feasibility and robustness of these analyses will depend on the number of super-spreaders in a given outbreak.

Additional Approaches to Study Risk Factors behind Super-Spreading

The large amount of patient data and samples available from the recent MERS-CoV and EBOV outbreaks provide

possible opportunities to investigate factors that may correlate with an increased risk for becoming a super-spreader. Using the MERS-CoV outbreak as an example, detailed records were kept for the majority of patients who were confirmed to be infected with MERS-CoV. Since the identities of the three super-spreaders are known as Patients #1, #14, and #16, studies can be performed to investigate whether these three patients have common traits (i.e., age, gender, pre-existing medical conditions or underlying co-morbidities, levels of virus shedding, etc.). Any common characteristics can then be compared with non-super-spreader patients to provide insight into possible risk factors behind enhanced spreading of infectious diseases.

Another approach would be to isolate MERS-CoV from the three known super-spreaders, perform sequence analysis of the viral genomes, and determine whether there are any shared mutations between these isolates. Any mutations that are identified and are absent from the viral genomes of other patients could be indicators of enhanced virus shedding, allowing for super-spreading to occur.

Concluding Remarks

A complex combination of factors likely plays a role in the number of subsequent infections initiating from a single super-spreader. In addition to host and virus factors, other important factors impacting the spread of infectious diseases are the environment and behavior of individuals. Environmental factors include the close proximity of other susceptible hosts and the airflow dynamics within an enclosed area. A high population density represents a greater number of susceptible hosts for direct/indirect contact with an infected person, whereas air recirculation would especially facilitate the transmission of airborne viruses, such as MERS-CoV and SARS-CoV. Hospitals, enclosed housing complexes, and mass transportation, such as airplanes, are documented sites of super-spreader events, especially during the MERS-CoV and SARS-CoV outbreaks (Table 1). Individual behaviors may also enhance disease spread. These include "doctor shopping"—going to multiple hospitals to treat the same ailments or traveling to other countries after the appearance of disease symptoms, which was observed with the MERS-CoV outbreak (Su et al., 2015). Traditional customs, such as unsafe funerals/burials in Africa, which involve direct contact with infectious bodily fluids of patients that passed away from EBOV disease, is another major reason why the outbreak persisted in Guinea and Sierra Leone (Table 1). A thorough study of host, virus, and environmental dynamics will be important to delineate the relative contribution of each factor to the phenomenon of super-spreading. Findings from these studies, combined with changes in behavior conducive to the spread of disease, will be important for the effective management of and preparation for future outbreaks.

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REFERENCES

Baize, S., Pannetier, D., Oestereich, L., Rieger, T., Koivogui, L., Magassouba, N., Soropogui, B., Sow, M.S., Keïta, S., De Clerck, H., et al. (2014). Emergence of Zaire Ebola virus disease in Guinea. N. Engl. J. Med. *371*, 1418–1425.

Braden, C.R., Dowell, S.F., Jernigan, D.B., and Hughes, J.M. (2013). Progress in global surveillance and response capacity 10 years after severe acute respiratory syndrome. Emerg. Infect. Dis. *19*, 864–869.

Cowling, B.J., Park, M., Fang, V.J., Wu, P., Leung, G.M., and Wu, J.T. (2015). Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015. Euro Surveill. *20*, 7–13.

Falzarano, D., de Wit, E., Feldmann, F., Rasmussen, A.L., Okumura, A., Peng, X., Thomas, M.J., van Doremalen, N., Haddock, E., Nagy, L., et al. (2014). Infection with MERS-CoV causes lethal pneumonia in the common marmoset. PLoS Pathog. *10*, e1004250.

Gire, S.K., Goba, A., Andersen, K.G., Sealfon, R.S., Park, D.J., Kanneh, L., Jalloh, S., Momoh, M., Fullah, M., Dudas, G., et al. (2014). Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science *345*, 1369–1372.

Kline, S.E., Hedemark, L.L., and Davies, S.F. (1995). Outbreak of tuberculosis among regular patrons of a neighborhood bar. N. Engl. J. Med. *333*, 222–227.

Lawler, J.V., Endy, T.P., Hensley, L.E., Garrison, A., Fritz, E.A., Lesar, M., Baric, R.S., Kulesh, D.A., Norwood, D.A., Wasieloski, L.P., et al. (2006). Cynomolgus macaque as an animal model for severe acute respiratory syndrome. PLoS Med. *3*, e149.

McAuliffe, J., Vogel, L., Roberts, A., Fahle, G., Fischer, S., Shieh, W.J., Butler, E., Zaki, S., St Claire, M., Murphy, B., and Subbarao, K. (2004). Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. Virology *330*, 8–15.

Paunio, M., Peltola, H., Valle, M., Davidkin, I., Virtanen, M., and Heinonen, O.P. (1998). Explosive school-based measles outbreak: intense exposure may have resulted in high risk, even among revaccinees. Am. J. Epidemiol. *148*, 1103–1110.

Promedmail.org (2015). MERS-COV (97): South Korea, Saudi Arabia. International Society for Infectious Diseases.

Riley, S., Fraser, C., Donnelly, C.A., Ghani, A.C., Abu-Raddad, L.J., Hedley, A.J., Leung, G.M., Ho, L.M., Lam, T.H., Thach, T.Q., et al. (2003). Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science *300*, 1961–1966.

Su, S., Wong, G., Liu, Y., Gao, G.F., Li, S., and Bi, Y. (2015). MERS in South Korea and China: a potential outbreak threat? Lancet *385*, 2349–2350.

WHO (2015a). Middle East respiratory syndrome coronavirus (MERS-CoV) – Republic of Korea. Disease Outbreak News. 24 May 2015. http://www.who.int/csr/don/24-may-2015-mers-korea/en/.

WHO (2015b). Sierra Leone: a traditional healer and a funeral. http://www.who.int/csr/disease/ebola/ebola-6-months/sierra-leone/en/.

Wong, G., Qiu, X., Richardson, J.S., Cutts, T., Collignon, B., Gren, J., Aviles, J., Embury-Hyatt, C., and Kobinger, G.P. (2015). Ebola virus transmission in guinea pigs. J. Virol. *89*, 1314–1323.