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Worldwide Reduction in MERS Cases and Deaths since 2016

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Since 2012, Middle East respiratory syndrome (MERS) coronavirus has infected 2,442 persons worldwide. Case-based data analysis suggests that since 2016, as many as 1,465 cases and 293–520 deaths might have been averted. Efforts to reduce the global MERS threat are working, but countries must maintain vigilance to prevent further infections.

From 2012 through May 31, 2019, Middle East respiratory syndrome coronavirus (MERS-CoV) has infected 2,442 persons and killed 842 worldwide (*1*). MERS-CoV is currently circulating in dromedary camels in Africa, the Middle East, and southern Asia; however, most cases of human infection have been reported in the Arabian Peninsula (*2*). Large hospital outbreaks in 2014 and 2015 (*3,4*) (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/25/9/19-0143-F1.htm) motivated affected countries to substantially invest in prevention and control activities.

To estimate the potential number of MERS cases and deaths that might have been averted since 2016 had the risk levels of 2014–2015 continued, we analyzed case-based data on laboratory-confirmed human cases of MERS-CoV infections reported to the World Health Organization (*5*). We categorized cases as either secondary (human-to-human transmission) or community-acquired (presumed camel-to-human transmission). In addition, we used case-based data on date of onset (for symptomatic infections) or report (for asymptomatic infections), outcome (died/recovered), and dates and sizes of reported clusters of human-to-human–transmission cases (*3,4,6–8*).

We compared incidence of camel-to-human–transmission cases (i.e., community-acquired cases, assuming all of those not positively attributed to human-to-human transmission were in this category) during 2016, 2017, and 2018 (through September only) with incidence during 2014–2015, assuming that case numbers were Poisson distributed

(yielding a 2-sided p value). Furthermore, we obtained the expected total number of cases in 2016, 2017, and through September 2018, conditional on the incidence of community-acquired cases, by simulating 10,000 times from the distribution of human-to-human–transmission cluster sizes observed during 2014–2015. Thus, the observed incidence rates in these years could be compared with simulations to test the null hypothesis that human-to-human transmission levels remained constant since 2014–2015 (yielding a 2-sided p value). The intervals reported are the 2.5th and 97.5th percentiles of the simulations (95% CIs). We examined a range of mortality rates from healthcare-associated outbreaks in South Korea and Saudi Arabia (*3,5*) and the case-fatality ratio (CFR) from all reported cases globally (35.5%, 800 fatalities/2,254 cases) (*9*). When numbers of cases averted were not statistically significant, we truncated the lower bound of the 95% CI to 0 cases averted.

Of the 2,254 laboratory-confirmed cases reported to the World Health Organization from 2012 through October 1, 2018 (Appendix Figure 1), 1,087 were classified as human-to-human transmssion cases and the remaining 1,167 as community-acquired cases. During this same period, clusters/outbreaks were reported each year (range 2–255 cases).

Although 739 cases were reported in 2014 and 768 cases in 2015, only 244 cases were reported in 2016, another 244 in 2017, and 113 through September 2018. We assessed potential components of this reduction (i.e., reduction of community-acquired cases, human-to-human transmission cases, or both). The incidence of community-acquired cases was 177 in 2016, 151 in 2017, and 86 through September 2018 (Appendix Table). These rates were each significantly ($p<0.001$) lower than expected compared with the incidence in 2014–2015 (334 for 2016, 334 for 2017, and 251 through September 2018). Conditional on the number of community-acquired cases, we observed no significant reduction in the risk for secondary cases from 2014–2015 to 2016, 2017, and through September 2018, although we did find nonsignificant trends. We estimated that 154 secondary cases (95% CI 0–495) were averted from the 177 community-acquired cases in 2016, 96 (95% CI 0–419) from the 151 community-acquired cases in 2017, and 80 (95% CI 0–338) from the 86 community-acquired cases through September 2018, totaling 330 (95% CI 0–819) from the 414 community-acquired cases during 2016–September 2018 (Table). Assuming a 20% CFR (*3,10*), these 330 (95% CI 0–819) cases averted correspond to 66 (95% CI 0–164) expected deaths averted; assuming a 35.5% CFR (*9*), they correspond to 117 (95% CI 0–291) expected deaths averted.

The total number of cases averted, when simultaneously taking into account reduced camel-to-human and human-to-human transmission, was estimated at 507 (95% CI 189–967) in 2016, 507 (95% CI 189–967) in 2017, and 451 (95% CI 191–855) through September 2018, totaling 1,465 (95% CI 895–2,165) cases averted and 293 (95% CI 179–433) expected deaths averted (under the assumption of a 20% CFR) from 2016 through September 2018. Assuming a 35.5% CFR, this estimate corresponds to 520 (95% CI 318–769) expected deaths averted.

We believe that affected countries are reducing the global threat of MERS by addressing knowledge gaps with regard to transmission, enhancing surveillance, and strengthening the ability to detect cases early and contain outbreaks through improved infection prevention and control measures in hospitals. Critical for preventing international spread and sustained transmission have been improved prevention and control measures in hospitals, restriction of camel movement in affected areas, stronger and more comprehensive investigations of cases and clusters, and improved communication.

Although global efforts seem to have prevented hundreds of infections and deaths, vigilance must be maintained by all countries. More needs to be done to limit spillover infections from dromedaries, which requires stronger surveillance of dromedary populations and persons in direct contact with infected herds and accelerated development of a vaccine for dromedaries (*2*). The international community and affected countries have a collective and shared responsibility to curtail a major health security threat such as MERS in the Middle East and beyond.

Table. Estimated Middle East respiratory syndrome cases and deaths averted because of reduced human-to-human transmission and camel-to-human transmission*

	Estimated cases and deaths averted because of reduced human-to-human transmission†				Estimated cases and deaths averted because of reduced camel-to-human and human-to-human transmission			
			Deaths averted				Deaths averted	
Year	Cases averted‡	2-sided p value	Assuming 20% CFR‡	Assuming 35.5% CFR‡	Cases averted‡	2-sided p value	Assuming 20% CFR‡	Assuming 35.5% CFR‡
2016	154 (0–495)	0.2714	31 (0–99)	55 (0–176)	507 (189–967)	<0.0001	101 (38–193)	180 (67–343)
2017	96 (0–419)	0.5810	19 (0–84)	34 (0–149)	507 (189–967)	<0.0001	101 (38–193)	180 (67–343)
2018§	80 (0–338)	0.4316	16 (0–68)	29 (0–120)	451 (191–855)	<0.0001	90 (38–171)	160 (68–304)
2016–2018§	330 (0–819)	0.0896	66 (0–164)	117 (0–291)	1,465 (895–2165)	<0.0001	293 (179–433)	520 (318–769)

*Values are estimated no. (95% range) except as indicated. CFR, case-fatality ratio.
†Conditional on reported community-acquired cases.
‡The 95% intervals reported are the 2.5th and 97.5th percentiles of the simulations. When cases averted were not statistically significant, we truncated the lower bound of the 95% CI to 0 cases averted.
§Through September 2018.

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Limited Scope of Shorter Drug Regimen for MDR TB Caused by High Resistance to Fluoroquinolone

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Resistance to second-line tuberculosis drugs for patients with multidrug-resistant tuberculosis has emerged globally and is a potential risk factor for unfavorable outcomes of shorter duration drug regimens. We assessed the proportion of patients eligible for a shorter drug regimen in Uttar Pradesh, India, which had the highest rate of multidrug-resistant tuberculosis in India.

India has the largest burden of multidrug-resistant (MDR) tuberculosis (TB) worldwide (*1*). The success rate for MDR TB treatment is low (47%), largely caused by death, suboptimal adherence of patients to long treatment courses, and frequent drug-related adverse events (*2*).

In 2016, the World Health Organization recommended a shorter drug regimen (9–12 months) for patients with MDR TB or rifampin-resistant TB who had not received second-line drugs (SLDs) and in whom resistance to fluoroquinolones and injectable SLDs is considered highly unlikely (*3*). A shorter regimen is a promising step toward high treatment success rates. Recently, this regimen was instituted in Uttar Pradesh, which has ≈20% of the total

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Worldwide Reduction in MERS Cases and Deaths since 2016

Appendix

Background

While to date this high-threat zoonotic respiratory pathogen typically has not caused outbreaks in community settings, it has repeatedly demonstrated its ability to cause large-scale outbreaks in healthcare settings in several countries including the Kingdom of Saudi Arabia (KSA), the United Arab Emirates and the Republic of Korea (ROK) with substantial public health, security and economic impacts (Appendix Figure 1) (*1*).

The prevention and control measures invested in to reduce MERS-CoV incidence included better surveillance in dromedary camel (*1*,*2*) and human (*3*-*5*) populations, rapid and accurate detection of cases and human-to-human-transmission clusters, risk assessment, transparency and information sharing with affected countries, to WHO and externally, evidence-based policy development and revisions (*3*-*6*), and improvements in basic infection prevention and control measures in healthcare settings.

Data on human MERS-CoV cases

Within WHO databases, human cases were classified as secondary cases due to human-to-human transmission if they reported recent direct contact with a known MERS patient and/or were identified as a household, occupational or healthcare worker contact of a known MERS patient in the 14 days before symptom onset. For these analyses, we treated all other cases as community-acquired recognizing that this category will include cases resulting from unidentified human-to-human transmission (Appendix Figure 1). Case classification by countries and investigations into the source of infection substantially improved through more systematic data collection since 2015 (*1*), and it is believed that human-to-human cases were more accurately

classified in recent years following the large hospital outbreaks of MERS in Jeddah and Riyadh in 2014.

The large multi-hospital outbreak in Jeddah in 2014 resulted in a total of 255 cases, however, a genomic analysis suggested that this outbreak included multiple introductions from contacts with dromedary camels (*7*). The largest outbreak resulting from one spillover event occurred in ROK in 2015 resulting in 186 cases and 38 deaths, following the return of one individual from the Middle East (*8*).

These analyses were conducted with anonymized case-based data reported to WHO under International Health Regulations and therefore neither informed consent nor approval from an institutional review board was required from WHO.

Simulations

The distribution of human-to-human-transmission cluster sizes observed in 2014–2015 was used to simulate the expected total number of cases in 2016, 2017 and 2018 (through September only), conditional on the incidence of community-acquired cases. The observed numbers were then compared with the distribution of the simulated values to obtain two-sided p-values.

Results

While 739 and 768 cases were reported in 2014 and 2015, respectively, only 244, 244 and 113 cases were reported in 2016, 2017 and 2018* (Appendix Figure 2).

The incidence of community-acquired cases in 2016, 2017 and through September 2018 was 177, 151 and 86, respectively (Appendix Table). These were each highly significantly ($p < 0.001$) lower than expected based on the incidence in 2014–2015 (334, 334 and 251, respectively).

Discussion

Our analysis has several limitations. First, for a virus like MERS-CoV that can cause super-spreading events, it may be challenging to test the hypothesis that human-to-human

transmissibility changed over time because superspreading events can cause high variability in cluster sizes, even in the absence of change. We may therefore have limited power to demonstrate here a significant reduction in human-to-human transmission; analysis of more detailed data capturing the complex transmission dynamics observed in human clusters could prove useful (*9*). Second, classification of cases as human-to-human transmitted or not (community-acquired) depends on the quality of data collection and completeness of the investigations around each case and the time of reporting to WHO. While WHO has regular dialogue with Ministries of Health regarding each case and cluster identified, the follow-up of investigations does not always result in identifying the source of each patient's infection. It is believed that the source of infection was more systematically investigated and reported to WHO since 2015 and that secondary cases resulting from human-to-human transmission were more accurately classified meaning that the distribution of observed cluster sizes in 2014–2015 will be biased toward smaller cluster sizes. This would have the effect of underestimating the number of cases (and deaths) averted due to reduced human-to-human transmission. Third, due to limitations on detailed information about the timing of specific interventions initiated by affected countries and hospitals, we are unable to determine which control measures have made this impact.

Although the trend needs to be confirmed by more detailed analyses, the apparent reduction in human-to-human transmission in healthcare facilities, particularly in the KSA since 2016, and the lack of onward human-to-human transmission in recently exported cases to the United Kingdom (*10*) and the ROK in 2018 (*11*), is likely to be at least partly explained by early suspicion and isolation of cases, immediate case management, improvements in standard infection prevention and initiating control measures and comprehensive identification, follow-up and laboratory testing of all high-risk contacts.

When we look at reported data from 2014/2015, the apparent clusters thus appear smaller on average than was actually true. This also happens 2016–2018*, but to a lesser extent if human-to-human transmission were identified more consistently later. Thus, any cluster size reduction we observe between 2014/2015 and subsequent years is likely an underestimate of the true reduction in human-to-human transmission.

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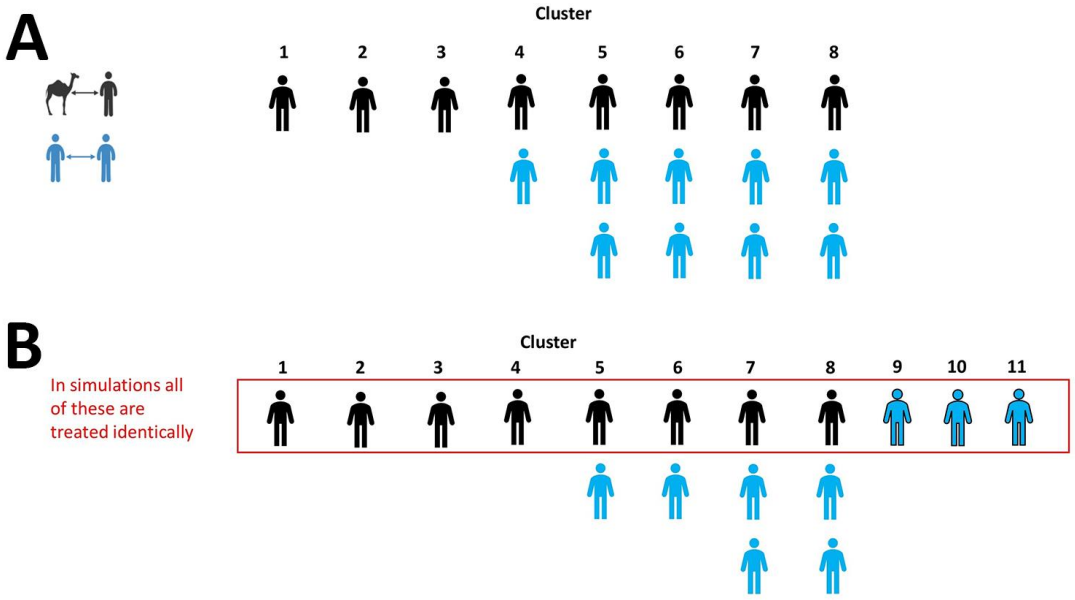
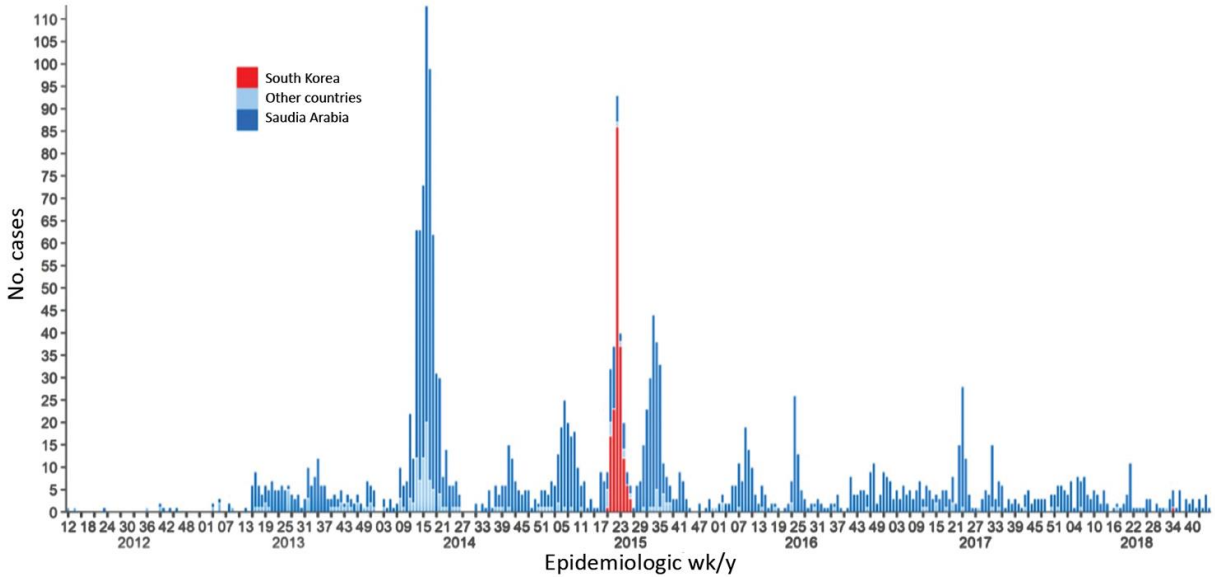
Appendix Table. Reported and expected cases of MERS-CoV infection by year

Year	Reported community-acquired cases*	Expected total cases based on the distribution of case clusters in 2014–2015† (95% range‡)	Expected total cases based on 2014–2015 levels of camel-to-human and human-to-human transmission (95% range‡)	Number of clusters reported by year§	Cluster size by year (range)
2012	6	–		2	2–3
2013	79	–		19	2–25
2014	397	–		10	2–255
2015	271	–		8	2–186
2016	177	398 (189–739)	751 (433–1211)	6	2–33
2017	151	340 (157–663)	751 (433–1211)	19	2–34
2018¶	86	193 (86–451)	564 (304–968)	10	2–12
2016–2018¶	414	931 (566–1420)	2066 (1496–2766)		

*Laboratory-confirmed cases reported to WHO as primary, index or sporadic cases (cases with contact with dromedary camels and without contact with known/probable human MERS cases) and cases under investigation without known contact with another human cases.
†Conditional on reported community-acquired cases
‡The intervals reported in parentheses are the 2.5th and 97.5th centiles of the simulations.
§Data on clusters as reported by WHO Member States and classified into clusters by WHO, and from publications (*3,4,6,7*).
¶Through September 2018.



Appendix Figure 1. Weekly incidence of laboratory confirmed MERS-CoV Infection reported to WHO.



Appendix Figure 2. Clusters of camel-to-human and human-to-human transmission. Panel A Scenario 1: There are clusters – some of size 1 – that all start with a camel-to-human transmission (black). Human-to-human transmission is shown in blue. This shows a situation if all transmission is identified fully. In this scenario, 17 individual cases are reported in 8 clusters and the average cluster size is 17/8, 37.5% (3/8) are single-case clusters and 62.5% (5/8) are clusters of size ≥2 and the average multi-case cluster size is 2.8. In this scenario, reduced human-to-human transmission would only reduce average cluster size. Panel B Scenario 2: There are some clusters where human-to-human transmission is not identified and illustrates that only 5 clusters (numbers 1, 2, 3, 7 and 8) are fully identified. In this scenario, 17 individuals are involved in 11 apparent clusters with an average apparent cluster size of 17/11. Seven of the 11 (63%) are single-case clusters and 4/11 (37%) are clusters of size ≥2 and the average multi-case cluster size is 2.5. In this scenario, reduced human-to-human transmission would appear to reduce both the number of clusters and average cluster size.