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SPECIAL REPORT

After Ebola in West Africa — Unpredictable Risks, Preventable Epidemics

WHO Ebola Response Team

SUMMARY

Between December 2013 and April 2016, the largest epidemic of Ebola virus disease (EVD) to date generated more than 28,000 cases and more than 11,000 deaths in the large, mobile populations of Guinea, Liberia, and Sierra Leone. Tracking the rapid rise and slower decline of the West African epidemic has reinforced some common understandings about the epidemiology and control of EVD but has also generated new insights. Despite having more information about the geographic distribution of the disease, the risk of human infection from animals and from survivors of EVD remains unpredictable over a wide area of equatorial Africa. Until human exposure to infection can be anticipated or avoided, future outbreaks will have to be managed with the classic approach to EVD control — extensive surveillance, rapid detection and diagnosis, comprehensive tracing of contacts, prompt patient isolation, supportive clinical care, rigorous efforts to prevent and control infection, safe and dignified burial, and engagement of the community. Empirical and modeling studies conducted during the West African epidemic have shown that large epidemics of EVD are preventable — a rapid response can interrupt transmission and restrict the size of outbreaks, even in densely populated cities. The critical question now is how to ensure that populations and their health services are ready for the next outbreak, wherever it may occur. Health security across Africa and beyond depends on committing resources to both strengthen national health systems and sustain investment in the next generation of vaccines, drugs, and diagnostics.

SCALE OF THE EPIDEMIC

Between December 2013 and April 10, 2016, a total of 28,616 suspected, probable, and con-

firmed cases of Ebola virus disease (EVD) were reported, although the true toll of the epidemic, especially the number of deaths, was probably greater. A total of 11,310 deaths was recorded, but the true toll was certainly greater. By far the largest numbers of cases and deaths occurred in Guinea, Liberia, and Sierra Leone, but an additional 36 cases were also reported from Italy, Mali, Nigeria, Senegal, Spain, the United Kingdom, and the United States.¹ After reaching a peak of 950 confirmed cases per week in September 2014, the incidence dropped markedly toward the end of that year. But it took much longer to stop all chains of transmission: the outbreaks in Liberia, Sierra Leone, and Guinea ended in May, November, and December 2015, respectively, although additional cases of EVD, probably arising from virus persisting in the tissues and body fluids of survivors, have continued to be reported in all three countries.

As case numbers mounted through 2014 and 2015, many questions emerged about the epidemiology of EVD, the medical and social effects of the disease, and the tools and techniques required to control the epidemic. What was the origin of human infection in West Africa? Why did this outbreak become the largest Ebola epidemic ever recorded? What are the most effective methods of control? This report addresses these questions, with a view to better understanding the 2013–2016 epidemic and to preventing large outbreaks in the future.

ORIGINS OF HUMAN INFECTION
IN WEST AFRICA

Since 1976, and before the recent epidemic, there were 23 known Ebola outbreaks in equatorial Africa (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The first reported human case in the 2013–2016 epidemic involved a 2-year-old boy living in the

village of Meliandou in Guéckédou prefecture, a forested region of southeastern Guinea.² In a retrospective investigation, it was reported that he had become ill on December 26, 2013, and had died 2 days later. The infection was caused by *Zaire ebolavirus* species. Its origin remains uncertain, but it is likely to have originated in an animal, possibly a bat (see the Supplementary Appendix).

SPREAD OF EBOLA IN GUINEA,
LIBERIA, AND SIERRA LEONE

Although the first case of human infection was probably acquired from an animal, all subsequent cases are likely to have arisen from human-to-human transmission.³ The main route of EVD transmission, in this as in previous outbreaks, was direct personal contact with the blood or other body fluids of a person with symptomatic disease (see the Supplementary Appendix). Viral RNA has also been detected by means of reverse-transcriptase–polymerase-chain-reaction assay and isolated from the body fluids of asymptomatic survivors, notably semen and breast milk, both of which represent additional, persistent sources of infection whose infectiousness decreases over time.^{4,7}

By March 2014, infection had spread within Guinea to the Kissidougou and Macenta prefectures (which neighbor Guéckédou) and, in the week of March 10 (week 11 of 2014), Ebola virus was reported for the first time in a West African capital city — Conakry (Fig. 1). A surge in transmission in Guinea during March and April 2014 (weeks 10 through 18) generated more than 100 new cases in total, and the failure to interrupt transmission allowed infection to become more fully entrenched in the southeastern part of the country. From there, infection spread farther within Guinea and across the nearby national boundaries. The disease appeared in Lofa and Margibi counties in northern Liberia before the end of March and in the Kailahun district in eastern Sierra Leone during May.

Even though human infection probably originated in Guinea, marked increases in case incidence at the three-country epicenter occurred first in the eastern region (administrative level 1) of Sierra Leone and next in North Central Liberia, followed by Nzérékoré in Guinea. At the western border between Guinea and Sierra Leone, despite frequent cross-border movements of infected

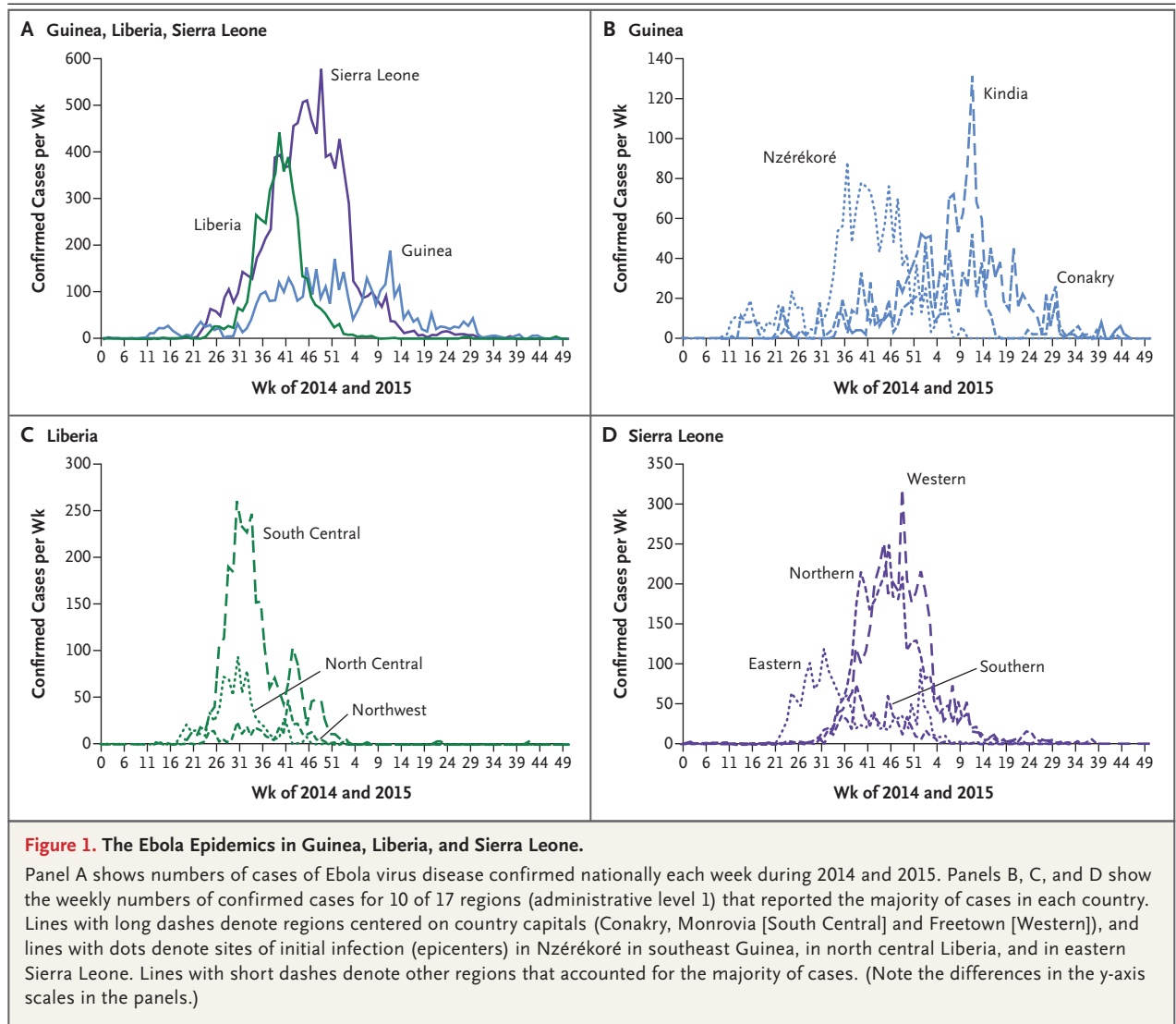
people, changes in the incidence of Ebola were synchronized among prefectures within Guinea (Conakry, Coyah, Forécariah) but not with the adjacent district in Sierra Leone (Kambia) (Fig. 2A). Thus, infection crossed national borders but, in these examples, not so frequently that districts in Sierra Leone and prefectures in Guinea acted as a single, homogeneous mixing unit.

Phylogenetic analysis provided valuable additional information about the origins of the virus and the migration of infected people.^{3,8,9} Genomic analysis has shown that the West African epidemic probably arose after a single introduction from an animal reservoir; the analysis has also revealed how people carrying Ebola virus moved quickly over large distances and through several countries (see the Supplementary Appendix).

GROWTH OF THE EPIDEMIC

The speeds at which infection traveled from the epicenter to national capitals were quite different in Guinea, Liberia, and Sierra Leone, as were the consequences. Conakry was the earliest affected capital city (from week 31 of 2014 onward), but the case incidence there remained inexplicably low throughout the epidemic (Fig. 1B). Ebola was reported in Monrovia, Liberia, later than it was reported in Conakry but only 3 weeks after cases were detected in the north central region of Liberia (Fig. 1C). Freetown ultimately bore the highest caseload of the three capitals (in terms of the number of cases and the number per capita), but the rise in case incidence in Western Sierra Leone (from week 31 onward) happened a full 12 weeks later than the incidence in the eastern region of the country (Fig. 1D). Neither the speed of travel of the virus across each country nor its effect on arrival could have been predicted.

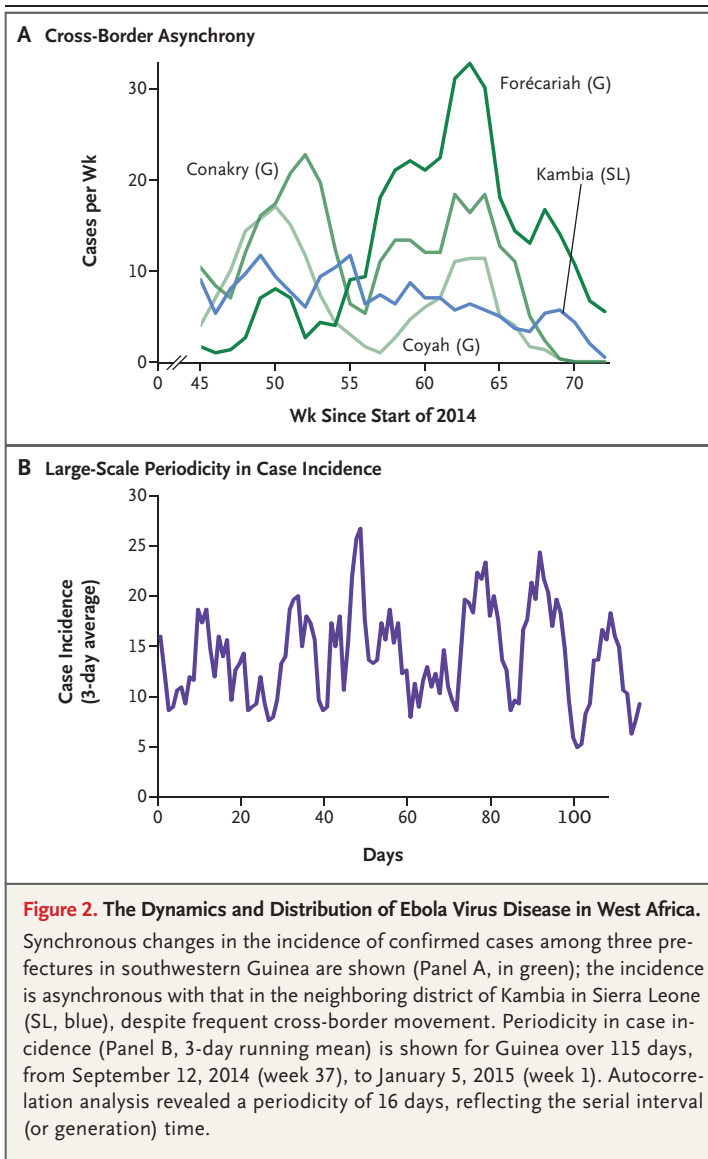
The initial incursions from Guinea into Liberia and Sierra Leone, and the spread of infection to the capitals, foreshadowed the principal periods of epidemic growth in the three countries. These periods were characterized by prolonged, exponential increases in the numbers of cases and the numbers of infected districts, beginning in Sierra Leone in May 2014 (week 20), in Liberia in June (week 23), and in Guinea in July (week 29) (Fig. 1B, 1C, and 1D). And it was the differences in the duration of exponential growth rather than the weekly growth rates in case incidence that accounted for the eventual sizes of the epidemics



in each of the three countries (Fig. 1A). In Sierra Leone, where the geographic spread from the epicenter to the capital was slowest, the main period of growth lasted 22 weeks from the end of May (week 22 of 2014) to early November, with case incidence doubling every 5.1 weeks (Fig. S2 in the Supplementary Appendix). In Liberia, where the movement of infection from epicenter to capital was faster than in Sierra Leone, growth lasted 15 weeks from mid-June (week 25), with a doubling time of 2.8 weeks. Guinea reported the shortest and fastest period of sustained exponential growth — for 9 weeks from early July (week 28), mainly in the southeast, with the case incidence doubling every 1.9 weeks.

Had exponential growth continued at this pace

in all three countries, the total number of confirmed and probable cases would have exceeded 20,000 by November 2.¹⁰ If growth continued at the same rate until early 2015, there would have been many more cases.¹¹ It turned out that case incidence peaked at 950 confirmed cases in the final week of September 2014. The total numbers of confirmed cases reported during the epidemic were 3358 in Guinea (plus 456 probable cases; suspected cases were resolved and not reported), 3163 in Liberia (1879 probable, 5636 suspected), and 8706 in Sierra Leone (287 probable, 5131 suspected). The numbers of confirmed cases per 100,000 population were 32, 87, and 137, respectively (with respective population sizes of 10.6 million, 3.6 million, and 6.4 million people).



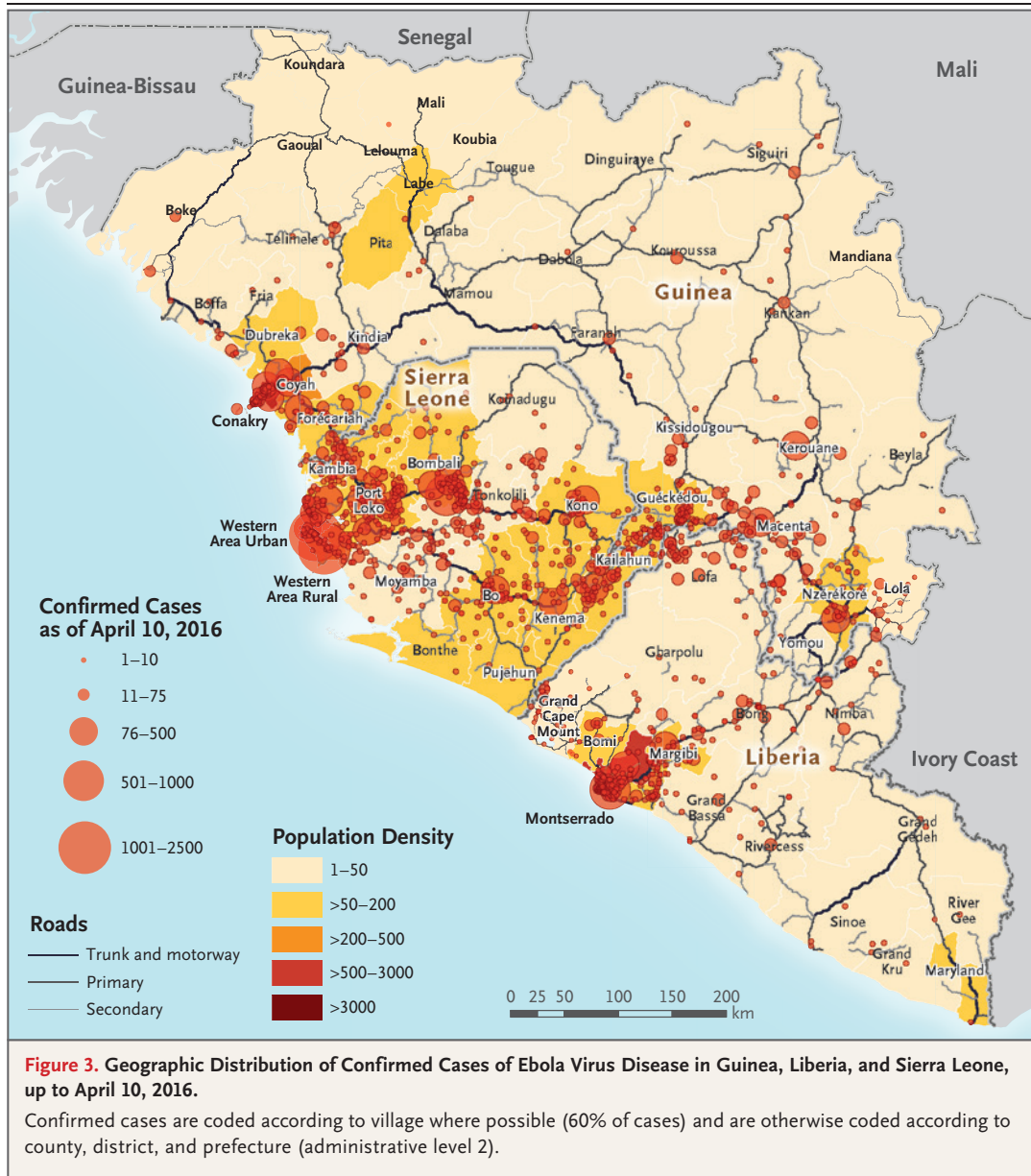
Thus, Sierra Leone sustained the worst effects of the epidemic as measured by the absolute numbers of cases (whether we count only confirmed cases or include suspected and probable cases) and in terms of the number of cases per capita. Despite uncertainties in the accuracy of reporting, there were clearly major differences in the magnitude of the epidemic and its effect from country to country (Fig. 3).

Differences in the growth rates of the epidemic among countries and districts reflect differences in the average case reproduction numbers (the average number of secondary cases caused by one case over a generation of Ebola

infection). The basic reproduction number, R_0 , which holds at the start of an epidemic and before intervention, has been estimated to lie in the range of 1.71 to 2.02 (range of point estimates) in Guinea, Liberia, and Sierra Leone,¹⁰ a range that is similar to estimates derived from previous, smaller outbreaks of Ebola in central Africa (Sudan and Zaire species, 1.3 to 4.7).¹² Once again, the large variation in the size of the outbreaks across Africa appears to be governed not primarily by differences in R_0 but by the period of epidemic growth and the size of the population at risk.¹³ In any event, the magnitude of R_0 estimates for West Africa, calculated at an early stage of the epidemic, indicated that a sustained reduction in transmission of more than 50% (i.e., by a factor of more than 2) would be enough to eliminate infection from the human population. Even during a large epidemic, the elimination of Ebola virus from the human population is a feasible goal.

These average case reproduction numbers conceal much of the variation in the number of infections transmitted by different persons. Both epidemiologic (Fig. 4A) and phylogenetic^{14,15} data show that a small minority of cases in one generation produced the majority of cases in the next generation. For Ebola, as for some other infectious diseases,¹⁶ roughly 20% of cases can be considered to be “superspreaders,” being sources of infection for about 80% of cases in the following generation (Fig. 4A). Thus, the average case reproduction numbers determine the criterion for the elimination of Ebola from most of the population, but pockets of resistance can be expected from subpopulations in which transmission rates are higher than average.

For Ebola, superspreading is a characteristic not only of the number of secondary cases but also of geographic dispersal. For example, during an outbreak in the fishing community of Aberdeen in Freetown during January and February 2015, EVD was confirmed in 24 people, with infection apparently acquired from a single source. These infections progressed to disease over the course of a single incubation period (Fig. 4B). A second generation was expected within the quarantined community in Aberdeen but actually occurred in the Bombali district, 200 km away, after one infected man fled quarantine, visited a traditional healer, died, and was buried secretly and unsafely in the village of



Rosanda. Throughout this epidemic, the sites where new cases would be found, or where transmission would persist, were largely unpredictable.

During the West African epidemic, distinct generations of cases were visible on scales large and small. The time series of confirmed cases from the whole of Guinea compiled during the 115 days after the main period of exponential growth had stopped show a periodicity of 16 days, which is roughly the serial interval, covering approximately seven generations of cases (Fig. 2B). Clearly, interventions were not effective

in breaking the cycle of transmission in Guinea up to January 2015.

EFFECT OF INTERVENTIONS

The duration of epidemic growth in each region of each country, and the number of people at risk, were determined in part by the timing and magnitude of the interventions against Ebola. After the epidemic peak in each country, the case incidence declined most quickly in Liberia and more slowly in Sierra Leone and Guinea



An animated map with timeline is available at NEJM.org

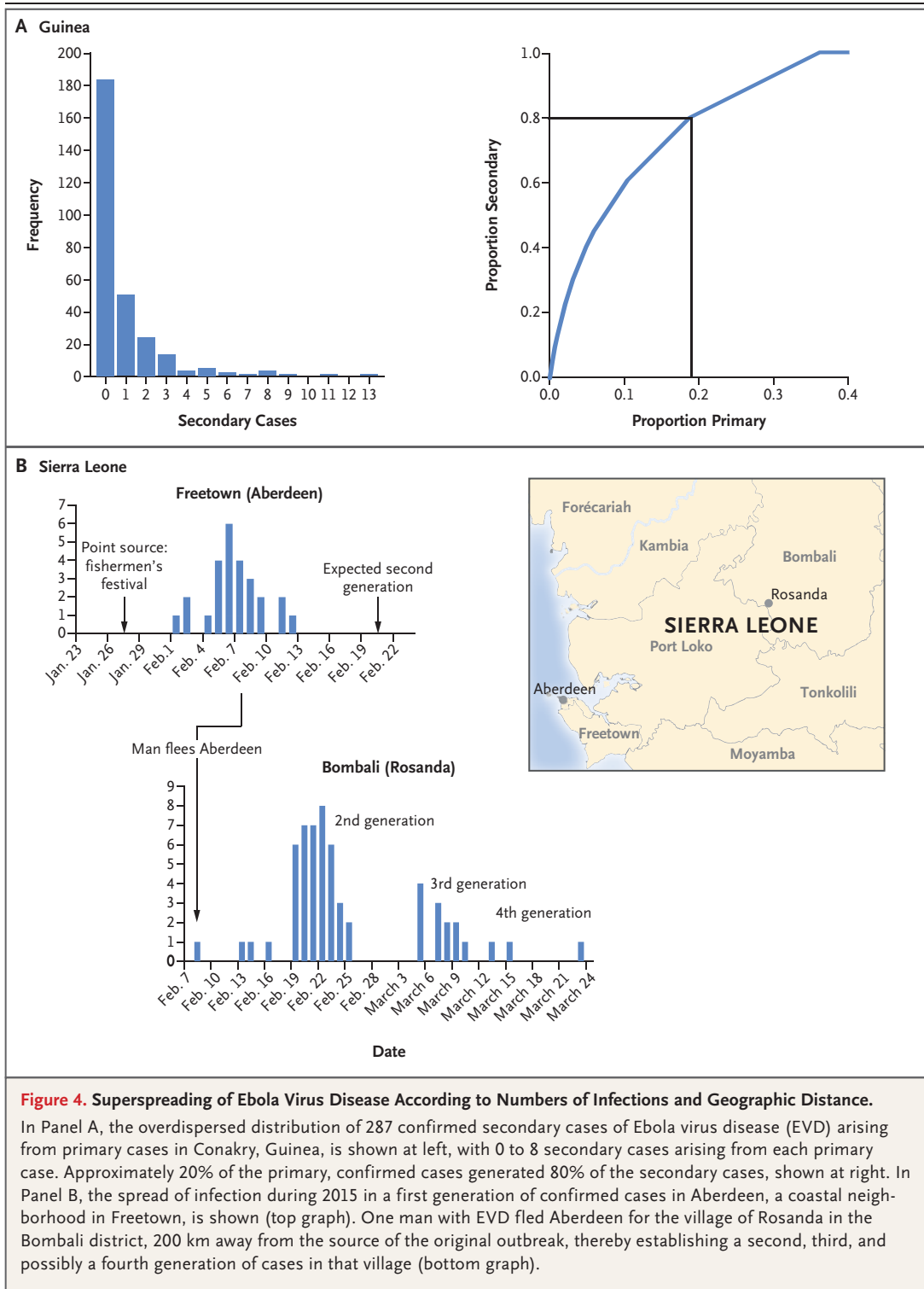


Figure 4. Superspreading of Ebola Virus Disease According to Numbers of Infections and Geographic Distance.

In Panel A, the overdispersed distribution of 287 confirmed secondary cases of Ebola virus disease (EVD) arising from primary cases in Conakry, Guinea, is shown at left, with 0 to 8 secondary cases arising from each primary case. Approximately 20% of the primary, confirmed cases generated 80% of the secondary cases, shown at right. In Panel B, the spread of infection during 2015 in a first generation of confirmed cases in Aberdeen, a coastal neighborhood in Freetown, is shown (top graph). One man with EVD fled Aberdeen for the village of Rosanda in the Bombali district, 200 km away from the source of the original outbreak, thereby establishing a second, third, and possibly a fourth generation of cases in that village (bottom graph).

(Fig. S3 in the Supplementary Appendix). It is conceivable, but has not been proved, that the more explosive spread of infection across Liberia, and within the capital of Monrovia, stimulated the development of more rapid and effective interventions than in Guinea and Sierra Leone. In any

event, it is the differing rates of decline in incidence, rather than the peak incidence rates per capita in each country, that explain (at least mathematically) why continuous transmission ended first in Liberia, then in Sierra Leone, and finally in Guinea.

Although vaccination probably helped to reduce the rate of transmission after April 2015 in Guinea,¹⁷ the dominant interventions used have been the classic methods of Ebola control: finding symptomatic cases and tracing potentially infected contacts; isolating cases, admitting patients to specially designed Ebola treatment centers, and providing supportive clinical care; and ensuring safe and dignified burial.¹⁸ The data supporting the evidence for the effectiveness of the control measures implemented in 2013–2016 are observational and circumstantial rather than experimental, and the most persuasive analyses are those linked to empirical data.

Mathematical modeling^{19–22} has been used to investigate what reduction in transmission, achieved by what means, would have been necessary to explain the epidemics in Guinea, Liberia, and Sierra Leone. All these modeling analyses show, as expected, that admitting patients to Ebola treatment centers and shortening the delay before hospitalization could have played a large part in slowing the increase and accelerating the decline in case incidence. In line with the differing rates of decline in incidence, bed capacity was scaled up first in Liberia, then in Sierra Leone, and eventually in Guinea (see the Supplementary Appendix).²²

Empirical evidence of the effect of rapid patient isolation and hospitalization comes from investigations of a series of small outbreaks in Liberia.^{23–27} Twelve outbreaks were included in a study of the Rapid Isolation and Treatment of Ebola (RITE) strategy, applied between July and November 2014. RITE encourages active case finding and contact tracing and the use of practices that prevent infection when caring for the ill and burying the dead. In a comparison of the effects of six outbreaks that occurred before the introduction of RITE and six that occurred afterward, the time between the first new case in remote areas and the notification of health authorities was reduced by nearly half, the proportion of patients isolated increased from 28% to 81%, survival improved from 13% to 50%, the case reproduction number fell below unity (the

replacement rate), outbreaks became shorter (median duration declined from 53 to 25 days), and the number of generations of cases dropped from a median of four to two.^{26,27} On their own, these observations made before and after the introduction of RITE do not provide the level of evidence afforded by a randomized trial, but they are consistent with the larger body of evidence on Ebola interventions.

The benefits of rapid case detection and prompt patient isolation were also made plain during the interruption of transmission at in the community of St. Paul's Bridge in Monrovia, between December 2014 and February 2015. The numbers of cases in successive generations of this transmission chain were 1 (index case), 5, 10, 6 and 0, with case reproduction numbers (ratios) of 5, 2, 0.6, and 0. Over generations 2 through 4, the average times to detection and isolation dropped from 6.0 days to 4.7 days to 1.5 days.²⁸ There was also an effective, rapid response to an EVD outbreak in Lagos, Nigeria, during July 2014, which was restricted to just 15 confirmed cases in a population of more than 20 million.^{29–32} Rapid response has been linked to the successful control of outbreaks elsewhere in Africa.^{33,34}

Although there was also improvement in patient-contact tracing during 2014 and 2015, this improvement occurred later than the expansion of Ebola treatment centers in Liberia and Sierra Leone (Fig. S4 in the Supplementary Appendix). The follow-up of contacts could have been more effective in preventing transmission during the early stages of this epidemic, had it been thoroughly implemented. As it happens, contact tracing appears to have played only a supporting role, mainly after case incidence had fallen in 2015.

END OF THE EPIDEMIC IN WEST AFRICA

The epidemic took 10 months to reach peak incidence (September 2014), but cases were reported for an additional 18 months (until April 2016), and there may be more to come. Although the number of new cases was held below 50 per week from April 2015 onward (Fig. 1), the outbreaks in each country were not declared over until May 9 in Liberia, November 7 in Sierra Leone, and December 28 in Guinea. These dates mark 42 days (two incubation periods) since the last reported case that arose according to the usual route of transmission — from one infectious, symptom-

atic patient with a primary episode of illness to another.

In the long tail of the epidemic, foci of transmission persisted for many months during 2015, particularly in areas of Sierra Leone and Guinea where symptomatic patients were unwilling to seek medical care, where contacts of patients fled quarantine, and where deaths from EVD were followed by unsafe burials (and where case reproduction numbers therefore remained higher than average). In addition, after the principal chains of transmission had been broken, additional cases emerged, apparently as a result of infections acquired from survivors of EVD. The possible mechanisms of transmission in each of these events — semen (male to female partner), breast milk (mother to child), or clinical relapse in a surviving patient (person to person) — are still under investigation.^{4,5,35} The most recent of these incidents began with three deaths reported on March 17, 2016, in Nzérékoré prefecture in southeastern Guinea. The origin of infection was a man who survived EVD in November 2014. In this outbreak, which generated 13 confirmed and probable cases, infection spread from Nzérékoré to Macenta prefecture in Guinea and into Monrovia. The persistent risk of infection from survivors is another reason (in addition to locally high rates of transmission) why we can expect any large Ebola epidemic to have a protracted end, demanding heightened surveillance, with routine testing of live and dead persons in whom EVD is suspected, for months after an outbreak has ended.

PREPARATION FOR FUTURE OUTBREAKS

The risk of human infection from animals and from Ebola survivors appears to be persistent, widespread, and locally unpredictable.³⁶ Even with 40 years of hindsight (since the first outbreak in 1976) we cannot fully explain — and thus confidently forecast — the timing, location, and rate of spread of EVD outbreaks in Africa. We also do not know whether West Africa remains vulnerable to another large outbreak in 2016 (see the Supplementary Appendix). The emphasis must therefore be on prevention and preparedness to protect populations — that is, to manage residual risks from survivors of the West African epidemic and to contain new outbreaks anytime, anywhere in Africa.

Until human exposure to infection can be more accurately predicted or prevented, the approach to managing future outbreaks will center on the classic, responsive approach to Ebola control: community engagement, early case detection and diagnosis, comprehensive contact tracing, prompt patient isolation, supportive clinical care, and rigorous infection control, including safe burial. During the 2013–2016 West African epidemic, this strategy was enhanced but not transformed. Accelerated research has begun to deliver a new generation of vaccines to prevent infection, rapid diagnostic tests for earlier case detection, and drugs to improve treatment outcomes.³⁷ There is now a deeper appreciation of the importance of community engagement that occurs through mutual adaptation of local cultural and public health practices.^{38,39} Strong survivor support services are critical not only to mitigate the risk of further outbreaks but also to provide essential clinical care. Standardized data collection and reporting on Ebola must be linked to national health information systems so that Ebola can be managed as part of Africa's system of integrated disease surveillance and response.⁴⁰

A vital next step is to ensure that there is dependable financial support to develop health services in the countries at risk for EVD, with a focus on primary health care and universal health coverage.⁴¹ In this context, the \$5.91 billion disbursed by 77 donors (out of \$8.91 billion pledged) during the West African epidemic (September 1, 2014, to October 31, 2015) concentrated largely on epidemic response (79% of funds), with only 18% targeted at recovery (as compared with 40% of funds pledged) and 3% for research and development.⁴² Looking to the future, the Commission on a Global Health Risk Framework for the Future has underscored the importance of resilient national public health services as the first line of defense against future epidemics of EVD or other diseases.⁴³ The commission recommended substantial additional investment in essential health services: an additional \$4.5 billion should be spent globally each year, of which \$3.4 billion (87%) should be used for primary prevention and treatment.

In conclusion, the weight of evidence suggests that a rapid response to the discovery of new Ebola cases can stop transmission, preventing minor outbreaks from becoming major epidemics in large, mobile populations. The critical question

now is how to ensure that populations and their health services are ready for the next EVD outbreak, wherever it may occur. Health security across Africa and beyond depends on the resources made available both to strengthen national health services and to sustain investment in the next generation of technologies for Ebola control.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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