A Case Study Evaluating the Risk of Infection from Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) in a Hospital Setting through Bio-aerosols

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Abstract

Middle East Respiratory Syndrome an emerging viral infection with a global case fatality rate of 35.5% caused major outbreaks first in 2012 and 2015, though new cases are continuously reported around the world. Transmission is believed to mainly occur in healthcare settings, through aerosolized particles. This study uses Quantitative Microbial Risk Assessment to develop a generalizable model that can assist with interpreting reported outbreak data or predict risk of infection with or without the recommended strategies. The exposure scenario includes a single index patient emitting virus-containing aerosols into the air by coughing, leading to short and long-range airborne exposures for other patients in the same room, nurses, healthcare workers, and family visitors. Aerosol transport modeling was coupled with Monte Carlo simulation to evaluate the risk of MERS illness for the exposed population. Results from a typical scenario show that the daily mean risk of infection to be the highest for the nurses and healthcare workers (8.49×10^{-4} and 7.91×10^{-4}, respectively); and the lowest for family visitors and patients staying in the same room (3.12×10^{-4} and 1.29×10^{-4}, respectively). Sensitivity analysis indicates that more than 90% of the uncertainty in the risk characterization is due to the viral concentration in saliva. Assessment of risk interventions showed that respiratory masks were found to have a greater effect in reducing the risks for all the groups evaluated (>90% risk reduction), while increasing the air exchange was effective for the other patients in the same room only (up to 58% risk reduction).

Keywords: MERS-CoV; risk characterization; hospital; QMRA; mitigation

1.

1. INTRODUCTION

1.1. Historical background

Coronaviruses are a common cause of upper respiratory infections in humans. Strains endemic to the human population include 229E, HKU`, NL63, and OC43 (Chan et al., 2015), which circulate continuously among children and adults worldwide with infection trends typified by seasonality and mild symptoms in healthy individuals. The new millennium, however, has marked the emergence via zoonosis of two highly virulent coronavirus strains novel to the human population. In 2003, a novel coronavirus (CoV) emerged in the Guangdong Province of China that caused a new and deadly outbreak of respiratory disease in humans termed as Severe Acute Respiratory Syndrome (SARS-CoV). Within months, SARS-CoV spread rapidly to 25 countries (in part due to the modern, highly globalized nature of air travel), with thousands sickened and close to 800 fatal cases (Hilgenfeld & Peiris, 2013). Investigation of the origin of SARS coronavirus led first to the exotic animal markets of China and the initial implication of palm civet cats and raccoon dogs (which were found to be intermediate hosts), with further study indicating bats as the true natural reservoir of SARS-like coronaviruses (Han et al., 2015). In April of 2012, an outbreak of severe respiratory viral illnesses localized in several intensive care units occurred in the Middle Eastern country of Jordan; both patients and healthcare workers were infected. Within several months, cases had also surfaced in several nearby Middle Eastern countries including Saudi Arabia, Qatar, and the United Arab Emirates, with rapid movement into 20 additional countries in North Africa and Europe (Al-Tawfiq, 2013; Breban, Riou, & Fontanet, 2013). Early indications pointed to a highly virulent infectious agent, as a high percentage of patients were dying, particularly those with comorbidities. A novel strain of coronavirus was soon isolated and named after the region of origin in conjunction with the primary manifestation of symptoms - Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) (de Groot et al., 2013).

1.2. MERS-related health issues

MERS-CoV affects the lungs and respiratory system with an estimated 35.5% mortality in patients globally (World Health Organization, 2018). There are currently no human vaccines available to counter infection with MERS-CoV, while veterinary vaccines for camels are currently under developments (Widagdo, Okba, Stalin Raj, & Haagmans, 2017). Therefore, to date, containment of infectious viruses via personal hygiene, use of personal protective equipment (PPE), isolation of MERS symptomatic persons, and quarantine of potentially exposed individuals to prevent contact with others is recommended (CDC, 2017a, 2017b). The published literature on MERS have consistently estimated a reproductive number (R_0; the average number of secondary cases generated by a primary case) of <1, suggesting that MERS-CoV does not yet pose a pandemic risk (Breban et al., 2013; Nishiura, Miyamatsu, Chowell, & Saitoh, 2015; Poletto, Pelat, Lévy-Bruhl, Boelle, & Colizza, 2016; World Health Organization, 2018). In Jeddah, Saudi Arabia 82 out of 168 clinical samples stemmed from a single hospital, and phylogenetic analyses of seven confirmed MERS-CoV isolates from those cases were found to cluster in a single monophyletic clade (Drosten et al., 2015).

MERS-CoV is primarily transmitted through infectious aerosolized particles. Under hospital settings, the attack rate has been reported to be 1.1% to 10% (Al-Abdallar, 2014; Al-Tawfiq & Perl, 2015), while 3.6% to 5% attack rates have been reported for the persons in close contact with infected patients (Al-Tawfiq & Perl, 2015; Memish, Assiri, & Al-Tawfiq, 2014). Mean incubation period for the virus has been reported to range from 2 to 15 days, with a median value of 5 days (Banik, Khandaker, & Rashid, 2015). MERS-CoV infection results in fever, cough sore throat, headache and occasionally, results in nausea, vomiting and diarrhea. In more severe cases, patients may experience shortness of breath, pneumonia and death (Banik et al., 2015). In the South Korean outbreak, the morbidity rate was estimated to be 1.08% (Ki, 2015). The patient mortality rate has been reported to vary greatly depending on the age and underlying conditions, such as diabetes, heart disease and chronic lung disease. In the South Korean outbreak, the overall mortality rate was reported to be 19.4%. MERS infected persons who were already hospitalized for other medical conditions had a higher mortality rate (33.8%) than the persons without prior medical conditions (9.2%). Likewise,

patients over 60 years of age had a higher mortality rate (38.1%) than younger patients (6.4%) (Ki, 2015).

1.3. The large outbreak in South Korea, 2015

A cluster of MERS-CoV cases arose in South Korea during May of 2015. The visitation of a single index patient to five different hospitals is believed to have resulted in 185 downstream nosocomial cases of MERS-CoV (Cowling et al., 2015; H. Y. Park et al., 2015; World Health Organization, 2015), although confirmatory phylogenetic analyses have not yet been performed. Unlike the previously documented case clusters, the South Korean outbreak was well-documented with regards to incubation time, transmission chains (i.e. 28 first generation cases, 125 second generation cases, and 32 third generation cases) and contact tracing of infected patients (Ki, 2015). The majority of infections were hospital-acquired; only one of the 186 patients in the South Korean cluster are believed to have been infected outside of a hospital, and two other individuals were infected by modes of transmission that are currently unknown (Ki, 2015).

Despite the fact that MERS has been reported to survive a maximum of 24 to 48 hours on surfaces (Van Doremalen & Munster, 2015), it has been proposed that based on the South Korean MERS outbreak, the virus would not survive long enough to be capable of involving spread through indirect fomite route (Cho et al., 2016). On contrast, studies suggested that the main transmission route of MERS was via the airborne route, especially over close contact airborne exposure (Xia et al., 2014). Hence, isolation of index patient in a negative-pressure room and quarantine of potentially exposed persons are considered key risk management measures for literature that investigated the South Korean MERS outbreak (Cowling et al., 2015; Kim et al., 2015; J. W. Park et al., 2017; S. H. Park et al., 2016; World Health Organization, 2015). In consequence, isolation and quarantine would be measures that would drastically lower the risk of MERS infection once patients are identified. From previous outbreaks, the index patient stay unidentified as a MERS carrier for up to 2 days (Cho et al., 2016). Additionally, the time for identifying MERS from a diagnostic laboratory in a patient

takes up to 3 days (Cowling et al., 2015), so probable exposure durations around 2-3 days are relevant scenarios to model.

1.4. Study objectives

The objective of this study was to use the Quantitative Microbial Risk Assessment (QMRA) approach to develop a generalizable model for quantifying the risk of infection associated with in-hospital exposures to MERS through infectious aerosols. The parameter values were selected from multiple sources including the latest reported large outbreak that occurred in South Korea, and data from other sources. Risk of infection is estimated for four types of at risk populations: nurses and healthcare workers visiting the index patient (before the patient was identified as carrying MERS) and other patients sharing the same room; family visitors coming to visit the index patient; and the other patients sharing the same room (Cho et al., 2016). Risk estimation is conducted by using the Monte-Carlo simulation method to incorporate uncertainty and variability in the risk characterization. Sensitivity of the model parameters is assessed to determine where additional data or knowledge could potentially reduce uncertainty and increase our understanding of these risks. Finally, the effectiveness of mask and increased ventilation risk management measures is evaluated. Rather than a retrospective case analysis, the study is intended to contribute a framework for analyzing current and future MERS risk in similar settings.

2. MATERIALS AND METHODS

2.1 Exposure Scenario and Assessment

The basis of the exposure scenario involves a symptomatic patient infected with MERS-CoV who has been admitted to a hospital without implementation of isolation or quarantine procedures. It was assumed that all exposed people were susceptible to infection and all infections led to illness (or death). A typical size of 230 m^3 hospital room was set for the model, which is four times the single patient room size noted in Yin et al. (Yin, Gupta, Zhang, Liu, & Chen, 2011) and is based on the fact

that over 50% of the hospital rooms in South Korea have four or more beds. The symptomatic patient was considered the only source of infection within the room (see Figure 1).

MERS-CoV is thought to be transmitted primarily via aerosols in a manner similar to endemic human respiratory coronavirus strains such as 229E and OC43. For the present assessment scenario, only the risk of infection from aerosolized particles and droplets expelled by coughing was considered. The influence of nebulizer treatments that can be done on the index patient was considered negligible and not included in the model. Though the contribution of this treatment was suggested by Park et al. (S. H. Park et al., 2016), studies have also demonstrated that nebulizers do not specifically impact transmission (W. H. Seto, 2015; Thompson et al., 2013). Fomites may also serve as a potential reservoir for MERS-CoV due to the settling of aerosols after release from infected persons. However, some studies stated that fomite-based exposure pathways were not significant compared to airborne routes, and so it was not considered in this study (Xiao, Li, Sung, Wei, & Yang, 2018).

Two forms of modeling were included in this MERS assessment: (1) modeling aerosol concentrations to identify at-risk populations in hospital settings; and (2) estimating exposure dose and characterizing risk. The risk of infection for several exposure populations was considered, as follows: (1) Other patients in the same room of index patient; (2) nurses; (3) other healthcare workers (e.g. doctors) visiting the index patient and others in the room; and (4) family members coming to visit the index patient.

Viruses released via coughing and transport in the hospital room was modeled using a mass balance approach to approximate a steady state concentration of viruses contained in aerosol droplets. The droplets are be removed from the system either due to settling to the floor or ventilation-based air exchange. The risk of infection for each of the four populations was assessed based on exposures occurring over 1, 8, 20, and 41 days. These time periods were based on reported durations from the symptom onset to discharge from the hospital during the Korean outbreak - a median of 20 days, minimum of 8 days, and maximum of 41 days (Ki, 2015) – and from estimated durations for other patient exposure – up to 44 hours (Cho et al., 2016).

2.2 Aerosol transport modeling

Aerosol transport modeling was undertaken to assess virus inputs from coughing and removal via settling onto surfaces and the air exchange processes (*i.e.*, heating, ventilation, and air conditioning (HVAC) systems). The model room system was assumed to have reached steady state, meaning that there is no accumulation or loss from the system over time, and that the input flow rates must equal the removal flow rates. This input-output relationship is shown in Equation 1.

$$N_{(in,coughing)} = N_{(out,setting)} + N_{(out,ventilation)} + N_{(inhalation)} \quad (1)$$

Where, *N* is the number of droplets containing viruses. In Equation 1, $N_{(inhalation)}$ or the number of viruses removed through inhalation by infected or uninfected persons (patients in the same room, health care workers, and visitors) was assumed to be non-significant as compared to the other two terms, $N_{(out,settling)}$ and $N_{(out,ventilation)}$, and thus was neglected as a sink. Expiratory events (*i.e.*, coughing) produces a broad distribution of aerosol particles, however this analysis was only concerned with aerosols that were likely to be inspirable and respirable. Aerosol production values were taken from Stilianakis and Drossinos (Stilianakis & Drossinos, 2010) and the references therein. Particles with a diameter of <10 μm were considered as respirable aerosols. Respirable aerosols are expected to be easily transported, due to their small diameter, and thus represent a potential exposure pathway for people that are farther away from the source (*e.g.*, more than 1-2 meters from the source). Thus, respirable particles were the only evaluated exposure pathway for patients sharing a room with an infected symptomatic patient. Aerosols with a diameter of 10-100 μm were considered as inspirable aerosols as these large particles are not expected to be transported long distances and are only relevant for persons in close contact. Nurses, healthcare workers and visitors were assumed to be exposed to both respirable and inspirable aerosols. Viral release into the room was calculated using Equation 2:

$$V_i = \frac{\pi d_i^2}{6} \times 10^{-12} \quad (2)$$

Where V_i (ml) volume for each droplet size d_i that are released into the room as inspirable or respirable droplets during each coughing event. Each cough produced N_i number of droplets of size d_i where each droplet is assumed to be spherical, and the droplet volume is calculated as $\frac{1}{6} \times \pi \times d_i^3$, where d_i is the diameter (μm). The droplets were assumed to be produced from a patient lying supine, such that the droplet cloud was produced at a 1 m height.

Following Stilianakis and Drossinos (Stilianakis & Drossinos, 2010), pathogen generation (*e.g.* coughing) and removal (*e.g.* settling, ventilation) were assumed to be a continuous process. Exhalation by the infected patient was not considered a source of virus-containing droplets.

After the particles were produced during a coughing event, droplet evaporation, droplet settling, and droplet removal via the ventilation were considered. Post-evaporation particle transport was evaluated, accounting for two removal mechanisms: droplet settling and ventilation-based droplet removal. Stoke's law was used to calculated droplet terminal settling velocity $v_{i(terminal)}$ (m/hr) (Equation 3), which was assumed to be impacted only by particle diameter d_i (Nicas, Nazaroff, & Hubbard, 2005).

$$v_{i(terminal)} = 0.108 \times d_i^2 \times \left[1 + \frac{0.166}{d_i}\right] \tag{3}$$

Terminal settling velocities were calculated for each of the representative particle sizes, d_i. A critical settling velocity, $v_{(critical)}$ (m/hr), was calculated as the required settling velocity to fall from the height of the patient bed $h_{(cough)}$ (m) during the air residence time τ (hr) (Equation 4). Air residence time, τ, is the average amount of time that a "parcel" of air is in the room, which depends on the volume of the room $v_{(room)}$ and the ventilation rate $q_{(ventilation)}$.

$$\tau = \frac{v_{(room)}}{q_{(ventilation)}} \tag{4}$$

$$v_{(critical)} = \frac{h_{(cough)}}{\tau} \tag{5}$$

Ventilation flow rate $q_{(ventilation)}$ was quantified by the number of air exchanges per hour (ACH) of the room volume, which was defined as shown in Equation 6:

$$q_{(ventilation)} = V_{(room)} \times ACH \quad (6)$$

Where $V_{(room)}$ is the volume of the hospital room (m^3) and $q_{(exchange)}$ is the air flow rate (m^3/hr) determined by the number of ACH $v_{(exchange)}$. As stated previously, height of the patient bed, $h_{(cough)}$, was 1 m. For particles that had a terminal settling velocity greater than the critical velocity ($v_{i(terminal)} > v_{(critical)}$), it was assumed that settling was a viable removal mechanism. It was further assumed that droplets that hit the floor were permanently removed from the system with no resuspension. This acknowledges that all the settleable aerosol droplets settled to the floor in a time interval less than τ. However, due to the continuous generation, there were some fractions of the settleable droplets that were not yet settled. At a given time, for the droplets with terminal velocity greater than the critical velocity ($v_{i(terminal)} > v_{(critical)}$), it was assumed that the aerosol concentration of settleable droplets was proportional to the ratio of settling velocities, as shown in the Equation 7. For the droplets that had terminal settling velocities less than the critical settling velocity ($v_{i(terminal)} \leq v_{(critical)}$), it was assumed that there was no droplet removal occurred via settling.

$$N_{i(room,settleable)} = N_{i(in,cough)} \times \left[\frac{v_{(critical)}}{v_{i(terminal)}}\right] \quad (7)$$

For these later particles, it was assumed that air currents in the room dictated their transport. However, this transport and homogeneous mixing did not include settling onto another surface resulting in removal (i.e. striking a piece of furniture, or a wall) and was considered entirely an elastic collision. Airborne particles were assumed to be homogeneously distributed within the volume of the room. Hence, the number of droplets containing viruses removed through settling for each droplet *i* is:

$$N_{i(out,settling)} = N_{i(in,cough)} \times \left[1 - \frac{v_{(critical)}}{v_{i(terminal)}}\right] \quad (8)$$

Air exchanges via ventilation was also considered a removal mechanism, in which air, including the homogeneously-mixed virus-containing aerosol droplets, was removed from the hospital room and replaced with new air. It was assumed that the replacement air contained no viruses. During

each air replacement, all the remaining droplets were assumed to be removed by the ventilation, which implies the relationship in Equation 9.

$$N_{i(out,ventilation)} = N_{i(in,cough)} - N_{i(out,settling)} \quad (9)$$

It was assumed that $N_{i(out,ventilation)}$, number of droplets remaining after settling, are suspended in the room until they are removed by ventilation. Hence, the concentration of saliva in the air produced by a single cough per unit volume of room air is calculated as

$$C_{(saliva\ in\ air)} = \frac{\sum_{i=1}^{n} N_i V_i}{V_{(room)}} \quad (10)$$

Where $C_{(saliva\ in\ air)}$ is the concentration of saliva in the room air produced by a single cough per hour (ml/m^3), V_i is the volume of each droplet calculated using Equation 2, and $V_{(room)}$ is the room volume.

We further assumed a standard air exchange rate of 6 times per hour (Zumla & Hui, 2014). The half-life of coronaviruses in the air is 67.33 hours (Ijaz, Brunner, Sattar, Nair, & Johnson-Lussenburg, 1985), but since we assumed that the air in the room was exchanged 6 times per hour, decay was not considered.

2.3 Aerosol concentrations in the air

In order to model the amount of virus released into the air, several studies were compared that specified the number and size of droplets expelled during coughing (Duguid, 1946; Loudon & Brown, 1967; Nicas et al., 2005; Papineni & Rosenthal, 1997) for selection of the data set that best fits the condition of patients exposed to MERS-CoV. The number of cough events per hour was modeled based on Loudon et al. (Loudon & Brown, 1967), using the estimates for the number of cough events in non-smokers with pneumonia. Based on Nicas and Jones (Nicas & Jones, 2009), we assumed that 0.044 mL of saliva was emitted per cough, which represents the most conservative estimate compared to other published volumes in the literature (Duguid, 1946; Loudon & Brown, 1967; Papineni &

Rosenthal, 1997). Saliva volume was assumed to have a uniform distribution with a ±10% of the reported value. Of the expired fluid, 0.00015% was considered respirable and 0.54% was considered inspirable. In other words, about 99.45% of the volume expired during each cough was considered to be non-respirable and non-inspirable, and therefore was not included in this analysis. Respirable droplets were modeled as aerosols with mean post-evaporation diameters of 4 and 8 μm (for small and large respirable droplets), which Stilianakis and Drossinos (Stilianakis & Drossinos, 2010) estimated were produced at a rate of 160 and 7.5 droplets per coughing event, respectively. Similarly based on Stilianakis and Drossinos (Stilianakis & Drossinos, 2010), representative inspirable droplets corresponded to aerosols with mean post-evaporation diameters of 7.3 and 74 μm diameter droplets (corresponding to inhalable aerosols), which were produced at 41.47 and 138.48 droplets per cough, respectively. Other than this initial evaporation, it is assumed that the aerosol droplets did not change in size, including that neither further evaporation nor particle aggregation occurred. Uncertainty in the droplet production numbers was investigated by holding the number of particles constant, and using bootstrap iterations to compare the uncertainty in the relative number of particles for each of the four respective representative particle sizes. The results of the bootstrap uncertainty analysis were used to model particle production as a stochastic input.

2.4 MERS-CoV concentration in saliva

Multiple papers have quantified levels of MERS-CoV in sputum, nasopharyngeal secretions, and saliva samples using qPCR methodology (Corman et al., 2015; Min et al., 2016; Muth et al., 2015). MERS-CoV titer data specified in these studies are in total viral units (non-infectious + infectious) of RNA genomic copies per milliliter (GC/mL) as the values were generated using real-time qPCR. Since the dose-response model unit was in PFU, according to the used best fit dose-response for SARS-CoV taken from the QMRA Wiki website (Huang, 2013), a conversion factor of 1239:1 (1239 GC equivalent units to one infectious PFU) reported by Houng et al. (Houng et al., 2004) and based on a SARS-CoV qPCR assay, was employed to calculate infectious PFU values for

the MERS-CoV exposure modeling. Recovered MERS-CoV concentration data was fitted to a lognormal distribution.

2.5 Exposed population behavior

Exposure scenarios for the nurses and healthcare workers were modeled based on the frequency and duration of their patient visits. For healthcare personnel, due to the wide range of reported durations per visit by Cohen et al. (Cohen, Hyman, Rosenberg, & Larson, 2012) a triangular distribution was specified with a median of 2 minutes and a range of 1 to 72 minutes) (Table I). Similarly, a triangular distribution with a median value of 2 minutes per visit and a range of 1 to 120 minutes was assumed for the nurses as inputs in the exposure model (Cohen et al., 2012). For both the healthcare workers and nurses, the number of patient visits and number of different patients visited were also taken from Cohen et al. (Cohen et al., 2012) and are tabulated in Table I with all model inputs and distributions. Nurses and healthcare workers were assumed to be exposed to inspirable and respirable particles while visiting the index case, and to the respirable particles while visiting other patients in the same room. Other patients in the room were assumed to be exposed to respirable particles only 24 hours a day (Ki, 2015). For the family visitors, a median visit duration of 14 minutes was used (Cohen et al., 2012). Furthermore, based on Cohen et al. (Cohen et al., 2012), frequency of visitors were assumed to range from 0 to 6.4 visits per hour with a median value of 1.3. Daily exposure doses for nurses, healthcare workers, the other patients, and family visitors was calculated by aggregating the exposure doses over the entire day consisting of multiple visits.

2.6 Estimated exposure dose

The daily exposure dose for the nurses and healthcare workers was calculated by considering that once entering the room, they would expose themselves both through respirable and inhalable aerosols during their visit to the MERS index patient, and through only respirable aerosols when visiting the other patients in the room. Hence, daily exposure dose for nurse and healthcare worker consisted of the sum of each of these two exposure routes:

$$D_{(expo/d,n-hcw)} = C_{(MERS\ in\ saliva)} \times C_{(saliva\ in\ air)} \times N_{(cough/hr)} \times \frac{1}{q_{(ventilation)}} \times V_{(inhaled/d)} \times \frac{N_{(room\ entries/hr)}}{N_{(patients\ visited/entry)}} \times t_{(spent/entry)} \times t_{(work/d)} \quad (11)$$

Where $D_{(expo)}$ is the daily MERS virus inhaled by exposed personnel while being one time near index patient and another time near patients sharing the room (PFU/day), $C_{(MERS\ in\ saliva)}$ is the concentration of MERS in saliva (PFU/ml), $C_{(saliva\ in\ air)}$ is the concentration of droplets in the air after one cough, $N_{(coughs/hr)}$ is the number of coughs per hour (#/hr), $q_{(ventilation)}$ is the ventilation air flow rate of the room derived from the ACH (#/hr), $V_{(inhaled/d)}$ is the air intake rate of the exposed person (m^3/hr), $N_{(room\ entries/hr)}$ is the number of entries nurse or healthcare worker make per hour to visit either the index patient or the other patients (#/hr), $N_{(patients\ visited/entry)}$ is the number of patients visited by nurses or healthcare workers per room entry visit (for the index patient or other patients) (#/visit), $t_{(spent/entry)}$ is the amount of time spent during each visit (hr/visit), and $t_{(work/d)}$ is the number of daily working hours for nurses and healthcare personnel (assumed 8 hrs/day).

For the other patients in the same room, daily exposure dose was calculated as follow:

$$D_{expo,op} = C_{(MERS\ in\ saliva)} \times C_{(saliva\ in\ air)} \times N_{(cough/hr)} \times \frac{1}{q_{(ventilation)}} \times V_{(inhaled/d)} \times t_{exposed/d} \quad (12)$$

Where the daily exposure duration $t_{exposed/d}$ where assumed to be continuous (i.e., 24 hours/day).

For the family visitors, daily exposure dose was calculated based on their number of visits per day of the index patient $N_{family\ visits/d}$:

$$D_{expo,fm} = C_{(MERS\ in\ saliva)} \times C_{(saliva\ in\ air)} \times N_{(cough/hr)} \times \frac{1}{q_{(ventilation)}} \times V_{(inhaled/d)} \times N_{(family\ visits/d)} \times t_{(spent/visit)} \quad (13)$$

A systematic literature review was conducted to determine the best estimates for each input parameter in the exposure model. A Monte Carlo simulation was conducted using the Crystal Ball®

program (Version 11.1.4512.0, Oracle, Redwood Shores, CA) to incorporate variability and uncertainty in the input parameters and to propagate it to the output parameters (i.e. exposure doses per subpopulation, risks of infection). Risks of infection for each scenario were calculated using a published dose-response model as described in the results section. A differential sensitivity analysis of model variance was performed to determine which input variables have the greatest effect on the risk estimates. To reduce the risk of MERS infection, two types of risk mitigation strategies were evaluated using the final risk models: increasing air exchange rate and using a mask as personal protective equipment.

2.7 Dose-response model

A primary knowledge gap in the study is the absence of a dose-response model for MERS-CoV. Therefore, the SARS dose-response model (Huang, 2013) was employed as a surrogate. MERS has several similarities to SARS: both have an animal origin and appeared around 2002 in approximately the same regions-Asia and Middle East (Sutton & Subbarao, 2015); both are respiratory coronaviruses with the same transmission route; both have a comparable protein structure for binding to host cells (Lu, Wang, & Gao, 2015), and both have reported similar tropism within cells (Zhou, Chu, Chan, & Yuen, 2015). Hence, despite probable differences in attack rates and mortality rates between the two viruses (Chan et al., 2015), it was assumed in this study that the SARS dose-response model is the best available model for MERS. Several dose-response studies for SARS were evaluated in order to determine a recommended dose-response model (De Albuquerque et al., 2006; DeDiego et al., 2008; Mitchell & Weir, n.d.; Watanabe, Bartrand, Weir, Omura, & Haas, 2010). Recommended SARS dose-response model follows the exponential dose-response relationship (Equation 14) for exposure dose expressed in PFU and the probability of a response based on an endpoint of death in mice (De Albuquerque et al., 2006; DeDiego et al., 2008). For translating this animal dose-response relationship to a human dose-response relationship, a generally accepted assumption that a death endpoint for an animal model may be used for examining the human risk of infection was applied (Haas, Rose, & Gerba, 2014).

The general equation for the exponential model is:

$$P_{Inf} = 1 - e^{(-kd)} \quad (14)$$

Where P_{Inf} is the risk (probability) of infection, k is the optimized dose-response function parameter (PFU^{-1}), and d is the dose (PFU). In the Monte Carlo analysis, the k value in the dose-response model was modeled with a normal distribution based on the 5th, 50th (median) and 95th percentile values reported by Huang (Huang, 2013) and reported in Table I.

The cumulative risk of the morbidity across multiple exposure days was modeled by Equation 14 (Charles, Rose, & Gerba, 2014):

$$P_M = 1 - (1 - P_{Inf})^n \quad (15)$$

Where, P_M is the probability of morbidity and n is the number of days of exposures with P_{Inf}, probability of infection from a daily exposure. The risk associated with each population was assessed for 8, 20, and 41 days of exposure, which represents the minimum, median and maximum hospitalization periods for a MERS infected patients (Ki, 2015).

2.8 Risk management evaluation - Air change per hour and wearing of mask

In order to reduce the amount of airborne respirable particles, Zumla and Hui (Zumla & Hui, 2014) recommend increasing the air changes per hour (ACH) from 6 to 12 in hospital facilities or rooms with high risk of airborne disease. Thus, in addition to the worst case scenario considering 0 ACH and the Korean outbreak scenario using 3 ACH (Cho et al., 2016), standard 6 ACH (Zumla & Hui, 2014), along with increased 9 and 12 ACH were evaluated for their efficacy in minimizing the infection risk.

The use of respiratory masks (N95) as a means of personal protection was also evaluated. Laboratory studies showed a large decrease (up to >4 log reduction) in virus exposure when wearing masks (Borkow, Zhou, Page, & Gabbay, 2010). However, the decrease did not take into account imperfect mask fit or lack of compliance in wearing the masks. Due to these factors, MERS-CoV reduction due to wearing N95 respirators was assumed to have a uniform distribution spanning 1 to 2

log reductions in MERS-CoV concentration (Bałazy, Toivola, Adhikari, et al., 2006; Bałazy, Toivola, Reponen, et al., 2006; Gupta, 2011; Rengasamy, Zhuang, & Berryann, 2004; Wen et al., 2013).

3. RESULTS

3.1 Risk of infection

Based on the results obtained from the Monte Carlo simulation, the risk of infection to each exposed group was characterized. Figure 2 shows the boxplot of daily risk of infection to each group for the base scenario, meaning without any preventive interventions - the standard rate for hospitals of 6 air changes per hour was considered (Zumla & Hui, 2014). The median (mean) daily risk for the nurses coming to visit the index patient and other patients in the same rooms; the healthcare workers (e. g. doctors); the family members coming to visit the index patient; and the other patients sharing the room were found to be 1.33×10^{-8} (8.49×10^{-4}), 1.18×10^{-8} (7.91×10^{-4}), 6.36×10^{-9} (3.12×10^{-4}), and 2.73×10^{-9} (1.29×10^{-4}), respectively. The estimated highest daily risk of infection for the healthcare workers and nurses suggested the frequently of airborne close-range exposure route plays a bigger role in the transmission of MERS, compare to the long-range airborne route to which other patients are exposed, confirming what was suggested by Xiao et al. work (Xiao et al., 2018). Statistical t-tests showed that the daily risk of infection for healthcare workers was significantly higher than the one for the other patients or the family visitors (p-value = 0.0014 and 0.0240, respectively at $\alpha = 0.05$). When comparing nurses and other healthcare worker the result is not significant (p-value = 0.8475), so they have similar risks. Other patients in the same room had a statistically significant lower risk of infection compared to nurses (p-value = 0.0017), but had non-significant statistical differences in risk with family visitors (p-value = 0.0547).

Figure 3 shows the aggregated risk of infection for the exposed populations during multiple daily exposures to the MERS-infected patient for typical hospital durations. As expected, the results show increased risk of infection to all the exposed populations over time. The rate of increase was

highest for the healthcare workers and nurses, in comparison to the family visitors, which itself had higher rate of increase compare to the other patients sharing the room. Similar to the daily risk, aggregated risk of infection was the highest for the healthcare workers and nurses, followed by family visitors and other patients. By day 41, the average risk of infection to the nurses was 1.01, 1.2 and 2.4 times the risk for the healthcare workers, family members and other patients, respectively.

3.2 Parameter sensitivity

Figure 4 shows the parameter sensitivity of the model for daily risk of infection. A parameter with a greater rank correlation coefficient indicates that the input parameter distribution was more correlated with the output risk of infection for the population specified. Input parameter sensitivity can either be due to the uncertainty in estimating the value of a parameter, the known naturally occurring variance of this parameter, or because disparate data from different sources were used to estimate the range of a parameter. Here, while many parameters were modeled stochastically, only the most sensitive parameters are shown in Figure 4.

For all exposed groups, the concentration of MERS virus in the saliva was the most sensitive parameter, which accounted for over 90% of the uncertainty in the daily risks. Because viral load of MERS in saliva is believed to naturally vary among people, sensitivity of this parameter is understood as being due to natural variance. For the family members, nurses and the healthcare workers, the duration of each visit was the second most sensitive parameter, with contribution to variance ranging from 1.7 to 2.6%. As the other patients were assumed to be continuously exposed, this parameter was obviously not important for them.

Other parameters contributing to the risk variability were the rate of coughing per hour from the infected index patient (about 1.5% contribution), the visit frequency of healthcare workers, nurses or family (about 1.2% contribution), and the dose-response parameter k (about 0.5% contribution).

3.3 Risk Management Evaluation

The results of the risk management evaluation showed that increasing the air ventilation rate from 6 to 9 or 12 air changes per hour (ACH) was an effective risk mitigation measure for the other patients sharing the room with the index patient, but not for the other persons in close contact (Figure 5). For the other patients, mean daily risk of infection could be reduced by about 30% or 58% through increasing the air ventilation from 6 to 9 or 12 ACH, respectively. For the nurses, healthcare workers and family visitors, only up to about 2% reduction in mean daily risk could be achieved by increasing the ACH from 6 to 12.

Using a mask was found to be the most effective intervention measure in minimizing the risk of infection. By using the mask, about 89-97% of the mean daily risk could be reduced for other patients, nurses, healthcare workers and family visitors. Higher risk reduction suggests that all the exposed groups should use mask as a personal protective equipment to minimize the associated risk of infection.

4. DISCUSSION

With the recent emergence of MERS-CoV on the global scene, much remains unknown about the way the virus behaves. Animal models are being evaluated for their suitability for dose-response models, and non-human-primates appear promising, exhibiting similar symptoms to human (Sutton & Subbarao, 2015). However, no dose-response models have been completed for MERS. Hence, the model developed applied a dose-response relationship based on SARS-CoV pathogen, believed to be the best surrogate to use for MERS-CoV because of their identical animal origin, same regions of main occurrence in Asia and Middle East (Sutton & Subbarao, 2015); their consistent respiratory transmission route; their comparable protein structure for binding to cells (Lu et al., 2015), and their similar tropism within cells (Zhou et al., 2015). For these reasons, the proposed best fit SARS-CoV dose-response from QMRA Wiki website was applied (Huang, 2013). However, it must be mentioned that some other researchers applied different SARS-CoV dose-response, such as the Xiao et al. team did (Xiao et al., 2018). Plus, since depending on the context, SARS-CoV and MERS-CoV may show different or higher infectivity (Chan et al., 2015), the question could arise to maybe use a developed

dose-response from other RNA viruses, such as influenza (Chabrelie, Mitchell, Rose, Charbonneau, & Ishida, 2018) or any other. Yet, estimated risk of infection is believed to slightly vary if using other SARS-CoV dose-responses, because of their relatively similar *k* parameter value: Xiao et al. referring to a *k* value of 0.0032 (Xiao et al., 2018), while DeDiego et al. estimated a median *k* value of 0.00297 (DeDiego et al., 2008) and De Albuquerque et al. estimated a median *k* value of 0.00214 (De Albuquerque et al., 2006), all to be compared with the median *k* value used of 0.00246 derived from the best fit SARS-CoV dose-response provided by QMRA (Huang, 2013).

Assumptions about the frequency and length of visits to patients in the hospital were based on the best available data. The visitor data (i.e., frequency and duration) was obtained from a hospital in New York City (Cohen et al., 2012), which may not accurately represent the visitor behavior in all countries. For instance, in South Korea the healthcare system can give responsibility to family members of the patients to provide some care for the patients, leading hospital rooms to be often crowded with patients and their families or privately hired healthcare aides taking care of the patients (Ki, 2015).

Regarding the RNA copies:PFU ratio parameter, no ratio was reported from literature for MERS-CoV, but several are for SARS-CoV, ranging from 1:1 (Xiao et al., 2018), to 300:1 (Sampath et al., 2005), and up to 1200-1600:1 (Houng et al., 2004). In consequence, this parameter appears to possibly change the risk estimation. Running the model with a 1:1 ratio gave daily risk of infection at 6 ACH about 2 log higher than the ones reported with a 1239:1 ratio (developed base model), with new mean daily risk of 3.07×10^{-2}, 2.96×10^{-2}, 2.26×10^{-2}, and 1.39×10^{-2} for nurses, healthcare workers family visitors and other patients, respectively (data not shown). Applying a uniform distribution from 1:1 to 1600:1 for the copies:PFU ratio lead this parameter to contribute for risk variance to about 3%. Because the RNA copies:PFU proposed by Sampath et al. (Sampath et al., 2005) was derived from SARS-CoV isolated from multiple different animals, and because Xiao et al. (Xiao et al., 2018) applied a 1:1 ratio simply because they recognized none ratio were reported for MERS-CoV, this study used the median ratio of 1239:1 proposed by Houng et al. (Houng et al., 2004).

Additionally, only the airborne exposure transmission route through inhalation was considered in the model. Despite the fact that literature suggests aerosol-generating procedures such as bronchoscopy or intubation might amplify viral transmission (Tran, Cimon, Severn, Pessoa-Silva, & Conly, 2012), this study did not consider this aspect, as a simplifying assumption in order to develop a simple and easily adaptable model. Since an index patient in the MERS was reported having undergone a bronchoscopic examination and nebulizer therapy (S. H. Park et al., 2016), risk of infection might be underestimated. However, it must be clarified that according to Seto et al. (W. H. Seto, 2015) and Thompson et al. (Thompson et al., 2013) works, nebulizer usage have been proven to not significantly increase the viral transmission through air. Other exposure routes of infection, such as the fecal-oral and fomite transfer routes that have been postulated for other coronaviruses, were not included in this analysis. This decision was motivated by the fact that literature suggests that MERS transmission mainly occurs through the short-range airborne exposure route (Xiao et al., 2018).

In order to assess the validity of the model developed, a scenario mimicking the South Korean conditions was run. The outbreak selected was one of the two major outbreaks that occurred in South Korea, specifically the one reported in the Samsung Medical Center hospital outbreak in Seoul, for which attack rates per population exposed were given from literature (Cho et al., 2016). No viral loads were reported from literature for the shedding index-patient in this outbreak. However, researchers suggest that major outbreaks occurred because of a "super-spreader" index-patient having a disproportionately higher viral load in their respiratory system (Xiao et al., 2018). Hence, the model was run applying a triangular distribution based on the reported highest observed MERS-CoV concentration found in sputum of MERS-carrying patients (Min et al., 2016), using the reported minimum of 5.00×10^8, average of 6.30×10^8, and maximum of 1.40×10^9 copies/ml. Corman et al. (Corman et al., 2015) even reported a concentration as high as 10^{11} copies/ml, but this value was not used since researchers suggested it to be very unlikely, mentioning that the probable highest concentration would more likely fall around 10^9 copies/ml during the first week of shedding. Additionally, a 2-day exposure duration (before diagnosis) was set based the observed 44 hour exposure time in the South Korean MERS outbreak (Cho et al., 2016). Finally, a rate of 3 ACH for the

ventilation rate in the emergency room was used to match the outbreak conditions (Cho et al., 2016). Under these conditions, the calculated median risks of infection were found to be in the same ranges of the ones reported from Cho et al. (Cho et al., 2016). Estimated median risks were found to be of 2.08×10^{-2}, 1.82×10^{-2}, 9.82×10^{-3}, and 7.14×10^{-3} for nurses, healthcare workers, family visitors and other patients sharing the room, respectively, while attack rates observed from the outbreak was measured at 2.72×10^{-2}, 1.85×10^{-2}, 5.56×10^{-2} and 4.44×10^{-2}, for same exposed groups. These comparable results provide validity to the model developed herein. Thus demonstrating its applicability to known outbreaks.

Finally, the model developed estimated risk of infection from transmission to 1st generation only patients – those infected from direct exposure to index patient- not from any potential 2nd or 3rd generation contacts. Therefore, risks might be under estimated, as additional contacts would increase the exposure dose.

5. CONCLUSIONS

Middle East Respiratory Syndrome (MERS), caused by the MERS-CoV virus, is believed to have started in Arabian Peninsula. Due to the movement of people, the virus has a potential to cause MERS outbreak in other parts of the world, which was highlighted in a recent MERS outbreaks in South Korea and China, and from the reported infected cases that occurred in 27 countries across all continents. In the main outbreaks, nearly all the cases were spread within a hospital setting, where the infected patient visited the hospitals, but was not quarantined. In this context, this study used the QMRA approach to characterize the risk of MERS-CoV infection under hospital settings. The exposed populations included in this study were the other patients sharing the same room, nurses, healthcare workers and family visitors.

The results showed that the nurses had the highest daily risk of infection under a standard 6 ACH ventilation for typical hospital room, followed by healthcare workers, family visitors, while patients housed in the same room had the lowest daily risk of infection. Cumulative mean risk of infection was also highest for the nurses, which, by day 41, was 1.01, 1.2 and 2.4 times the risk for the

healthcare workers, family members and other patients, respectively. Sensitivity analysis showed that the concentration of MERS-CoV in patient's saliva was the most sensitive parameter, constituting over 90% of the parameter uncertainty. The concentration of viruses in sputum is an inherently variable parameter that changes during the course of infection, illness and recovery. Reducing the uncertainty contributed by this parameter is therefore unlikely. However, characterization of "super-spreader" in diagnostic laboratory tests could help prevent spread.

Increasing the air exchange rate was found to be an effective risk reduction measure for the other patients in the same room, but not for the other groups exposed to close-range airborne route. Using mask was found to be the most effective strategy, which could reduce over 90% of the risk for the exposed groups studied. Surgical and N95 masks has been reported to be highly effective (up to 100%) in preventing transmission of respiratory diseases, however; some reports have found less than 50% of the healthcare workers wearing masks even in the developed countries like the US and Canada (Nichol et al., 2008; B. Park et al., 2004; W. Seto et al., 2003).

The generalizable model developed herein using the QMRA approach is intended to allow future risk assessors to adapt this framework to their specific risk scenarios, by adapting each input parameter, accordingly based on newly available data. Such a model can be used to test hypotheses about control measures and risk management strategies.

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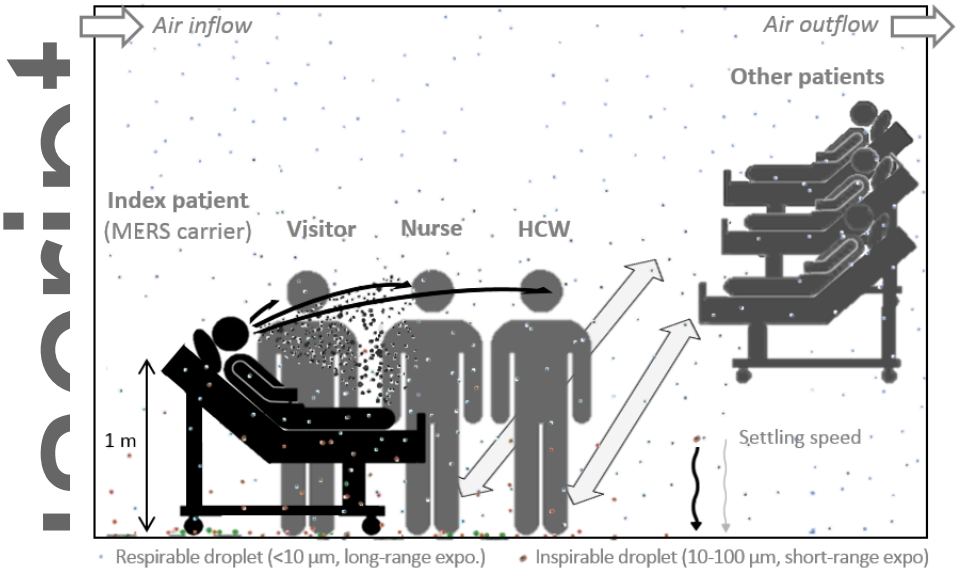
Table I. Parameters used in the exposure model

Parameters	Unit	Description	Input values (a; b)*	Distribution	Sources
$V_{(saliva/cough)}$	mL	Volume of saliva expelled/cough (±10%)	0.044 (0.0396; 0.0484)	Uniform	Nicas & Jones 2009
$R_{(GC:PFU)}$	-	Genomic copies-to-PFU conversion factor	1239:1	Point-value	Houng 2004
$C_{(MERS\ in\ saliva)}$	PFU/mL	Virus conc. saliva = Conc. [#GC/ml] x $R_{(GC:PFU)}$	41734 (7; 201,945)	Lognormal	Wang 2004, Houng 2001
$N_{(cough/day)}$	day^{-1}	# of coughs /day = $N_{(cough/hr)} \times 24$	6.25 (0.125; 39.25)	Triangular	Loudon 1967
d_i	µm	Droplet diameter (4 & 8 µm for <10µm respirable droplets, 7.3 & 74 µm for 10-100 µm inspirable)	4; 8; 7.3; 74	Point-value	Stilianakis & Drossinos, 2010
N_i	#	# of droplets /diameter d_i emitted/cough	160; 7.5; 41.47; 138.48	Point-value	Stilianakis & Drossinos, 2010
V_i	ml	Vol. each droplet /diameter $d_i = (\pi di^2)/6\times10^{-12}$	Calculated	Point-value	Stilianakis & Drossinos, 2010
$V_{(room)}$	m^3	Hospital room size	230	Point-value	Yin 2011
$v_{(critical)}$	m/hr	Required droplet settling velocity to fall on ground $= 0.108 \times d_i^2 \times (1 + 0.166/d_i)$	Calculated	Point-value	Nicas 2005
$C_{(saliva\ in\ air)}$	#/m^3	Conc. droplets in the air /cough $= (\sum_{i=1}^{n} N_i V_i)\ /V_{(room)}$	Calculated	Normal	Stilianakis & Drossinos, 2010
$N_{(room\ entries/hr)}$	hr^{-1}	Visit frequency of nurse	2.5 (0; 12.6)	Triangular	Cohen 2012
$N_{(room\ entries/hr)}$	hr^{-1}	Visit frequency of healthcare workers	1.6 (0; 8.12)	Triangular	Cohen 2012
$N_{(room\ entries/hr)}$	hr^{-1}	Visit frequency of a family member	1.3 (0; 6.4)	Triangular	Cohen 2012
$N_{(patients\ visited/entry)}$	#	# of different patient visited by a nurse	4.5 (0.5; 18)	Triangular	Cohen 2012
$N_{(patients\ visited/entry)}$	#	# of patient visited by healthcare a worker	2.8 (0.5; 7)	Triangular	Cohen 2012
$t_{(spent/entry)}$	min	Time spend /visit of a nurse	2 (1; 120)	Triangular	Cohen 2012

$t_{(spent/entry)}$	min	Time spend /visit of healthcare a worker	3 (1; 72)	Triangular	Cohen 2012
$t_{(spent/visit)}$	min	Time spend /visit of a family member	14 (1; 124)	Triangular	Cohen 2012
$t_{exposed/d}$	Hrs/day	Contact time of other patient in the same room/d	24	Point-value	Assumed
$V_{(inhaled/d)}$	m^3/hr	Respiration rate of an exposed person	0.5	Point-value	US-EPA 2011
k	PFU^{-1}	Parameter of the exponential dose-response	0.00246 (0.00135; 0.00459)	Normal	QMRA Wiki
ACH	hr^{-1}	Air exchange rate (for the base scenario)	6	Base case	Zumla & Hui, 2014
$F_{(droplets\ out\ mask)}$	%	% droplets out mask (from log reduction)	0.032 (0.010; 0.100)	Uniform	Borkow 2010, Wen 2013

*a: Min value for triangular and lognormal distribution and 5th percentile value for normal distribution, respectively.

*b: Max value for triangular and lognormal distribution and 95th percentile value for normal distribution, respectively.



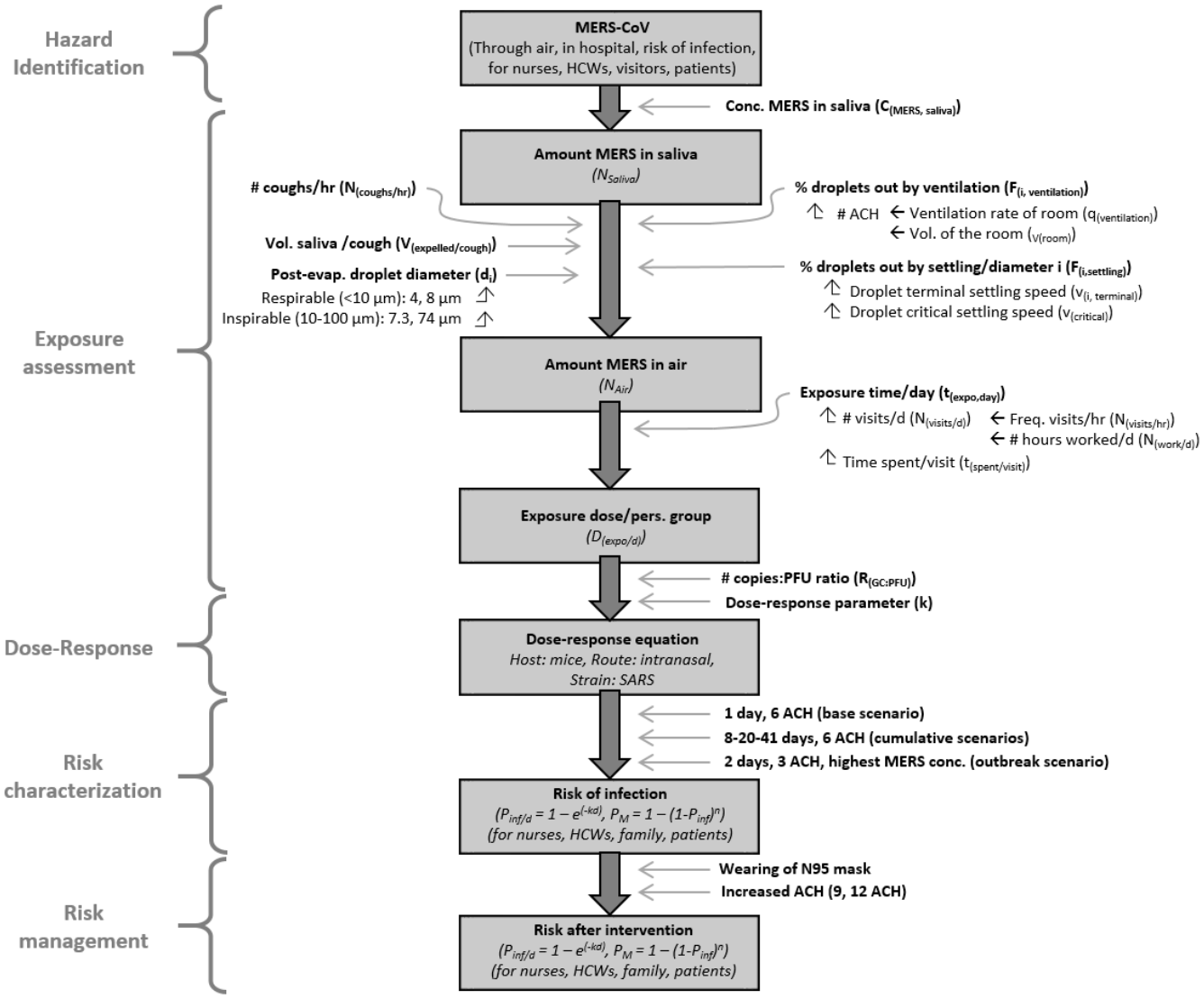


Fig. 1. Exposure scenario and QMRA outline steps. QMRA: Quantitative Microbial Risk Assessment. MERS: Middle East Respiratory Syndrome virus. HCW: Healthcare worker.

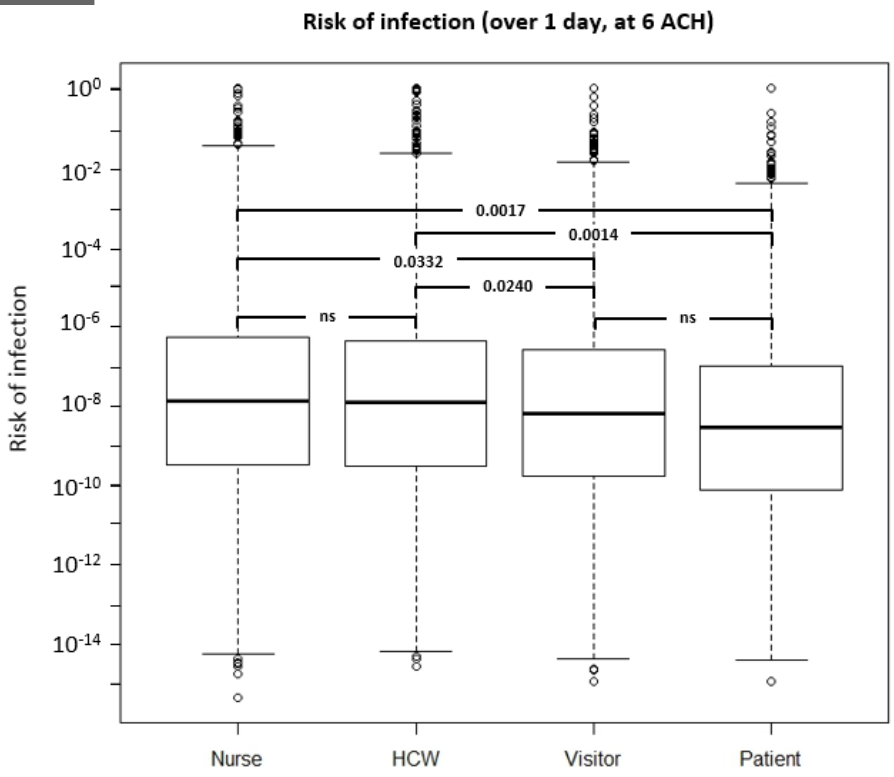


Fig. 2. Box plots of daily risk of MERS infection with 6 ACH air exchange rate illustrating the p-values calculated for pairwise t-tests between groups. ACH: Air Change per Hour. HCW: Healthcare worker.

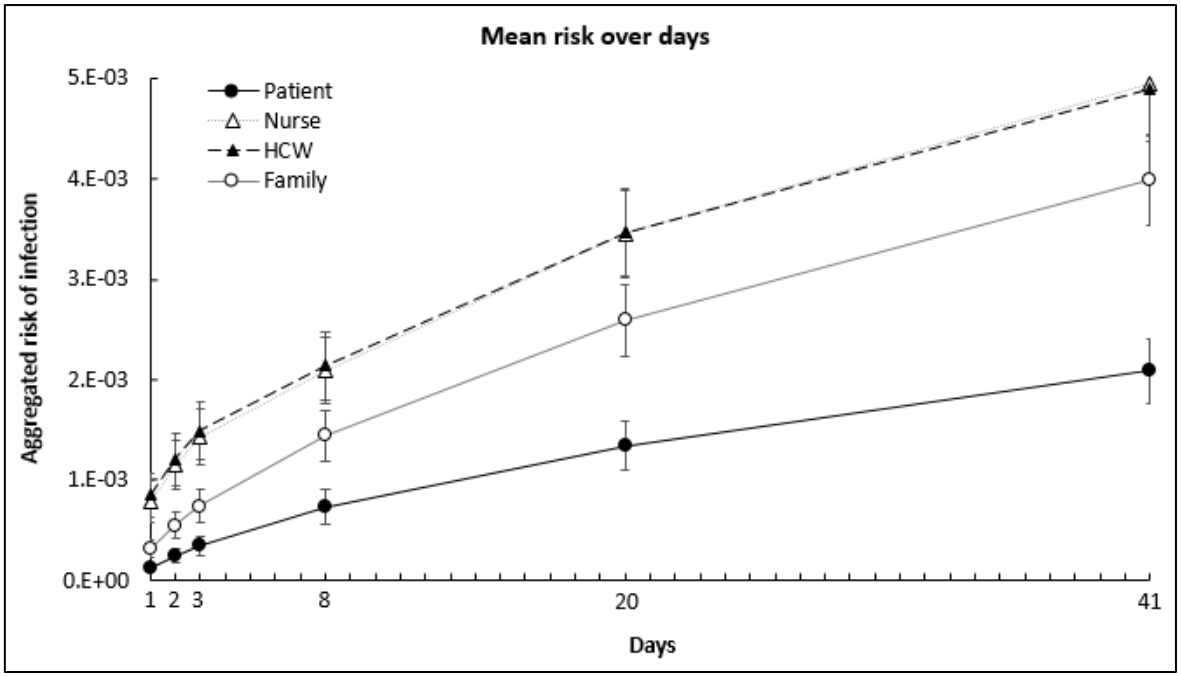


Fig. 3. Aggregated mean risk of infection rate with 6 air changes over days exposed. Vertical bars denote standard error. HCW: Healthcare worker.

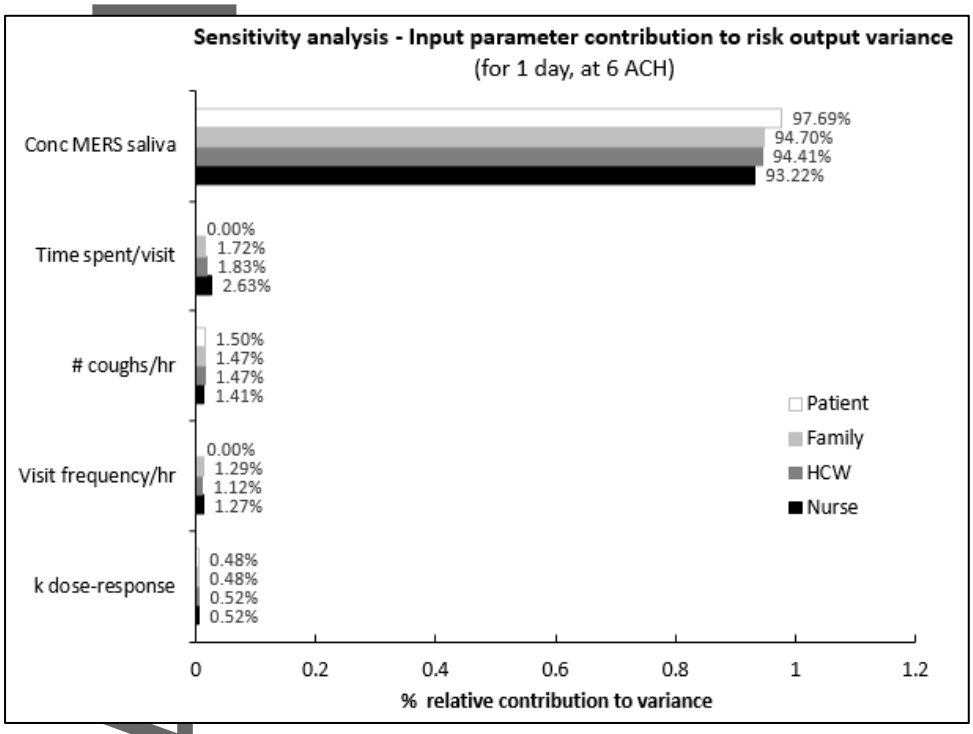


Fig. 4. Parameter sensitivity of the daily risk. ACH: Air Change per Hour. HCW: Healthcare worker.

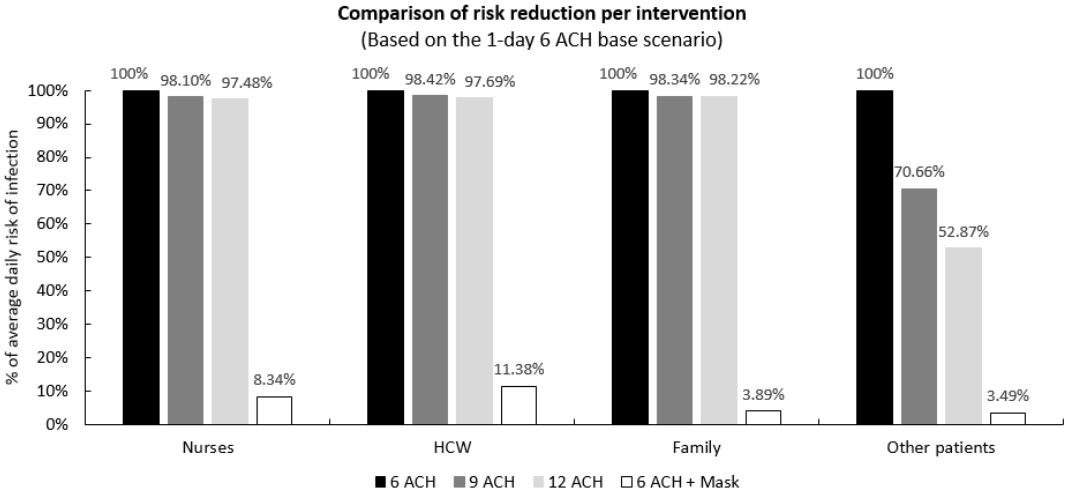


Fig. 5. Effect of risk management strategies on average daily risk of infection. ACH: Air Change per Hour. HCW: Healthcare worker.