Risk of global spread of Middle East respiratory syndrome coronavirus (MERS-CoV) via the air transport network

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Abstract

Background: Middle East respiratory syndrome coronavirus (MERS-CoV) emerged from the Kingdom of Saudi Arabia (KSA) in 2012 and has since spread to 26 countries. All cases reported so far have either been in the Middle East or linked to the region through passenger air travel, with the largest outbreak outside KSA occurring in South Korea. Further international spread is likely due to the high travel volumes of global travel, as well as the occurrence of large annual mass gathering such as the Haj and Umrah pilgrimages that take place in the region.

Methods: In this study, a transport network modelling framework was used to quantify the risk of MERS-CoV spreading internationally via air travellers. All regions connected to MERS-CoV affected countries via air travel are considered, and the countries at highest risk of travel-related importations of MERS-CoV were identified, ranked and compared with actual spread of MERS cases.

Results: The model identifies all countries that have previously reported a travel acquired case to be in the top 50 at-risk countries. India, Pakistan and Bangladesh are the highest risk countries which have yet to report a case, and should be prepared for the possibility of (pilgrims and general) travellers returning infected with MERS-CoV. In addition, the UK, Egypt, Turkey and the USA are at risk of more cases.

Conclusions: We have demonstrated a risk-analysis approach, using travel patterns, to prioritize countries at highest risk for MERS-CoV importations. In order to prevent global outbreaks such as the one seen in South Korea, it is critical for high-risk countries to be prepared and have appropriate screening and triage protocols in place to identify travel-related cases of MERS-CoV. The results from the model can be used by countries to prioritize their airport and hospital screening and triage protocols.

Key words: MERS-CoV, air travel, risk, network modeling

Introduction and Background

A novel coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV) emerged from the Kingdom of Saudi Arabia (KSA) in 2012 and has since spread to 26 countries.1 As of March, 2016 around 1700 laboratory confirmed cases of MERS-CoV have been reported to the World Health Organization (WHO), with a case fatality rate of CFR 36%.2 The vast majority of cases in Middle East have been reported from KSA, followed by United Arab Emirate (UAE), Jordan and Qatar. All cases of MERS-CoV reported so far have either been reported in the Middle East or can be linked to the region through passenger travel, with the largest outbreak outside of the Middle East occurring in South Korea, following an imported case. In that instance a failure in identification, hospital triage and infection control resulted in 186 cases (185 in the Republic of Korea and 1 in China).3 The large number of highly travelled airports in MERS-CoV affected countries poses a risk of further international spread through infected air passenger
travellers. In addition, KSA hosts annual mass gathering events such as the Haj and Umrah pilgrimages, during which millions of pilgrims from around the world travel to and congregate in regions where MERS-CoV is actively being reported.

To further complicate the risk of spread, the origin of MERS-CoV is unknown, and there are still many uncertainties surrounding the sporadic epidemic patterns and transmission mechanisms. MERS-CoV is phylogenetically related to bat coronaviruses, and known to have been circulating for decades in dromedary camels in northeast Africa. Serological surveys in camels during the recent outbreaks also report presence of anti-MERS-CoV antibodies in camels in Egypt, Kenya, Oman, Saudi Arabia and UAE. Previous studies have also identified dromedary camel exposure to be a risk factor for MERS-CoV and transmission from a dromedary camel to human has been confirmed. It is generally believed that the MERS-CoV entered human populations from direct and indirect contact with camels or camel-related products. However, details of camel-to-person transmission are unclear, many cases have not reported camel contact or epidemiologic links, and large studies of handlers of infected camels fail to show transmission to humans.

With the exception of South Korea, large epidemics have not seeded outside of the Middle East. Travel-related cases have been reported from the UK, Germany, Austria, France, Turkey, Greece, Netherlands, Malaysia, Philippines, China, Tunisia, Algeria and the USA, with the number of secondary cases in all locations very small. South Korea represents the largest outbreak outside of the Middle East, resulting in 186 cases and 36 deaths (CFR: 19%). All secondary cases in South Korea were linked to a single chain of transmission and associated with health care facilities.

As was the case in South Korea, human-to-human transmission has so far been mainly nosocomial, and modelling studies have revealed a 4-fold higher risk of transmission in healthcare setting compared with community settings. Yet, there is still no evidence of sustained human-to-human transmission. Without a clear understanding of local transmission combined with ongoing cases in the Middle East, the risk of global spread will continue. As such, risk analysis to identify countries at high risk of imported cases is critical for disease control.

Network models have been used previously to quantify the risk of disease transmission posed by the global air traffic system and airline travel data have been previously used to model the potential spread of MERS-CoV through air traffic network. Khan et al. utilized the flight itinerary and historic Haj pilgrim data to predict the spread of MERS-CoV to other countries during Haj season. The study-based risk on 2012 travel volumes departing all airports in four countries, Saudi Arabia, Jordan, Qatar and the UAE. In addition, Poletto et al. assessed the risk of MERS-CoV, where the focus was estimating local level transmission parameters, and the global level risk analysis was simply based on the capacity of traffic volumes between the Middle East and other countries. This study, similarly, proposes a global transport network modelling framework that accounts for international air travel originating in MERS-CoV-affected regions to quantify the importation risk of MERS-CoV posed to other countries via air travel passengers, but defines the risk more precisely, and at a more spatially disaggregate scale than the previous studies. The countries at highest risk of travel-related importations of MERS-CoV are identified, and the relative risk posed to each is quantified. The results provide a country level ranking and corresponding expected relative risk, which can be used by public health authorities in each country to ensure the appropriate screening and triage protocols are in place to identify travel-related cases of MERS-coronavirus.

**Methods**

The proposed model quantifies the relative risk of disease spread by MERS-CoV-infected travellers departing from the Middle East and arriving at any given world airport. In the modelled network structure, airports are represented as nodes, and the links in the network represent directed air travel routes between airports (with and without stopovers). The risk of MERS-CoV spread posed by air travel between an origin airport and destination airport is quantified. The relative risk posed to each airport is defined in Equation (1):

$$r_{ij} = a_i \cdot o_i \cdot v_{ij}.$$  

Equation (1) is specific to the origin–destination (OD) pair $(i,j)$, and is dependent on the origin being in an active region (i.e. the virus is assumed to be in circulation and/or in the environment, and therefore this region poses a risk of local infection), the outbreak intensity at the origin $(o_i)$, and the total passenger volume $(v_{ij})$ travelling between $(i,j)$. The variable, $a_i$, is a binary variable which indicates whether MERS-CoV is active in a given region. If a region is assumed to be active then the status of $a_i$ is set to one for all airports in that region, otherwise it is set to 0. Active airports therefore pose the risk of exporting infected travellers. The outbreak intensity, $o_i$, is equal to the relative outbreak size at the origin, and is normalized to the largest outbreak size across all active regions. This variable is assumed to be correlated with the outgoing travel risk posed by a region, and thus inflates the risk per outgoing traveller at a constant relative rate. The passenger flow variable, $v_{ij}$, or the total passenger volume originating at airport $i$ and travelling to airport $j$, captures the potential dispersal for the disease, and includes travel on both direct routes and indirect routes with stopovers between airport $i$ and airport $j$.

The OD level travel risk can be aggregated across all origin airports, $i$, which are connected via travel routes to destination airport $j$, to quantify the risk posed to a destination airport. The aggregated risk posed to destination $j$ is defined by Equation (2):

$$r' = \sum_i r_{ij}.$$  

The destination level risks are then normalized (as shown in Equation 3) by dividing by the highest value computed over all destinations, $j$, thus what is being estimated is the expected relative risk posed to a destination airport $j$ from all incoming travel:

$$R' = r'/\max_j(r').$$  

Finally, the country-level risk is computed by aggregating the risk posed to all airports in a given country. Similar to the airport-level destination risk, the country-level risk is normalized by dividing by the highest country-level risk across all
countries. The final outcome is the expected relative risk of MERS-CoV-infected passengers arriving in each country. Similar measures for importation risk have been used previously in the context of vector borne diseases.19

Data

The model requires passenger air travel data and case report data for MERS-CoV. Passenger air travel data were purchased from the International Air Transport Association (IATA),26 and includes the calibrated passenger travel volumes for all international air travel routes, where a route is defined by the origin, destination and stopover airports. The route-specific passenger travel volumes supplied by IATA were calibrated based on data from 240 airlines comprising 84% of global air traffic, and includes over 9000 airports (IATA). The passenger volumes were available at a monthly temporal resolution, which thus determined the temporal resolution of the model. The analysis was conducted using travel volumes from January to August, 2015. This data are used for the passenger flow variable, \( v_{ij} \).

The MERS-CoV case data used in the model were collected from FluTrackers.27 Detail of each case was sought from various sources including World Health Organization (WHO),28 and European Centre for Disease Prevention and Control (ECDC).17,27. The location and number of cases reported in each city in KSA between January and August 26 of 2015 was provided by ECDC.17 These data define the outbreak intensity variable for each region, \( o_i \). The complete set of cities where MERS-CoV has been reported since 2012 was collected from WHO,28 which is used to determine the status of region, \( x_i \).

Case Studies

Two case studies are evaluated to quantify the global risk posed by travellers departing from two different specified regions (denoted as Scenarios 1 and 2). Thus, the scenarios differ by the set of active regions specified in the model.

Scenario 1

Scenario 1 quantifies the global risk posed by travellers departing MERS-CoV affected cities in KSA. In Scenario 1 all cities in KSA which have reported cases in 2015 are assumed to be an active transmission region (\( x_i = 1 \)), and the outbreak intensity variable, \( o_i \), is set equal to the number of reported cases for each city between January and August 26 of 2015. While this estimate is likely an underestimation of the actual number of people infected with MERS in a given city, the value acts as a proxy for the number of infected individuals in a given city and inflates the outgoing (per person) travel risk proportionally. In Scenario 1, all regions outside KSA are designated as inactive, and considered potentially at risk of imported cases.

The input data for Scenario 1, including the list of cities in KSA with confirmed cases, corresponding number of cases and assigned airport for each city are listed in Supplementary Table S1. The airports were selected by identifying the closest (in terms of vehicle travel distance) major airport to each active city.

This analysis is of particular relevance for events such as the Haj and Umrah, which attract millions of pilgrims to KSA, and more importantly, to cities where MERS-CoV is known to be in circulation. After congregating in masses at these events, the pilgrims return to their countries of origin. The results from Scenario 1 can be used to help the home countries be better prepared for the return of potentially infected pilgrims post such mass gatherings in KSA. The relative risk posed to each country is computed, allowing those countries at highest risk to be identified and targeted for increased surveillance.

Scenario 2

Scenario 2 increases the set of active regions identified in Scenario 1 to include all regions that have reported non-travel-related cases since MERS-CoV was first diagnosed in humans in 2012. Scenario 2 is based on the assumption that the cases in these regions could have been contracted from either an infected human or alternatively, an animal or environmental source. Thus our active regions are assumed to still pose a risk because the virus may still be in circulation in the environment, even if there has not been a recently reported case. This assumption is further supported by the evidence of MERS circulating in animal populations in these active regions, which was noted previously. In efforts to conduct a conservative risk analysis, we consider all such regions potential sources of infection for travellers. The set of active transmission regions in Scenario 2 includes a more comprehensive list of cities in KSA (listed in Supplementary Table S2) in addition to cities in Jordan, Kuwait, Yemen, Qatar, Oman, UAE, Lebanon and Iran. This scenario excludes South Korea as an active transmission region because all cases in the South Korea outbreak were traceable to the original human source, thus knowingly not contracted from the local environment. Our list of active transmission regions is restricted to those in which cases were locally acquired and the source of infection is unknown (i.e. not from an infected traveller).

Supplementary Table S3 lists the set of countries defined as active (in addition to KSA) in Scenario 2 and the corresponding airports assumed to pose an ongoing risk.

Because it is impossible to accurately estimate the number of infected individuals in each active region at any given time, the outbreak intensity variable is set to a constant for each active region in Scenario 2. Therefore, in Scenario 2, each active region is considered equally likely to have an infected traveller departing the city. While this is a major simplifying assumption of the model, it is still able to capture the risk as a direct function of the relative connectivity to regions with confirmed local cases, and the method is illustrated to predict the likelihood of imported infection cases accurately.

For each scenario evaluated, the results are presented in both tables and figures. Tables 1 and 2 list the top 50 countries at-risk of importing a MERS-CoV infected traveller from an active region, and corresponding relative expected risk for Scenarios 1 and 2, respectively. Figures 1 and 2 present the same information on a global map.

To validate the model the results are compared with the set of confirmed travel imported cases that have been reported. The set of travel-related cases reported since 2012 are listed in Supplementary Table S4. This list excludes cases that were reported in Jordan, Kuwait, Yemen, Qatar, Oman, UAE, Lebanon and Iran because the existence of locally acquired cases in these regions makes it impossible to confirm whether the reported
cases in patients with travel histories acquired the virus locally or abroad.

The airport-level risks which were aggregated to generate the country level risk are provided in Supplementary Tables S5 and S6 for Scenarios 1 and 2, respectively. The tables include the top 50 airports at-risk of importing a MERS-CoV-infected traveller from an active region, and their corresponding relative expected risk.

### Results

The country-level results are presented in Tables 1 and 2 and Figures 1 and 2 for Scenarios 1 and 2, respectively. Each table includes the top 50 at-risk countries, their respective ranking in terms of the relative risk posed, and the last column specifies if the country has previously reported a travel related MERS-CoV case (from the specified set of active regions which is scenario-specific), and if so how many.

In Scenario 1, where KSA is the only source of infected travellers considered in the model, India is identified to be at the highest risk, which has surprisingly not yet reported a case. The UAE and Egypt rank 2nd and 3rd, respectively, and both have reported travel-acquired cases from KSA. In total there have been 23 travel-imported cases confirmed from KSA in 15 different countries; 9 of the countries were included in the top 20 at-risk countries, and all were captured in the top 50. Of the top 10 at-risk countries in Scenario 1, 6 (60%) have previously reported cases from KSA. Additional countries in the top 10 for Scenario 1 that have not yet reported imported cases from KSA included Pakistan, Sudan and Bangladesh.

In Scenario 2, where the set of MERS-CoV source regions is expanded to include all Middle East countries that have previously reported locally acquired cases as potential sources. 9 of the 22 travel-imported cases reported outside the Middle East (41%) were reported in one of the countries falling in the top 10 of our list, and 6 of the top 8 ranked countries (75%) have previously reported travel acquired cases. India is again identified as the most-at-risk country, and along with Pakistan which is ranked third, have yet to report MERS-CoV cases. Countries such as UAE and Jordan, which were identified as high-risk in Scenario 1, are no longer included in Table 2 because they are treated as high-risk travel origins (rather than considered potentially at-risk destinations). In addition, because Scenario 2 considers a more comprehensive set of travel sources, the risk is increased to highly connected regions such as the UK and Germany, which both appear in the top 10 at-risk countries.

### Discussion and Conclusions

The proposed model identifies the set of countries at greatest risk of importing MERS-CoV-infected travellers. Two scenarios are evaluated, which differ by the set regions from which infected travellers are assumed to depart from. Scenario 1 limits the ongoing travel risk to be from KSA only, while Scenario 2 considers all regions which have reported locally acquired cases as potential sources. Scenario 2 results are more likely to represent the expected risk posed globally by MERS-CoV. Scenario 1 may be more appropriate for evaluating the risk during and immediately after major mass gatherings in KSA. For both scenarios, the quantified relative risk and ranking can be useful for informing public health authorities on the optimal locations for airport screening and travel protocols.

For both scenarios, India is identified as the highest at-risk country, while Pakistan and Bangladesh are also included in the

### Table 1. Top 50 at-risk countries for Scenario 1 (excluding KSA), with relative risk and number of confirmed travel-related MERS-CoV case

| Rank | Country   | Expected relative risk | Confirmed travel cases from KSA |
|------|-----------|------------------------|--------------------------------|
| 1    | India     | 1.000                  | 2                              |
| 2    | UAE       | 0.821                  |                                |
| 3    | Egypt     | 0.804                  | 1                              |
| 4    | Pakistan  | 0.547                  |                                |
| 5    | Philippines| 0.258                 | 2                              |
| 6    | Jordan    | 0.213                  | 2                              |
| 7    | Turkey    | 0.203                  | 1                              |
| 8    | Sudan     | 0.203                  |                                |
| 9    | USA       | 0.194                  | 2                              |
| 10   | Bangladesh| 0.190                  |                                |
| 11   | Lebanon   | 0.169                  |                                |
| 12   | Indonesia | 0.151                  |                                |
| 13   | UK        | 0.150                  | 1                              |
| 14   | Kuwait    | 0.124                  |                                |
| 15   | Sri Lanka | 0.085                  |                                |
| 16   | Nepal     | 0.080                  |                                |
| 17   | Malaysia  | 0.076                  |                                |
| 18   | Bahrain   | 0.066                  |                                |
| 19   | Qatar     | 0.065                  | 3                              |
| 20   | Morocco   | 0.064                  |                                |
| 21   | France    | 0.064                  |                                |
| 22   | Germany   | 0.059                  |                                |
| 23   | Ethiopia  | 0.057                  |                                |
| 24   | China     | 0.053                  |                                |
| 25   | Italy     | 0.049                  |                                |
| 26   | Iran      | 0.035                  |                                |
| 27   | Switzerland| 0.033                 |                                |
| 28   | Spain     | 0.033                  |                                |
| 29   | Oman      | 0.029                  |                                |
| 30   | Tunisia   | 0.025                  | 1                              |
| 31   | Canada    | 0.024                  |                                |
| 32   | Yemen     | 0.021                  |                                |
| 33   | Australia | 0.014                  |                                |
| 34   | Kenya     | 0.013                  |                                |
| 35   | Singapore | 0.012                  |                                |
| 36   | Afghanistan| 0.012                 |                                |
| 37   | Hong Kong | 0.012                  |                                |
| 38   | South Korea| 0.011                 | 1                              |
| 39   | Thailand  | 0.011                  |                                |
| 40   | South Africa| 0.010                |                                |
| 41   | Algeria   | 0.010                  | 2                              |
| 42   | Austria   | 0.010                  | 1                              |
| 43   | Netherlands| 0.010                 | 2                              |
| 44   | Nigeria   | 0.008                  |                                |
| 45   | Belgium   | 0.008                  |                                |
| 46   | Ireland   | 0.007                  |                                |
| 47   | Greece    | 0.007                  | 1                              |
| 48   | Japan     | 0.006                  |                                |
| 49   | Maldives  | 0.005                  |                                |
| 50   | Poland    | 0.004                  |                                |
|      | Total number of travel reported cases (from SA) | 23                         |
Furthermore, each of these countries has substantial Muslim populations who may travel to KSA for religious pilgrimages, and should be prepared for the possibility of (pilgrims and general) travellers returning infected with MERS-CoV. In addition to the Pilgrimage, a large number of people from these countries work in the Middle East, and travel back and forth regularly. Although these countries are already preparing for MERS outbreaks and have issued policy documents, actual capacity to diagnose and treat cases as they arrive is questionable. It is likely that MERS-CoV cases may have already been imported to these countries, but the cases were not picked up by local surveillance due to mild disease, lack of diagnostic capacity and reporting. Lack of proper diagnosis can pose significant harm to a country, as was illustrated by the episode in South Korea, where the index case visited four hospitals before properly diagnosed, by which time he had spread infection to many people. Surveillance systems should be improved to identify cases, and travellers from high risk areas should be screened and monitored for associated symptoms. A rapid response system should be developed accordingly, and healthcare workers should be trained to identify symptoms and manage the cases safely.

In contrast to India, Pakistan and Bangladesh, the remaining seven of the top 10 at-risk countries across the two scenarios, have previously reported travel-imported cases, and these countries are likely to remain at-risk of importing infected travellers, and should continue surveillance and public travel health awareness campaigns, especially for religious pilgrims.

For both scenarios all countries that have previously reported travel acquired cases were identified in the top 50, with the majority of countries reporting travel imported cases identified in the top 20. These results suggest that the model is able to capture the risk posed to most countries for importing MERS-infected travellers. As further validation, the model results are consistent with previous travel-related studies. Poletto et al. reported the highest air traffic from Middle East was to India (11.7%), Bahrain (8.7%), Pakistan (8.6%), UK (8.4%), Oman (5.8%) and Egypt (5.2%). In addition, Khan et al. found India, Egypt, Pakistan, UK, Kuwait, Bangladesh, Iran and Bahrain to be the highest risk countries of importing MERS-CoV cases. Each of these countries were identified as high-risk in Scenario 1 ranking as well, but in Scenario 2 Iran and Kuwait were included as potential sources of infection in our model (which was not the case in 2012). While our country-level rankings are similar to Khan et al., the variation is due to three main factors, (i) our model incorporates a weighting for each travel origin based on the outbreak intensity variable (included only in Scenario 1) which serves to differentiate the outgoing traveller infection risk posed by different regions in the Middle East where MERS-CoV has been reported, (ii) outgoing infected travellers departures are restricted to airports nearest the set of regions with reported locally acquired cases, rather than the entire Middle East and (iii) more current air travel data are used. Since 2012, when Khan et al. conducted their study, the regions where MERS-CoV has been locally acquired have grown, and the travel patterns within the Middle East have also changed. Thus, the results in this study should be more accurate estimates of importation risk to countries connected to the Middle East via the air traffic network.

It should be noted, however, that several high-risk countries identified by the model have not had an imported case as of yet,

| Rank | Country     | Expected relative risk | Confirmed travel cases from the Middle East |
|------|-------------|------------------------|--------------------------------------------|
| 1    | India       | 1.000                  | 1                                          |
| 2    | Egypt       | 0.583                  | 1                                          |
| 3    | Pakistan    | 0.433                  |                                            |
| 4    | UK          | 0.241                  | 1                                          |
| 5    | Turkey      | 0.196                  | 1                                          |
| 6    | USA         | 0.192                  | 2                                          |
| 7    | Germany     | 0.156                  | 2                                          |
| 8    | Philippines | 0.156                  |                                            |
| 9    | Bangladesh  | 0.153                  |                                            |
| 10   | Bahrain     | 0.134                  |                                            |
| 11   | Indonesia   | 0.131                  |                                            |
| 12   | France      | 0.101                  | 1                                          |
| 13   | Sudan       | 0.082                  |                                            |
| 14   | China       | 0.073                  |                                            |
| 15   | Sri Lanka   | 0.073                  |                                            |
| 16   | Malaysia    | 0.073                  | 1                                          |
| 17   | Italy       | 0.073                  | 1                                          |
| 18   | Thailand    | 0.067                  | 2                                          |
| 19   | Iraq        | 0.064                  |                                            |
| 20   | Nepal       | 0.059                  |                                            |
| 21   | Morocco     | 0.046                  |                                            |
| 22   | Ethiopia    | 0.042                  |                                            |
| 23   | Switzerland | 0.040                  |                                            |
| 24   | Spain       | 0.040                  |                                            |
| 25   | Australia   | 0.040                  |                                            |
| 26   | Russian Federation | 0.038 | | |
| 27   | Afghanistan | 0.037                  |                                            |
| 28   | Canada      | 0.036                  |                                            |
| 29   | Nigeria     | 0.036                  |                                            |
| 30   | Singapore   | 0.029                  |                                            |
| 31   | South Africa| 0.029                  |                                            |
| 32   | Tunisia     | 0.028                  | 1                                          |
| 33   | Algeria     | 0.027                  | 2                                          |
| 34   | Netherlands | 0.026                  | 2                                          |
| 35   | Austria     | 0.025                  | 1                                          |
| 36   | Hong Kong   | 0.022                  |                                            |
| 37   | Kenya       | 0.022                  |                                            |
| 38   | Japan       | 0.022                  |                                            |
| 39   | Greece      | 0.019                  | 1                                          |
| 40   | Belgium     | 0.017                  |                                            |
| 41   | South Korea | 0.014                  | 1                                          |
| 42   | Cyprus      | 0.014                  |                                            |
| 43   | Kazakhstan  | 0.014                  |                                            |
| 44   | Tanzania    | 0.014                  |                                            |
| 45   | Ukraine     | 0.014                  |                                            |
| 46   | Sweden      | 0.014                  |                                            |
| 47   | Maldives    | 0.014                  |                                            |
| 48   | Denmark     | 0.014                  |                                            |
| 49   | Czech Republic | 0.011 | | |
| 50   | Ireland     | 0.010                  |                                            |

Top 10 in both scenarios. Critically, none of these countries have reported MERS-CoV cases as of June 2016, and may therefore be unprepared to diagnose and treat a case were one to arise. Furthermore, each of these countries has substantial Muslim populations who may travel to KSA for religious pilgrimages,
whilst lower risk countries have. This outcome has substantial implications: (i) countries with lower risk should not be complacent, as South Korea was ranked below the top 30 countries, yet experienced a large epidemic, and (ii) countries such as India and Pakistan, identified at highest risk but yet to report any cases, should be prepared for potential imported cases.

This model is subject to various limitations. The first limitation results from the uncertainty surrounding MERS-CoV transmission. The analysis quantifies the relative expected risk of MERS-CoV-infected (air travel) passengers arriving at airports based on a set of active transmission regions, the outbreak size at each and travel patterns; the model does not include the potential importation of infected intermediary hosts or intermediary host by-products since the influence of that possibility is yet to be established. Second, an estimate of the true number of cases in each region based on the confirmed reported case count is not included, and the reported number of cases is instead used as a proxy. Third, the potential harm posed to a region by local transmission (if successfully introduced into the population by an infected traveller) is not accounted for in the risk assessment. Fourth, the model is limited by the available travel data. Air travel reliably captures human mobility patterns at large spatial scales such as travel between countries and across large bodies of water; however, it does not fully capture travel patterns within countries due to the availability of alternative modes of travel such as road and rail. Because the proposed model is solely based on air travel data, the intra-country mobility patterns are not fully captured. For this reason the risk is modelled and validated at the country level rather than a more disaggregate spatial scale, such as the city level, which cannot be reliably quantified without a more comprehensive multi-modal data set. The same issue regarding travel via alternative modes can also arise at the inter-country level, especially for smaller neighbouring countries. These limitations may all be factors in why several high-risk

Figure 1. Top 50 at-risk countries and corresponding expected relative risk identified by the model for Scenario 1

Figure 2. Top 50 at-risk countries and corresponding expected relative risk identified by the model for Scenario 2
countries identified by the model have not had an imported case as yet, whilst lower risk countries have. Other modelling approaches which focus on intra-country transmission are needed to inform internal disease control policy for a particular country.

In summary, MERS-CoV has persisted in human populations for more than 4 years.\textsuperscript{23,30} Despite uncertainty about transmission, a mixed pattern of both sporadic and epidemic spread continue to be observed,\textsuperscript{7} suggesting the virus is still present in the environment in various regions of the Middle East. The risk of travel-related cases will therefore remain as long as MERS-CoV transmission persists in the region. Furthermore, the Haj pilgrimage to Mecca in KSA and other regional mass gatherings pose an ongoing risk of spread by international travellers. Although travel cases were not reported after Haj in 2013–2015 despite increase likelihood of secondary infection during such mass gathering,\textsuperscript{5} several travel acquired cases of MERS-CoV were reported in travellers who had returned from Umrah, a minor pilgrimage, in 2014.\textsuperscript{31} Luckily, the numbers of secondary cases resulting from these Umrah travellers was not high, and the number of secondary cases resulting from infected travellers is typically very low. A recent modelling study analysed the data of 36 travel-related cases and estimated 22.7% risk of secondary transmission and 10.5% risk of tertiary transmission in event of importation of a MERS case from Middle East.\textsuperscript{32} None the less, the potential harm posed by a single MERS-CoV-infected traveller to an unprepared country can be significant, as was exemplified by the South Korean epidemic, in which 186 cases resulted from a single index case. In this instance, failure to recognize MERS coronavirus infection at the hospital and lack of appropriate, timely triage and infection control procedures resulted in a large epidemic. For this reason, it is critical for all countries to be prepared and have appropriate screening and triage protocols in place to identify travel-related cases of MERS-CoV, and for risk stratification to be utilized to prioritize awareness and preparedness for MERS-CoV. Countries higher on the risk scale, such as India and Pakistan could invest more in preparedness and review existing protocols and policies.

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