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# Evaluating the potential impact of targeted vaccination strategies in mitigating Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks in the healthcare setting

Fatima Abdirahim Abdirizak  
*Georgia State University*

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**TITLE OF THESIS:** Evaluating the potential impact of targeted vaccination strategies in mitigating Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks in the healthcare setting

**ABSTRACT (150-250)**

The Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) are two coronaviruses that have generated substantial nosocomial outbreaks. In particular, MERS continues to pose a significant threat in the Middle East since 2002. Currently, no licensed vaccine or drug treatment is available to treat patients infected with either virus. However, there are some MERS vaccines in the preclinical stage of development. We sought to evaluate the potential impact of targeted vaccination strategies for mitigating SARS and MERS outbreaks in healthcare settings by using simple statistical methods and detailed transmission trees describing the progression of prior nosocomial outbreaks. Our proposed vaccine strategies target two groups, patients and healthcare workers, who have contributed disproportionately to transmission. We assumed vaccination coverage levels at 50% and 75%. Our study found that vaccine strategies targeting patients averted nearly 50% of MERS and SARS. Thus, considering that SARS and MERS are amplified in healthcare settings due to diagnostic delays and suboptimal infection control measures, which facilitate the generation of super-spreading events, our results suggest that implementing a vaccine deployment strategy targeting patients has the potential to substantially limit transmission in the healthcare setting.

**By**

Fatuma Abdirizak

**DATE**

April 22, 2016

Evaluating the potential impact of targeted vaccination strategies in mitigating Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) outbreaks in the healthcare setting

by

Fatuma A. Abdirizak

B.A., Agnes Scott College

A Thesis Submitted to the Graduate Faculty  
of Georgia State University in Partial Fulfillment  
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30303

APPROVAL PAGE

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by

Fatuma A. Abdirizak

Approved:

Gerardo Chowell  
Committee Chair

Glen Abedi  
Committee Member

April 22, 2016  
Date

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## Author's Statement Page

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Fatuma Abdirizak  
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## **Introduction:**

Saudi Arabia has reported approximately 78.8% of MERS-CoV cases worldwide [1]. The first MERS-CoV case was identified in Saudi Arabia and since then the country has experienced nosocomial outbreaks each year [1]. Outbreaks in healthcare settings have been associated with overcrowding conditions, movement of undetected cases through the facility, and insufficient implementation of infection prevention and control measures [2]. The transmission dynamics seen with MERS-CoV resembles those of SARS-CoV-a coronavirus that is responsible for the 2003-2004 global epidemic [3]. The modes of transmission and risk factors for MERS infection remain unclear, however, camels appear to play an important role in triggering human-to-human transmission [2, 4]. Thus, given the recurrent nature of MERS-CoV outbreaks in Saudi Arabia, it is important to understand the transmission dynamics of specific interventions to mitigate outbreaks in the healthcare setting [5-8]. Preventing and limiting the size of future outbreaks, especially of MERS-CoV, remains a priority, and use of a vaccine in high-risk populations can serve as a preventive tool. Though there have not been any SARS cases reported for 13 years, modeling SARS transmission in the healthcare setting may inform strategies for controlling MERS outbreaks, which are still occurring [2, 9]. It is increasingly important to consider the most effective method of deploying a vaccine, such as targeting groups that generate the most MERS and SARS cases, once a vaccine is available [10]. This study is designed to model the potential impact of targeted vaccination strategies by using stochastic simulations and detailed transmission trees that describe the course of past MERS and SARS outbreaks in healthcare settings.

## **Literature Review:**

### **Virology of MERS-CoV and SARS-CoV:**

Coronaviruses are single-stranded RNA viruses that can cause respiratory, enteric, hepatic, and neurological diseases in both animals and humans [11]. Before 2003, there were two known coronaviruses, human coronavirus 229E (HCoV-229E) and HCoV-OC43, which were associated with mild colds and, among infants, the elderly, and immunocompromised individuals, severe lower respiratory tract infection [12] [13]. In the last decade and a half, two novel betacoronaviruses ( $\beta$ CoV), Severe Acute Respiratory Syndrome (SARS) coronavirus and the Middle East Respiratory Syndrome (MERS) coronavirus, have emerged as pathogens with the potential to cause large outbreaks in human populations [11]. Unlike HCoV-229E and HCoV-OC43, the SARS and MERS coronaviruses have often resulted in severe clinical outcomes, whereas HCoV-229E and HCoV43 have less frequently been associated with lower respiratory tract infections, including pneumonia [13].

The SARS virus was detected in palm civets and raccoon dogs from wild-animal markets in the Guangdong Province of China [14]. Civets were believed to have amplified transmission in these markets in southern China [14]. The culling of palm civet played a fundamental role in the control of SARS [14]. For MERS, dromedary camels seem to play a greater role in the transmission of the virus. [15]. Multiple serological studies found MERS infection among dromedary camels in the Middle East including countries like Saudi Arabia, Qatar, UAE, and Jordan as well as countries outside the Middle East such as Somalia, Sudan, and Egypt, which are where camels found in the Arabian Peninsula originated from [15].

Individuals with SARS infection can present a variety of symptoms including feverishness, chills, rigors, sore throat, nonproductive cough, and dyspnea [14-17]. Severe cases

of SARS have resulted in acute pneumonia with rapid respiratory deterioration [14, 15]. Clinical deterioration typically occurs one week after the onset of illness [14]. Children typically present with milder symptoms than adults and the elderly may not even experience fever or respiratory symptoms [14]. MERS patients may be asymptomatic, have mild respiratory symptoms, or severe respiratory disease that can lead to death [2]. Symptoms of MERS include fever, chills or rigor, cough, shortness of breath, myalgia, and gastrointestinal pain specifically diarrhea [18]. The virus has caused more outcomes among older individuals, with a median age of 45, and who have a weak immune system or pre-existing conditions [2, 6]. According to the World Health Organization (WHO), a confirmed case of MERS coronavirus is one that has been laboratory confirmed regardless of symptoms however, countries may have their own case definitions [19] [20]. However, the WHO defines a patient to have SARS if they have a positive laboratory result and present with clinical symptoms related to SARS [3].

### **Nosocomial Outbreaks of SARS and MERS**

The section below discusses publically available information on healthcare outbreaks of MERS and SARS found in the scientific literature and government reports.

#### **Global SARS Outbreak 2003-2004:**

On November 16, 2002, a case of abnormal pneumonia was first reported in the Guangdong province in southern China [21]. On March 12, 2003, the World Health Organization issued a global alert concerning atypical pneumonia from China, Vietnam and Hong Kong [21]. Severe Acute Respiratory syndrome (SARS) was reported in 26 countries with a total of 8098 cases after six months [21, 22]. Although many countries reported cases of SARS, the disease was often contained to a few imported cases without any further spread [23].

However, five areas- Canada, China, Hong Kong, Singapore, and Vietnam- experienced SARS outbreaks [23].

The outbreak in Hong Kong initially started with health care workers and then spread to the community and, later, other countries [24]. Hong Kong provided a link between cases in China and other countries [25]. Between February 15 to May 31, 2003, 1755 cases and 302 deaths occurred in Hong Kong [25]. The majority of the SARS cases in Hong Kong resulted from outbreaks in hospital settings and in one housing community [22, 23]. In fact, 49% of the total cases were linked to healthcare facilities [25].

Additionally, the virus spread to Toronto, Canada when a traveler from Hong Kong spread the virus to family contacts and a hospital in Toronto [26]. Toronto experienced two waves of SARS. The first wave was from February 23 to April 19, 2003 [26]. During the first wave, 216 cases were connected to a single hospital [27]. The second wave was from April 21 to Jun 12, 2003 [26]. The spread of SARS during the first wave led to improved infection control measures in an effort to contain the virus [26]. However, after the last SARS case was reported in mid-April, infection control measures were relaxed, prompting the second wave of transmission [26]. Overall, WHO reported 251 total cases in Canada, among which 109 were healthcare workers [23].

Similarly to Canada, Singapore's SARS outbreak began with a traveler from Hong Kong [28]. When the traveler arrived in Singapore, she was admitted to an acute care hospital [28]. The virus ultimately spread to three major acute care hospitals [28]. According to WHO, Singapore reported 238 cases of SARS, of whom 41% were healthcare workers, between February 25 to May 5, 2003 [23]. Vietnam also experienced a SARS outbreak, when the virus was detected in a traveler from Hong Kong [29]. All of the SARS cases in Vietnam were linked

to the Hong Kong traveler and further amplified in hospital settings [29]. From the period of February 23 to April 14, 2003, there was a total of 63 SARS cases of which 83% of the cases were linked to healthcare settings in Vietnam [22].

### **Global MERS Outbreaks 2013-2015**

Since September 2012, there have been 1,714 laboratory-confirmed cases of MERS reported to WHO[2]. The virus has been reported in 26 countries [2]. Sporadic importation of MERS outside of the Middle East has primarily been due to returning travelers from the Middle East [2]. Sustained MERS transmission outside of the Middle East was atypical until the South Korea outbreak, which is also considered to be the largest MERS outbreak outside of the Middle East [2]. Currently, 80% of the global MERS cases have been reported in Saudi Arabia [30]. This section will describe nosocomial outbreaks in Saudi Arabia, Jordan, United Arab Emirates, and South Korea.

### **MERS Outbreak in the Kingdom of Saudi Arabia:**

#### ***Al Hasa (April-May 2013):***

There was a total of 23 MERS-CoV human-to-human transmissions from four healthcare facilities reported in Al-Hasa, Saudi Arabia in 2013 [18, 31]. In brief, the outbreak started with one patient (patient A) who was admitted to the hospital due to dizziness and diaphoresis [31]. This patient also had a son who was positive for MERS-CoV [31]. The outbreak transpired after Patient A was housed in an adjacent room from a patient receiving hemodialysis who three days later developed MERS-CoV [31]. Next, nine other patients became infected during hemodialysis in the same hospital [31]. Soon after, the virus spread to patients, healthcare workers, and contacts as patients were transferred to other hospitals [31].

***Jeddah and Riyadh (Mid-March-May 2014):***

The MERS-CoV outbreak in Jeddah involved multiple healthcare facilities and spanned from mid-March to May [6, 32, 33]. A study investigating the 2014 outbreak in Jeddah found that there were 255 patients and 81 healthcare workers infected [6]. Laboratory results obtained during the period of the outbreak found that 49% of the 168 positive lab results were from King Fahd Hospital [33]. The outbreak in Jeddah was considered to have been caused by secondary human-to-human transmission and then amplified in health care settings [6].

During this time period, 45 cases also occurred in Riyadh [32]. Drosten et al. demonstrated a link between the viruses circulating in Jeddah and Riyadh, which included a cluster of infections linked to the Prince Sultan Military Medical City (PSMMC) [33]. Another study that examined viral genetic data from the King Fahad Medical City in Riyadh found that the outbreak involved forty-five positive patients, of whom eight were patients, and twenty-three were healthcare workers. [32].

***Taif (September 2014- January 2015):***

In September 2014, a multiple healthcare facility outbreak was reported in Taif involving 38 MERS cases [34]. Of the 38 cases, 38% were healthcare professionals including a clerk and cleaners [34]. The index patient was a 45-year-old military man who was admitted to the tertiary acute-care facility with respiratory compromise [34]. Next, fifteen patients were reported to be infected in the dialysis unit, which is a building separate from the acute-care facility [34]. In the third hospital, a MERS positive patient was transferred in from another hospital in Taif and shortly after three healthcare workers became ill with MERS [34]. In the last healthcare facility to report MERS, the index patient was a 75-year-old woman who was transferred from the third hospital [34]. A patient staying in the same room as the index patient developed MERS as well as the cleaner [34].

### ***Hofuf, Al-Hasa Outbreak (April-June 2015)***

The outbreak was first ignited in the region of Al-Hasa by an index patient who infected six family members before admission to a hospital [35]. Once the index patient's family contacts were admitted to a hospital, the virus was transmitted to a healthcare worker that was attending the index patient's family member [35]. Also, a MERS positive patient was transferred to a specialized cardiac center [35]. This transferred patient generated nine secondary cases of which six of those cases died [35].

### ***Riyadh Outbreak (August-September 2015)***

The outbreak in Riyadh was linked to National Guard Hospital in Riyadh city, a 1,200-bed tertiary care hospital with 150 emergency room beds and 250,000 visitors each year [7] [36, 37]. The cases were first found in the emergency room of the hospital [38]. Although a triage system was established, the virus continued to spread due to over-crowding, diagnostic delays, and breaches in infection control [38]. The nosocomial outbreak generated 130 cases, and fifty-one deaths [36]. Of the 130 cases 81 (62%) were confirmed and 49 (38%) were probably of whom 43 (47%) were healthcare workers [7].

### **MERS Nosocomial Outbreaks Outside of KSA:**

The 2012 Zarqa outbreak in Jordan was identified through retrospective analysis after two fatal cases in Jordan tested positive for MERS-CoV [39]. Epidemiologists from Jordan's Ministry of Health, US Centers for Disease Control and Prevention (CDC), and regional partners conducted a retrospective seroepidemiologic study [39]. The goal of this study was to assess whether contacts from this outbreak had MERS-CoV antibodies present during testing, if transmission was prevalent among household contacts or hospital contacts, and finally to understanding the clinical features present in MERS-CoV cases in Jordan [39]. In the review, 97 healthcare workers were enrolled in the study [39]. This population represented individuals that



were present in the intensive care unit (ICU), coronary care unit (CCU), or who had contact with persons involved in the outbreak between February and April 2012 [39]. Of the 57 healthcare workers that remained in the study, six had MERS-CoV [39]. In regard to household transmission, the investigation mentioned a wife who tested positive for MERS-CoV [39]. The Zarqa outbreak was attributed to several infection control problems including lack of separation between beds in ICU and CCU, the absence of negative pressure rooms, and noncompliance with infection control procedures [39].

By September 2015, the United Arab Emirates reported 74 cases of laboratory-confirmed MERS-CoV primarily in Abu Dhabi [40]. Hunter et al. study described the epidemiologic and clinical characteristics of healthcare-associated MER-CoV in Abu Dhabi [40]. Their research included cases reported from January 1, 2013, to May 9, 2014[40]. Of the 65 MERS case-patients, 47% were healthcare associated infections, of whom 70% were HCWs and 22% were hospitalized patients [40]. In the investigation, there were three healthcare-associated clusters identified from three separate hospitals [40]. Healthcare transmission of MERS was associated with HCWs, patients, and visitors coming into contact with a positive MERS case before the case was diagnosed with MERS and proper infection control measure were implemented [40].

More recently, South Korea experienced its first case of MERS-CoV [41]. The index patient was a 68-year-old man who traveled to Bahrain, the UAE, KSA, and Qatar [41]. Initially, the man was asymptomatic but subsequently developed symptoms and sought care at four different healthcare facilities [41]. MERS was not suspected in the patient at first so proper isolation was not practiced [41]. This issue left all hospital attendees including HCWs, patients, and family members exposed to the virus. During the outbreak, a confirmed case who was symptomatic disregarded medical advice and traveled to Guangdong, China [41]. Furthermore,

the index patient alone visited five hospitals in South Korea and infected thirty individuals [42, 43]. Potential superspreader, patient no. 14, further fueled the MERS-CoV outbreak in South Korea. This patient waited two and a half days in the emergency room until a bed was available at Samsung Hospital in Seoul [44]. Once the patient tested positive for the virus, it was discovered that about 900 healthcare personnel, patients, and visitors could have been possible contacts of this patient [44]. Unlike the sporadic cases of MERS-CoV on the Arabian Peninsula, South Korea rapidly concluded their outbreak of 186 cases as of late with no new cases [43].

## **Vaccines**

Currently, there are no approved vaccines to prevent human infections with SARS-CoV and MERS-CoV [13]. For SARS and MERS, there is no specific treatment plan so a supportive approach is taken to treat patients based on their clinical condition [11, 45]. During the global SARS outbreak, 50 leading SARS researchers and countries expressed the urgency for a safe and effective vaccine to contain the epidemic [46]. Although there is not an active vaccine for SARS, researchers have made strides that have aided in the vaccine development for MERS. While designing an antiviral for SARS it was discovered that the S protein is the major immunogenic components of coronaviruses [15]. There have been no new reported SARS cases for over ten years; however, MERS still continues to be a global concern especially in light of the large outbreak in South Korea that was given rise by an exported case that visited multiple countries in the Middle East [3, 11]. Thus, a vaccine for MERS that is safe, stable, and effective could potentially be vital in reducing transmission in healthcare facilities [11, 13, 47].

To date, there are 11 MERS vaccines under development that use viral vectors, recombinant proteins, DNA, a combination of DNA and recombinant proteins, nanoparticles and finally recombinant virus but these vaccine candidates are either in the cell culture or preclinical

stage[47]. Researchers at the University of Washington are working on therapeutics by examining human genes that disrupt during infection [48]. The outcome of this research will contribute to identifying which classes of drugs that may be able to stop the virus or the genetic disruptions [48]. Their study found that SARS-CoV and MERS-CoV affect human cells differently. In fact, MERS-CoV disrupts more genes than SARS-CoV[48]. NIAID Rocky Mountain Laboratories scientists are currently studying a combination of two antiviral drugs- ribavirin and interferon-alpha 2b [48]. They discovered that a combination of the two drugs can prevent the virus from reproducing in laboratory-grown monkey cells [48]. In the monkey disease model, the antivirals reduced MERS-CoV replication and improved clinical outcome. Above all, scientists have identified 27 drugs that have shown activity against both MERS-CoV and SARS-CoV, in test-tube experiments [48]

### **Guidelines for the Immunization of Healthcare Workers in GCC Countries**

The Infection Prevention & Control Manual for GCC countries developed by the Gulf Cooperation Council-Centre for Infection Control (GCC-CIC) outlines recommended vaccines for healthcare workers (HCWs) as well as guidelines that HCW should abide by if infected with any infectious disease [49]. Though a vaccine is not available for MERS and SARS, another respiratory virus, influenza does have a vaccine and all HCWs are recommended to take the vaccine annually [49]. Also, measles, a highly contagious rash illness, played a prominent role in nosocomial transmission during the 1989-1991 measles resurgence much like MERS today [50]. In the case of measles, healthcare workers are required to provide evidence of immunity to measles [50]. However, infection control measures are fundamental in controlling measles outbreaks, similar to SARS and MERS outbreaks [50]. Of note, HCWs that have been exposed or infection with viral respiratory infection are generally instructed to be excluded from caring

for patients that are considered high risk during outbreaks [49]. In the case of MERS in KSA, HCWs that have had contact with a MERS case for more than 10 minutes and within 1.5 meters are instructed to get tested for MERS [51]. For HCWs that were in contact with a MERS case for less than 10 minutes, more than 1.5 meters away, and present to be asymptomatic are not required to be tested for MERS [51].

## **Methodology:**

Our methodology to assess targeted vaccination strategies was adapted from Coltart et al.'s study "Role of Healthcare Workers in Early Epidemic Spread of Ebola: Policy Implications of Prophylactic Compared to Reactive Vaccination Policy in Outbreak Prevention Control" [10]. In this study, we modeled the potential impact of targeted vaccination strategies on nosocomial outbreaks of MERS and SARS using data on transmission trees describing the evolution of epidemics coronavirus outbreaks (Figure 1). Our study extends the study by Coltart et al. [10] by generating multiple stochastic realizations of the vaccination process.

## **Data Source:**

Transmission trees provide detailed information on the epidemiological links between cases, help identify super-spreaders, and highlight the duration of an outbreak in terms of disease generations. The transmission trees used in this analysis have been previously published in reference [3]. To identify the transmission trees, we searched for any recently published past and present outbreak transmission trees in healthcare settings. We searched PubMed for articles on SARS published after 1 January 2003 using the following search terms: (SARS and Hospital Outbreak), (SARS and hospital), and (SARS and healthcare). Similarly, for MERS, we searched for articles published after 1 January 2012 using the following search terms: (Novel Coronavirus and Hospital Outbreak), (Novel Coronavirus and hospital), (Novel Coronavirus and healthcare) (MERS and Hospital Outbreak), (MERS and hospital), and (MERS and healthcare). Of the relevant articles found, we screened the citations of these articles for any additional transmission trees. We found detailed transmission trees for three MERS and SARS outbreaks, however, we excluded the Al-Hasa outbreak due to the small number of cases reported especially among healthcare workers. Additionally, we reconstructed the transmission trees for Singapore and

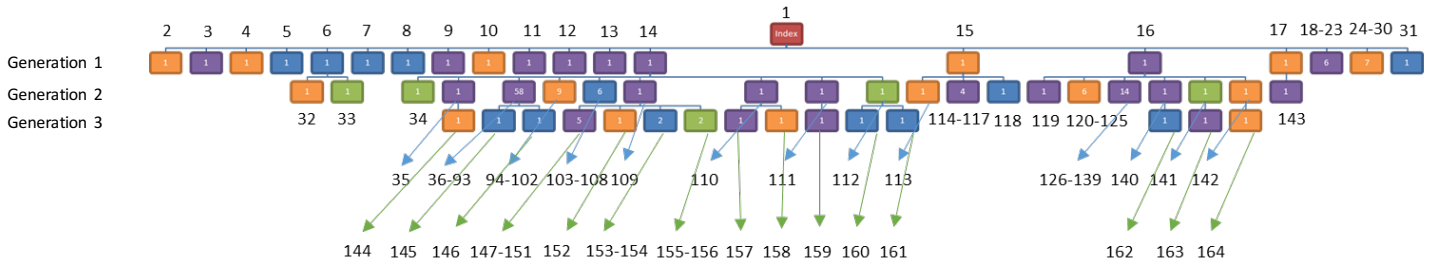
Toronto by removing cases with multiple links across generations or those not linked to a case due to the difficulty of identifying if the case would actually be averted.

The South Korea transmission tree was developed using case data from WHO, the Korean Centers for Disease Control, and the Ministry of Health & Welfare of South Korea. The transmission trees for Singapore and Toronto were extracted from previously published studies [27, 52]. The South Korea MERS outbreak took place in the summer of 2015 from May to July. The transmission tree constructed for the outbreak consists of 164 cases with 64% of those cases being patients (Figure 1A). The SARS outbreaks in Singapore and Toronto occurred relatively around the same in time 2003 and unlike the MERS outbreak, most of these cases were among HCWs and family/visitors. The transmission trees developed for these SARS outbreaks consist of 186 and 90 cases each for Singapore and Toronto (Figure 1B-C). Super-spreading events involve a single case, exposure to which results in a large number of secondary cases (Figure 4). Super-spreading events appeared to occur in the SARS and MERS outbreaks, with the number of cases resulting from each ranging from 8 to as many as 79 cases as seen in Table 3 and depicted in Figure 4.

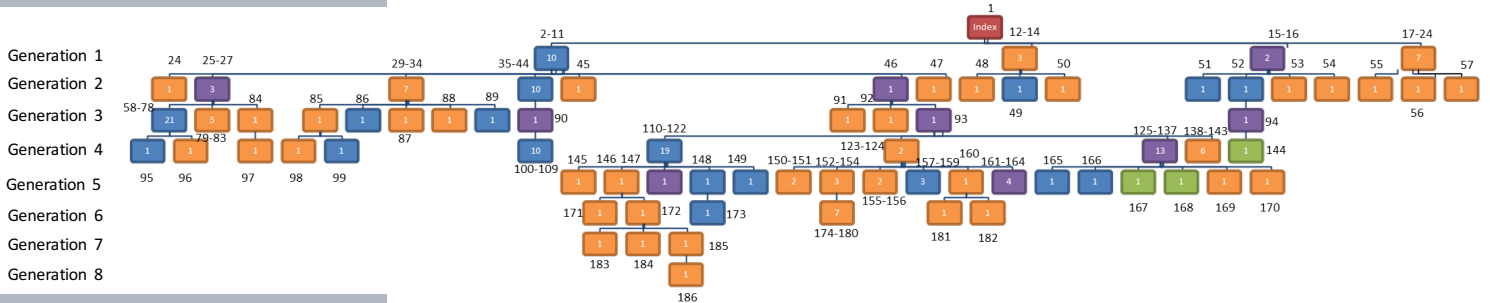
Vaccine strategies were developed based on the distribution of cases among specific exposure categories: patients, healthcare workers, family or visitor, and other clinical staff (Table 1 & figure 2). Chowell et al's comparative analysis on SARS and MERS found that patients are mostly infected with MERS whereas SARS greatly infects healthcare workers [3]. Given this result, the strategies were formulated by considering target population and vaccine coverage. Vaccine efficacy for each vaccination strategy is assumed to be 100%.

**Figure 1:** Healthcare outbreak transmission trees of Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome. A. MERS outbreak in South Korea from May to July 2015 [30, 53-55]. B. SARS outbreak in Singapore from February to May 2003 [52]. C. SARS outbreak in Toronto from February to April 2003 [27]. The nodes in the transmission tree correspond to cases in the outbreak and the colors indicate the exposure category: patients, family/visitor, healthcare worker, and non-clinical staff.

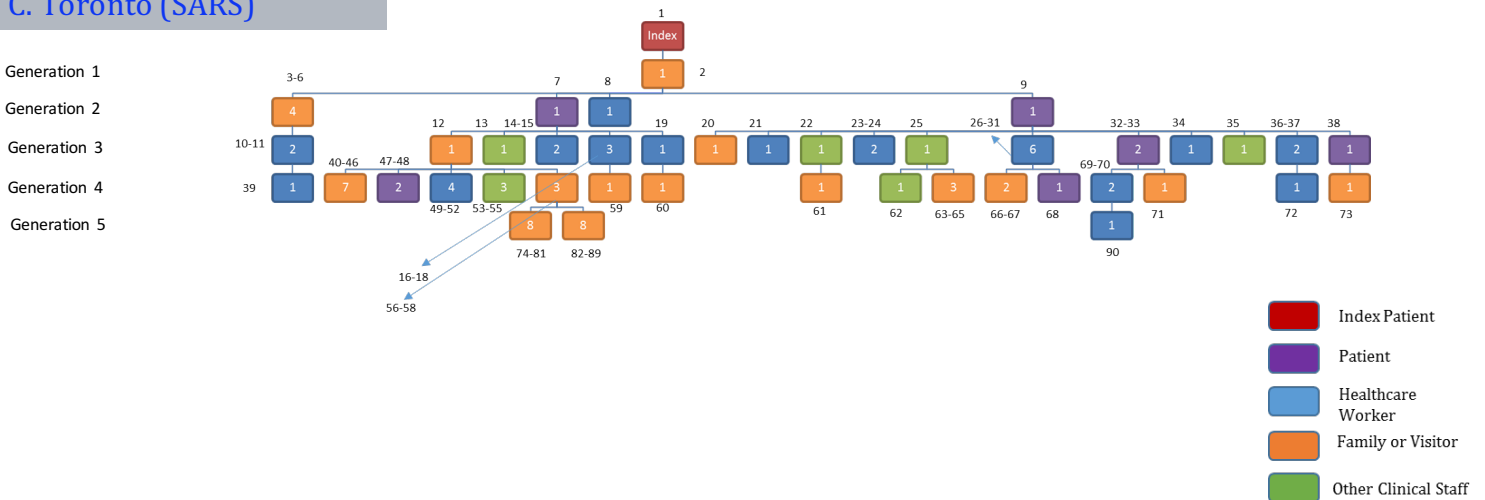
### A. South Korea (MERS)



### B. Singapore (SARS)



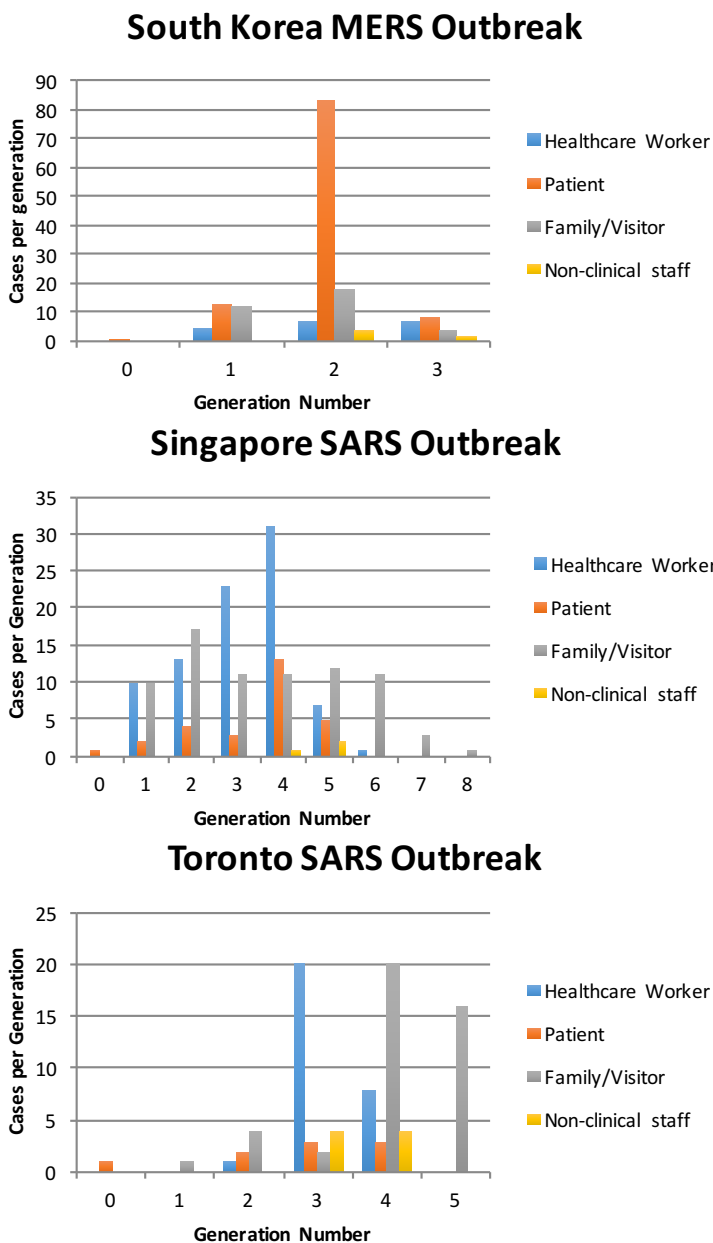
### C. Toronto (SARS)



**Table 1:** Outbreak-specific total number of cases among exposure categories for MERS and SARS outbreak

Outbreak	Type of Coronavirus	Time of Outbreak	Total Cases	Patients (%)	Healthcare Worker (%)	Family/Visitor (%)	Other Clinical Staff (%)	References:
South Korea	MERS	May -July 2015	164	105 (64)	19 (12)	34 (21)	6 (4)	[30, 54, 55]
Singapore	SARS	February - May 2003	186	28 (15)	79 (42)	76 (41)	3 (2)	[52]
Toronto	SARS	February - April 2003	90	9 (10)	30 (16)	43 (23)	8 (4)	[27]

**Figure 2:** Total number of cases per generation for each exposure category (Healthcare worker, patient, family/visitor, and non-clinical staff) for MERS and SARS healthcare outbreaks





## **Vaccine Strategies:**

### Vaccination Strategy 1 (Healthcare Workers):

In this strategy, vaccination targets healthcare workers and assumes that vaccination covers 75% of healthcare workers.

### Vaccination Strategy 2 (Healthcare Workers):

This strategy is similar to strategy I in that it also targets healthcare workers, but vaccination coverage is reduced to 50%.

### Vaccination Strategy 3 (Patients):

Patients have been seen to play a significant role in MERS transmission, which is evident in the South Korea transmission tree. Thus, this strategy involves vaccinating 75% of patients in the hospital. Achieving a higher vaccination coverage could be challenging.

### Vaccination Strategy 4 (Patients):

In the case of MERS especially, individuals infected with MERS are seen to be older in age and present with pre-existing conditions. Since some patients may not be eligible to receive the vaccine, we consider a reduced vaccination coverage at 50%.

The algorithm employed to model the stochastic vaccination strategies consists of the following three steps: (see Figure 3)

Step 1: Case Selection for Vaccination

Starting from a single transmission tree, the specific cases to be vaccinated are determined using a random number generator developed using SAS 9.4

Step 2: Case Vaccination

Once the cases to be vaccinated are selected those cases are automatically averted and removed from the outbreak

Step 3: Removal of Links

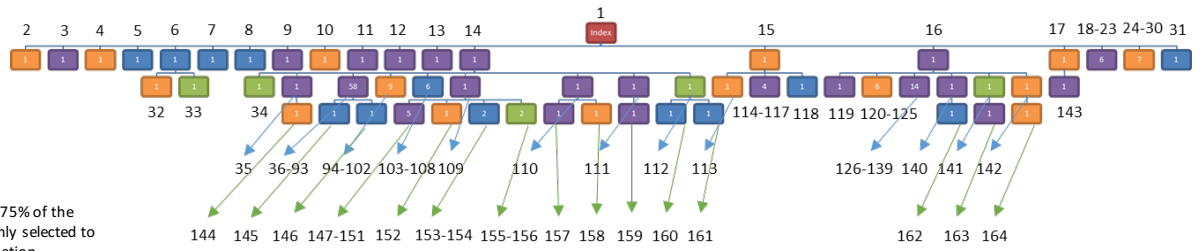
After averting the cases that have been vaccinated all subsequent secondary cases stemming from vaccinated cases are considered averted.

Step 4: Repeat

In this study, we carried out 20 realizations of this vaccination process per transmission tree for each vaccination strategy.

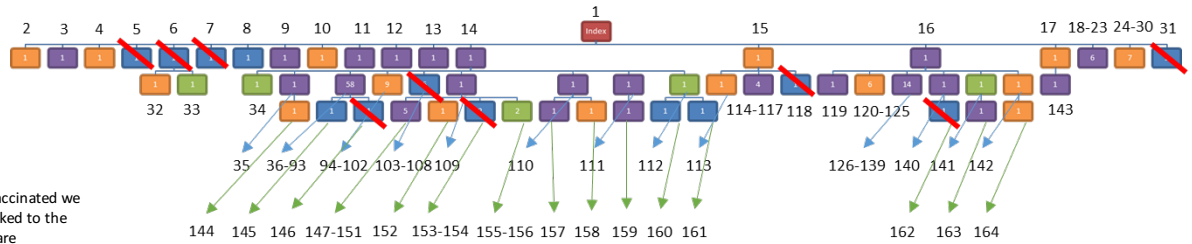
**Figure 3:** A vaccination strategy was modeled according to the following algorithm:

Step 1:

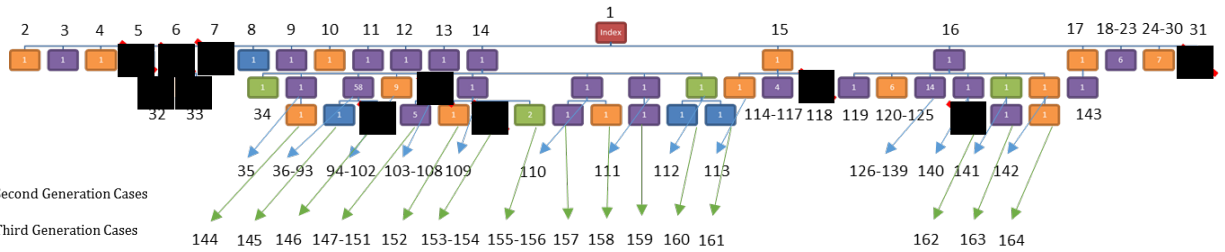


```
proc surveysselect data= random method=SRS rep= 20
samplesize=14 seed=19 out=HCW;
run;
```

Step 2:



Step 3:



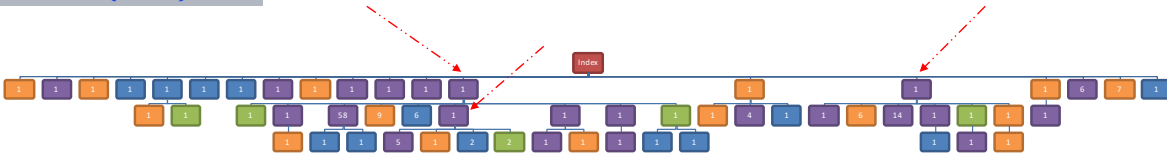
- Index Patient
- Patient
- Healthcare Worker
- Family or Visitor
- Other Clinical Staff
- Second Generation Cases
- Third Generation Cases
- / Third Generation Cases
- Averted Cases

**Analysis:**

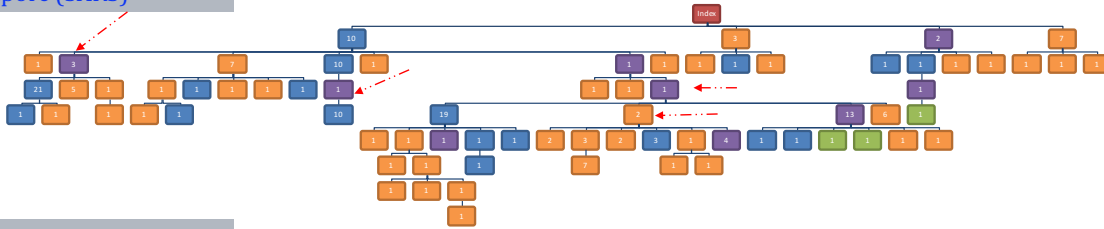
Vaccinated cases were determined using a random number generated produced by SAS 9.4. A total of twenty simulations were manually run for each vaccination strategy (Figure 3). Due to the complexity of the transmission trees in which a case could have been potentially infected by multiple cases, the chance of averting that case was determined probabilistically (Figure 3). If there was more than a 50% probability that the chance would be averted, then that case was deemed averted. An example of the way the simulation is demonstrated in Figure 3 for the South Korea transmission tree.

**Figure 4:** Superspreaders in each nosocomial outbreak have been identified using red arrows

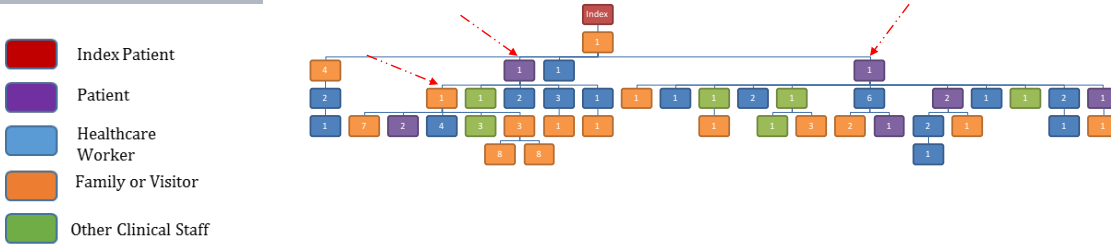
South Korea (MERS)



Singapore (SARS)



Toronto (SARS)



- Index Patient
- Patient
- Healthcare Worker
- Family or Visitor
- Other Clinical Staff

**Table 2:** The proportion of cases generated by each super-spreader during the MERS and SARS outbreak. Cluster cases are cases that collectively infect a case or several cases

Super-Spreader ID	Outbreak	Type	Single/Cluster Case	Total Cases Infected (%)
14	South Korea	Patient	Single	79 (48)
16	South Korea	Patient	Single	24 (15)
109	South Korea	Patient	Single	10 (6)
25	Singapore	Patient	Cluster	27 (15)
26	Singapore	Patient	Cluster	27 (15)
27	Singapore	Patient	Cluster	27 (15)
123	Singapore	Family/Visitor	Cluster	15 (8)
124	Singapore	Family/Visitor	Cluster	15 (8)
90	Singapore	Patient	Single	10 (5)
93	Singapore	Patient	Single	40 (22)
7	Toronto	Patient	Single	8 (9)
9	Toronto	Patient	Single	19 (21)
12	Toronto	Family/Visitor	Single	19 (21)

## **Results:**

### Strategy 1:

Vaccinating 75% of HCWs appears to be most effective strategy in the case of SARS rather than for MERS. Only 9% of cases were averted in the MERS outbreak. For Toronto, 29% of the 90 cases were averted. Singapore would have benefitted the most from strategy 1, with a total of 45% case averted (Table 3 & Figure 5).

### Strategy 2:

Reduction in coverage among HCWs inevitably averted fewer cases than strategy 1. In the South Korea transmission tree, lessening vaccination coverage resulted in a 50% decrease in the number of cases averted compared to strategy 1. Similar results were seen in the Singapore outbreak, only 25% of cases were averted. In the Toronto outbreak, 20% of cases were averted which is only a 9% decline from the percent of averted cases in strategy 1 (Table 3 & Figure 5).

### Strategy 3:

Compared to vaccinating HCW, vaccinating 75% of patients produced an aversion of more than 50% of cases in all of the outbreaks. For South Korea, between 70%-80% of the cases were averted. Interestingly, vaccinating patients was also the most effective strategy in both SARS outbreaks. With this strategy, 76%, 63%, and 66% of cases are averted respectively for South Korea, Singapore, and Toronto (Table 3 & Figure 5).

### Strategy 4:

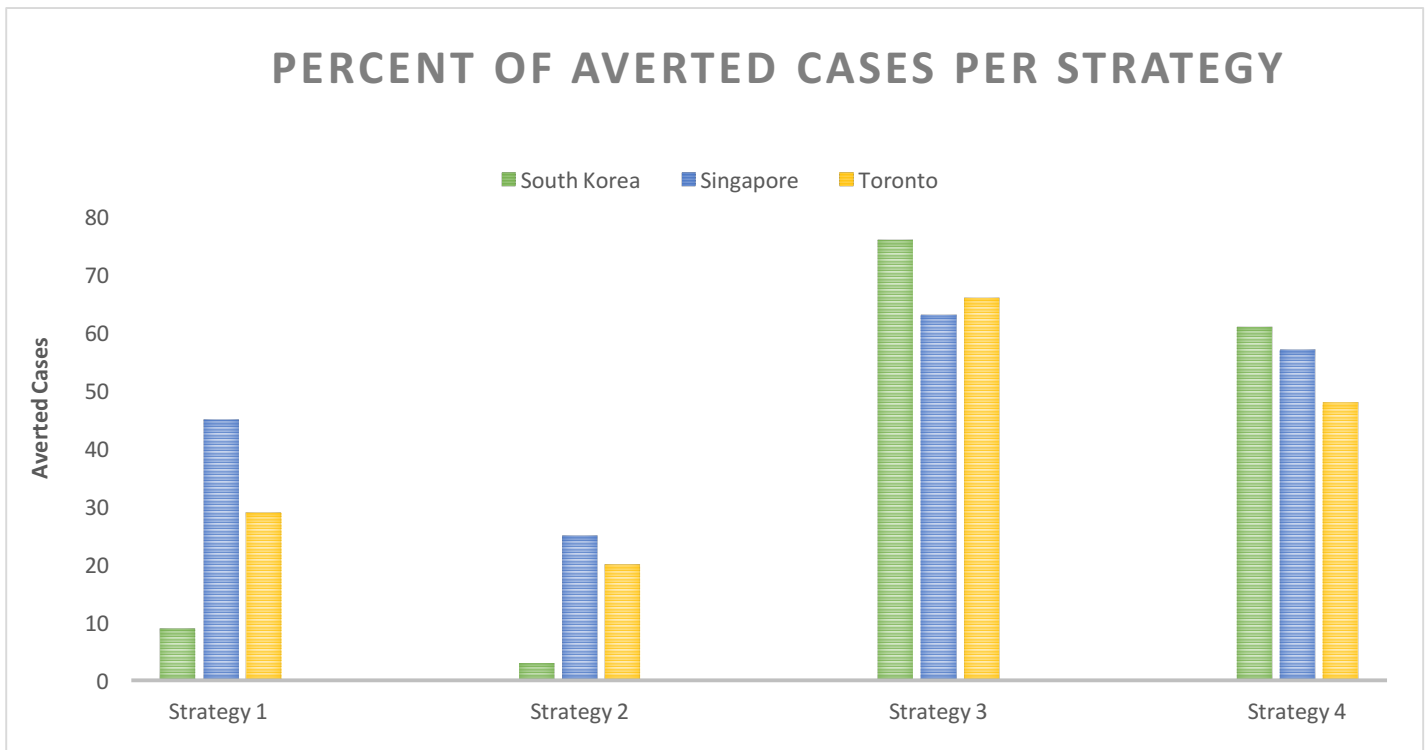
Although vaccine coverage was reduced among patients, the percent of averted cases were either very close to 50% or much higher. Reducing vaccination coverage among patients resulted in a slight decline of 15%, 6%, and 18% for South Korea, Singapore, and Toronto in the total number

of cases averted. Consequently, 61% of cases were averted for South Korea, 57% and 48% of cases were prevented for Singapore and Toronto (Table 3 & Figure 5).

**Table 3:** Proportion of cases averted by each targeted vaccination strategies in each MERS and SAR healthcare setting outbreak

Outbreak	Total Number of Cases	Strategy 1: 75% coverage (HCWs)	95% Confidence Limit (%)	Strategy 2: 50% coverage (HCWs)	95% Confidence Limit (%)	Strategy 3: 75% coverage (Patients)	95% Confidence Limit (%)	Strategy 4: 50% coverage (Patients)	95% Confidence Limit (%)
South Korea	164	9%	9.20-9.70	3%	3.06-3.52	76%	70.66-80.64	61%	52.40-69.73
Singapore	186	45%	38.70-50.39	25%	23.66-26.33	63%	56.62-69.31	57%	52.58-61.62
Toronto	90	29%	28.08-29.33	20%	19.58-20.81	66%	54.52-76.82	48%	35.93-59.97

**Figure 5:** Illustration of the proportion of cases averted per vaccine strategy in each MERS and SARS outbreak



## **Discussion:**

Our study provides the first analysis of coronavirus vaccine deployment strategies using stochastic methodology and multiple simulations. Our results indicate that for both viruses vaccinating at least 75% of patients yields a higher number of averted cases than the other tested vaccination strategies. Although HCWs appear to be the group most infected with SARS, patients tend to infect the most people; therefore, vaccinating patients would reduce the number of HCWs infected. Additionally, for all the outbreaks the superspreaders were mostly patients and very few were family/visitors.

Furthermore, superspreaders are the hallmark of SARS and MERS transmission, which have been evident in the observed outbreaks, as well as the transmission trees in Figure 4. For example, in South Korea, the index patient infected thirty individuals and in addition to two other patients collectively infected 75% of the cases involved in the outbreak [56]. Similarly, several super-spreading events occurred during the SARS epidemic. The index case in the Hong Kong outbreak was responsible for at least 125 cases and the same was observed at the Amoy Gardens housing complex and on the Air China flight [56]. Above all, early detection and compliance to infection control measures are fundamental in reducing the transmission of SARS but more importantly MERS, which still remains an issue [3, 56]. However, in the absence of such interventions, our study supports the deployment of vaccines targeting patients to lessen the risk of super-spreading events and ultimately avert the most cases.

Although patients play a prominent role in transmission in both SARS and MERS outbreaks, simply vaccinating all patients that enter a healthcare facility may be problematic and infeasible in some high-risk areas. Planning to vaccinate all patients is similar to implementing a national vaccination campaign. Additionally, patients have various lengths of hospital stay



depending on the severity of their condition. A patient visiting an emergency room for a few hours may not have the same risk for MERS as a patient staying in the hospital for days or even months. It typically takes the body a few weeks to produce T-lymphocytes and B-lymphocytes after vaccination [57] so vaccinating patients during an outbreak may not be effective considering that immunity would not be built in time. We propose vaccinating patients with chronic diseases that require them to have multiple encounters with healthcare facilities such as those who are diabetic, have a respiratory illness, hypertension, or heart disease. For example, Saudi Arabia has a population of roughly 30 million people and 4,642,636 visits to chronic disease clinics (statistical yearbook). In the Al-Hasa outbreak, 52% of patients had end-stage renal disease, 74% had diabetes mellitus, 39% had cardiac disease, and 43% had lung disease [31]. In the Jeddah outbreak, 35% of patients had secondary exposure to MERS in the renal dialysis outpatient facility [6]. This evidence suggests a benefit in vaccinating patients with chronic diseases that put them at risk for MERS infection to ultimately reduce MERS transmission in healthcare settings.

There are limitations to this study. First, only three transmission trees were used in the analysis due to the limited number of transmission trees available that consist of patients and healthcare workers. Having multiple transmission trees for MERS that capture the interaction between various exposure categories would provide additional evidence in determining the most effective vaccination strategy. Considering the comparability between SARS and MERS especially in the transmission dynamics among superspreaders we were able to observe the effects of vaccines in MERS transmission using SARS data. Second, given the complexity of the trees we were unable to employ a program to run the simulations and thus had to resort to manually running the models, which could potentially introduce human error. To decrease this

risk, each simulation was run several times. Third, since the transmission trees were extracted from multiple open-access sources and compiled by multiple individuals, completeness and effective contact tracing may have affected transmission patterns.

Our analysis strongly supports vaccinating patients primarily to prevent the most cases especially those with chronic diseases that put them at risk for MERS infection. Since there is still a significant need for more research on MERS vaccines, deployment of such a strategy currently is not plausible. Those infected with MERS tend to be older people with preexisting conditions such as diabetes, chronic lung disease, and cancer [2]. Thus, vaccinating patients with chronic illnesses may prove challenging and in the absent of a readily available vaccine, however, results from clinical trials would provide some insight into the matter. The potential impact of vaccines in the control of MERS will remain unknown until the vaccines under study move beyond the preclinical stage and into clinical trials. Considering that MERS is a continuing threat among the Gulf countries, the use of the Infection Prevention & Control Manual for GCC countries aids in the implementation of the first and second vaccination strategies across these countries in the Middle East, if HCW vaccination were to be undertaken. Again, before implementation, without an available vaccine for MERS to study, cost-effectiveness remains unknown. Without further research on the above concerns, the ultimate effect of vaccination is unclear; nonetheless deploying strategies to achieve vaccination coverage among hospitalized risk groups looks to be quite essential in the control of MERS and possible SARS transmission.

## **Conclusion:**

With the use of stochastic simulations and detailed transmission trees of MERS and SARS nosocomial outbreaks, we explored the impact of targeted vaccination strategies and found that a vaccination strategy targeting 75% of the patients appeared to be the most effective. While sporadic MERS outbreaks have been seen to be due to diagnostic delays and lack of adherence to infection control measures which support super-spreading events, a MERS vaccine may have a fundamental effect on reducing the burden of MERS in these circumstances by preventing early transmission events and possibly averting future MERS and SARS outbreaks in healthcare settings.

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