Potential for Seasonal Lassa Fever Case Exportation from Nigeria

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Abstract. The largest epidemic of Lassa fever in recent history occurred in Nigeria in 2018. We assessed the potential for cases of Lassa fever originating in Nigeria to arrive at international destinations via air travel using a probabilistic model. We estimated no exported cases in 62% of 1,000 model simulations. In 30% of simulations, a single exported case was projected. Greater than 40% of outbound travelers from Nigeria arrived in the United States, the United Kingdom, and Ghana, placing these countries at greatest risk for receiving an exported case. There was a wide range in the capacity of highly connected countries to respond to infectious disease threats, as measured by the Infectious Disease Vulnerability Index. Although we quantified a low probability of case exportation during this outbreak, countries with the greatest connectivity to Nigeria should be alert to the potential risks of Lassa fever importation and be prepared to manage infected individuals.

Lassa fever, a viral hemorrhagic fever caused by the Lassa virus (LASV), is endemic to several West African countries. The virus is transmitted to humans through a rodent reservoir, *Mastomys natalensis*, commonly known as the multimammate rat.¹ Lassa virus infection in humans mainly occurs through contact with infected rodent feces and urine.² Human-to-human transmission occurs through contact with infected urine, feces, or blood.²

Nigeria has the highest annual incidence of Lassa fever cases in West Africa. Disease transmission is reported year-round, with seasonal peaks typically occurring during the dry season (November to March).³ In recent years, the case burden has ranged from 25 to 150 cases annually.⁴ However, the largest epidemic of Lassa fever in recent history occurred in 2018, with 420 confirmed cases and 106 deaths reported between January 1 and April 29, 2018. Cases occurred in 21 of 36 Nigerian states, including those that border Benin and Cameroon. Initial phylogenetic analysis suggests that reservoir spillover events are the major cause of the epidemic, with limited human-to-human transmission events.⁵

In previous LASV outbreaks, cases have been exported from West Africa to neighboring countries and to more distant locations.^{6–9} Given the significant international connectedness of Nigeria and the notable size of the outbreak, we sought to estimate the potential for cases of Lassa fever originating in Nigeria to arrive in international destinations via air travel.

We adapted a previously described model¹⁰ and incorporated data on Lassa fever natural history, case occurrence in Nigeria, and outbound passenger volumes from Nigeria to quantify the number of cases (both symptomatic and asymptomatic) that might be exported internationally over the outbreak period (Figure 1 and Supplemental Appendix). We used publicly available reports to determine monthly laboratory-confirmed symptomatic case occurrence between January and April 2018.⁴ We limited the analysis to this time

period, as case counts through May and beyond indicate that the outbreak had waned.¹¹ We used passenger-level flight itinerary data from the International Air Transport Association (IATA) to evaluate the potential international dissemination of Lassa fever. The IATA data account for approximately 90% of all commercial air travel, with the remaining 10% of trips modeled using airline market intelligence.¹² We included all outbound international travel from Nigeria (regardless of destination) between January 1 and April 30, 2017 (the most recent year for which these data are available). Separate calculations were performed for residents of and visitors to Nigeria, to account for their different potential exposure times, based on the time spent in the country. For the main analysis, the proportion of travelers leaving Nigeria who were tourists was estimated using data on inbound tourists to Nigeria¹³ and overall outbound passenger numbers.¹² We varied this assumption in sensitivity analysis.

The probability of infection for a given month was calculated as follows:

$$1 - e^{-\left(\frac{\text{symptomatic incidence}}{\text{probability symptomatic}} \times \text{ratio}_{\text{unreported:reported}} \times \frac{\text{exposure duration}}{365}\right)}.$$

Given the long incubation period for Lassa fever,² we also calculated the infection probability in the month before the month of travel for Nigerian residents, using incidence in the prior month and an exposure duration of 30 days. The expected number of infected passengers was calculated assuming a binomial distribution (binomial [n = number of monthly passengers, P = monthly probability of infection]). Again, for Nigerian residents, this calculation was also repeated using the prior month's infection probability. We assumed that an individual could be infected at any point in time while in Nigeria. Latent and infectious periods were assumed to follow lognormal distributions. For each infected individual, if the sum of time of infection, latent duration, and infectious duration was greater than the time spent by the individual in the country, this represented an exported case (i.e., that individual could be in the latent or infectious stage on departure from Nigeria). We also determined the stage of infection on departure from Nigeria for each case. The model is stochastic and was run for 1,000 simulations for each monthly time point. The main outcome was total expected exported cases to any international destination via air travel over the 4-month period.

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FIGURE 1. Overview of the case exportation estimation model. The probability of infection for each outbound passenger was calculated using estimated Lassa fever rates in Nigeria^{4,19} (adjusted for the probability that a case is symptomatic²⁰ and possible underreporting [assumption]) and exposure times for residents and visitors to the country.¹³ This was combined with the total number of outbound airline passengers¹² and information on infection natural history² to estimate the number of exported cases. Exported cases include incubating and infectious stages of infection and do not differentiate between symptomatic and asymptomatic infections. This figure appears in color at www.ajtmh.org.

Although there has been strengthened surveillance in the region in response to the Lassa fever outbreak,¹⁴ using reported case data may underestimate the true burden of symptomatic infection in Nigeria. As many of the rural areas endemic for LASV have limited access to health care, those with symptomatic infection may not present for medical care or may present to a facility without the capacity to diagnose this infection. We therefore calculated expected exported cases assuming a range of ratios of unreported to reported cases.

When we assumed no underreporting of symptomatic Lassa fever cases in Nigeria over the January to April 2018 outbreak period, the expected number of exported cases (regardless of symptom status) was small. In 62% of simulations, we projected no exported cases, whereas in 30% of simulations, a single exported case was projected (Figure 2).

Accounting for possible underreporting, the expected number of exported cases increased. For example, assuming 10 actual symptomatic cases for every reported case, we would expect at least one exported case in 99% of simulations, with 4.7 cases observed on average (95% credible interval [CrI] = 1–9). In simulations where exported cases did occur, almost 85% of infections were projected to be in the latent stage on departure from Nigeria.

In the main analysis, we assumed that 25% of departing passengers were residents of Nigeria, who experience a longer potential exposure risk than tourists. When we increased this proportion to 50%, the potential for exported cases increased (Supplemental Figure 1). In the absence of underreporting, 55% of simulations resulted in no exported

cases, whereas 32% of simulations predicted a single exported case over the outbreak period. When the ratio of unreported to reported cases was 10, 99.5% of simulations resulted in at least one exported case, with an average of 6.1 exported cases projected (95% CrI = 2–12).

Although cases of Lassa fever have been exported internationally via air travel in the past, we estimate a relatively low frequency of exported cases in association with the 2018 outbreak in Nigeria, even when allowing for the possibility of underreporting. Lassa virus has a latent period that ranges between 1 and 3 weeks.² In our model simulations, we demonstrate that when case exportation does occur, few infected travelers will have entered the infectious stage prior the onset of their travel. An important concern is that infected travelers may subsequently develop symptoms and present for medical attention in locations where frontline health-care workers are unfamiliar with Lassa fever, leading to delayed diagnosis and/or nosocomial transmission.¹⁵ To identify countries most likely to receive an imported case of Lassa fever, we used country-level air passenger volumes from Nigeria over the outbreak period. Of the 597,704 outbound passengers departing Nigeria between January and April of 2017, greater than 40% of all travelers arrived in three destination countries: the United States, the United Kingdom, and Ghana (Table 1).

As a measure of the capacity of countries to respond to a potential case importation events, we included the Infectious Disease Vulnerability Index (IDVI) score for the 20 countries with the most outbound passengers from Nigeria. The IDVI is a validated measure of a country's capacity to cope with an infectious disease outbreak.¹⁶ The index ranges from 0 to 1.

FIGURE 2. Lassa fever case occurrence in Nigeria and estimated number of exported cases. **(A)** Cumulative case counts and estimated weekly cases of Lassa fever in Nigeria, January to April 2018, as reported by the Nigeria Centre for Disease Control. Weekly cases were estimated using cumulative case count data. **(B)** Exported cases were estimated based on case occurrence in Nigeria. The estimated number of cases in international outbound passengers includes latent, symptomatic, and asymptomatic infections over the 4-month outbreak period. Model outputs are shown for various levels of underreporting, represented by the ratio of unreported to reported symptomatic cases in the outbreak location. Boxes represent the mean, whereas lines represent the 95% credible interval for 1,000 simulations. This figure appears in color at www.ajtmh.org.

Lower scores represent increased vulnerability and reduced ability to respond to infectious disease outbreaks. There was a wide range in the capacity of countries with strong connectivity to Nigeria via air travel to respond to infectious disease threats, as measured by the IDVI. Among the 20 countries with the greatest numbers of passengers, scores ranged from 0.21 (Benin) to 0.97 (Canada). Despite the estimated low frequency of Lassa fever exportation, it is important to note that many of the countries that are closely linked to Nigeria via air travel may not have the capacity to diagnose or manage imported cases. Eight of the top 20 countries with close air travel connections to Nigeria have IDVI values of less

than 0.5, indicative of limited public health infrastructure to effectively respond to imported transmissible infectious diseases, including Lassa fever.¹⁶ Of the eight countries with IDVI indices less than 0.5, Ghana, Cameroon, Benin, Cote d'Ivoire, and, to a lesser extent, Senegal are in regions with suitable ecological conditions for endemic LASV transmission.¹⁷ Air travel is just one potential mode for dispersal of LASV-infected individuals. Neighboring countries of Benin, Cameroon, Niger, and Chad could see cases imported via land travel, and methods such as the use of mobile phone data to track human population mobility may better delineate patterns and risks of disease spread.¹⁸

TABLE 1
Outbound passenger volumes from Nigeria to top 20 destination countries (January 1 through April 30, 2017) with the IDVI score

Destination country	Number of passengers	Percent of all passengers*	IDVI score†	IDVI rank‡
United States	101,381	17	0.92	188
United Kingdom	82,297	13.8	0.9	181
Ghana	66,744	11.2	0.46	63
United Arab Emirates	36,404	6.1	0.77	161
South Africa	35,783	6	0.7	141
Saudi Arabia	21,882	3.7	0.74	153
China	21,849	3.7	0.66	129
India	15,878	2.7	0.49	71
Italy	13,938	2.3	0.82	171
Senegal	12,768	2.1	0.33	34
Ethiopia	11,136	1.9	0.38	47
Cameroon	10,461	1.8	0.39	50
Benin	10,019	1.7	0.21	14
Kenya	9,532	1.6	0.39	48
Cote d'Ivoire	9,153	1.5	0.27	28
Canada	9,031	1.5	0.97	194
Germany	7,789	1.3	0.97	192
Egypt	7,634	1.3	0.53	80
France	6,482	1.1	0.86	173
Turkey	6,410	1.1	0.68	134

IDVI = Infectious Disease Vulnerability Index.

* Denominator includes all outbound passengers from Nigeria for this time period (597,704), whereas the totals in the table reflect the top 20 countries.

† Scores from 0 to 1, with a lower value indicating increased vulnerability to infectious disease threats.

‡ Countries are rank-ordered from 1 to 195, from the most to least vulnerable.

In summary, despite a large outbreak of Lassa fever in Nigeria in 2018, there is a low probability of exporting cases via air travel. However, countries with the greatest connectivity to Nigeria should still be aware of the potential risks of Lassa fever importation and be prepared to manage infected individuals and prevent nosocomial transmission. Many of the countries at risk for LASV importation have limited public health capacity, potentially compromising their ability to detect and respond to imported cases.

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