Kush Kapur, Ph.D.
Christopher Hug, M.D., Ph.D.

Boston Children's Hospital
Boston, MA

Supported by the Harvard University Center for the Environment and the Harvard–National Institute of Environmental Health Sciences (NIEHS) Center (ES000002) and by a Mentored Career Development Award from the NIEHS, National Institutes of Health (K23 ES017437, to Dr. Mazumdar).

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

1. Bomberger JM, Coutermarsh BA, Barnaby RL, Stanton BA. Arsenic promotes ubiquitinylation and lysosomal degradation of cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels in human airway epithelial cells. J Biol Chem 2012;287:17130-9.
2. Breton CV, Houseman EA, Kile ML, et al. Gender-specific protective effect of hemoglobin on arsenic-induced skin lesions. Cancer Epidemiol Biomarkers Prev 2006;15:902-7.
3. Seow WJ, Pan WC, Kile ML, et al. Arsenic reduction in drinking water and improvement in skin lesions: a follow-up study in Bangladesh. Environ Health Perspect 2012;120:1733-8.
4. Frisbie SH, Mitchell EJ, Yusuf AZ, et al. The development and use of an innovative laboratory method for measuring arsenic in drinking water from western Bangladesh. Environ Health Perspect 2005;113:1196-204.
5. Chen KL, Amarasiriwardena CJ, Christiani DC. Determination of total arsenic concentrations in nails by inductively coupled plasma mass spectrometry. Biol Trace Elem Res 1999;67:109-25.

DOI: 10.1056/NEJMc1413312

West African Ebola Epidemic after One Year — Slowing but Not Yet under Control

TO THE EDITOR: During the period from early June to mid-September 2014, the epidemic of Ebola virus disease (EVD) in Guinea, Liberia, and Sierra Leone grew exponentially, with national doubling times of between 16 and 30 days.[1] On the basis of case reports through mid-September, and assuming no change in the trajectory of the epidemic, we predicted a cumulative total of 21,000 cases in these three countries by November 2.[1] In fact, the epidemic did change course in September: the increase in case incidence appears to have halted in Guinea and Sierra Leone and has reversed in Liberia (Fig. 1). Now, 1 year after the first case was reported in December 2013,[2] we report updated epidemiologic findings for the three countries that have been most affected, using data recorded through December 14.

In the 4 weeks preceding December 14, the number of confirmed or probable cases of EVD ranged from 77 to 154 per week in Guinea, 73 to 138 in Liberia, and 327 to 537 in Sierra Leone. By December 14, a total of 18,625 confirmed, probable, or suspected EVD cases had been reported in eight affected countries (the three mentioned above, plus Mali, Nigeria, Senegal, Spain, and the United States), with 6971 recorded deaths.[2] The true burden of illness and death is certainly higher, but the changes in epidemic trends between August and December are clear (Fig. 1).

National summary statistics do not tell the whole story, however; within the affected countries, the geographic distribution of cases has shifted markedly (Fig. S3 and S7 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In Gueckedou, Guinea, where the epidemic began, the incidence of EVD has decreased from an average of 11 confirmed or probable cases per week between March and September to 2 cases per week since the beginning of October, whereas the incidence has increased sharply in the neighboring districts of Kerouane, Macenta, and N'zerekore. Districts at the epicenter in eastern Sierra Leone (Kailahun and Kenema) and northern Liberia (Lofa) reported an average of 120 cases per week during July and August but only 2 per week since the beginning of November. EVD has been persistently active in Conakry, the capital of Guinea, since March and highly active in all three national capitals since June. During the period of peak incidence between August 11 and October 5, Monrovia, Liberia, averaged close to 200 confirmed or probable cases per week. In Sierra Leone, the center of activity had moved from the east to the west of the country by October; by the second week of December, the rise in case incidence had slowed in Freetown, but the case incidence may still not have peaked (Freetown is shown as part of Western Area in Fig. S6 and S10 in the Supplementary Appendix).

Guided by targets for patient isolation and safe burial practices set by United Nations Mission for

The New England Journal of Medicine
Downloaded from nejm.org on February 6, 2015. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

Ebola Emergency Response, control measures have been stepped up since October 1.[3] By December 14, the total number of beds (>2000) in Ebola treatment centers far exceeded the number of patients reported each week, though there were substantial gaps in treatment capacity in some areas of all three countries — in western Sierra Leone (Freetown and Western Area), in the southeastern forest area and some northern districts of Guinea (Kerouane, N'zerekore, and Siguiri), and in western Liberia (Grand Cape Mount). The capacity to carry out safe burials has more than doubled since October 1; approximately 200 burial teams were covering all but a small number of districts by December 14. And yet, knowing that many deaths are still unreported, and with continuing resistance to safe burial practices in some areas, deaths from EVD still pose a considerable hazard.

With the changes in the incidence of EVD and with the scale-up of case isolation and safe burial measures, there have been concomitant changes in key epidemiologic parameters. The case reproduction numbers (R_t) for all three countries, averaged across all districts, have now fallen to values close to 1 (Fig. 1, and Fig. S24 in the Supplementary Appendix). The precise reasons for these changes are still being investigated. However, in a comparison of periods before and after October 1, the average time from symptom onset to hospitalization decreased from 5.3 days to 4.3 days, which indicates a reduction in opportunities for transmission in communities (Table 1, and Tables S7 and S8 in the Supplementary Appendix). Further quantitative analysis is expected to support strong anecdotal evidence that comprehensive measures to interrupt transmission, including careful case finding and contact tracing, have had an effect — for instance, in eastern Sierra Leone (Kenema) and northern Liberia (Lofa).

An animated map with timeline is available at NEJM.org

The uneven success of EVD control measures to date, in the face of shifting geographic patterns of transmission, illustrates the continuing threat posed by the Ebola virus 1 year after the start of the epidemic. A total of 625 confirmed or probable cases were reported from Guinea, Liberia, and Sierra Leone in the first week of December, a number similar to the average for the preceding 10 weeks (667), but these cases are now spread over a wider geographic area. The worst fears of persistent exponential growth beyond September were not realized; nevertheless, Ebola

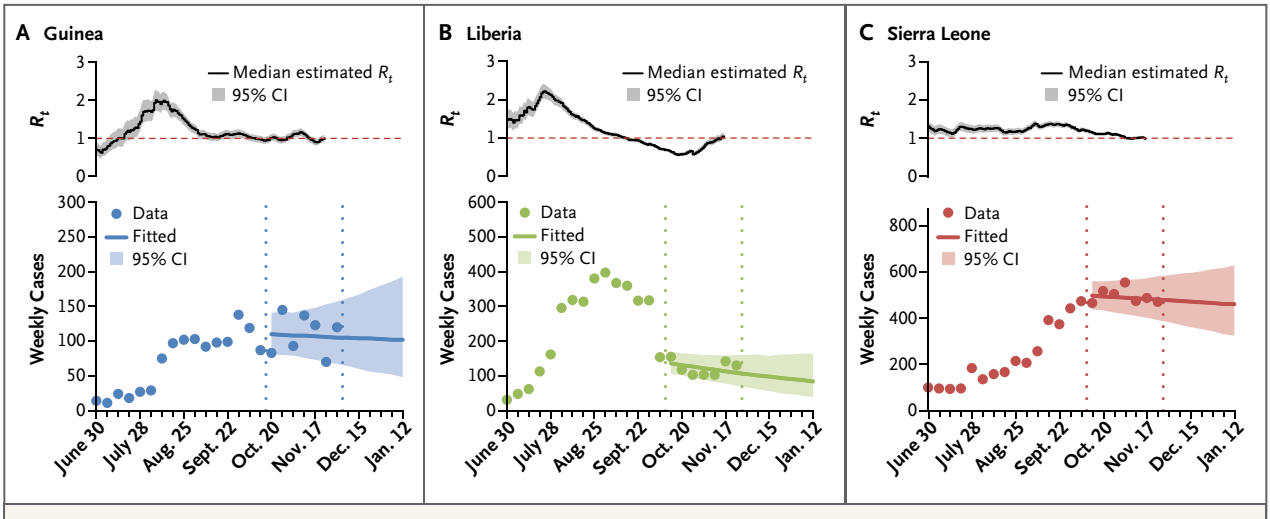

Figure 1. Case Reproduction Numbers and Weekly Incidence in Guinea, Liberia, and Sierra Leone.

Shown are the estimated case reproduction number (R_t) over time (upper panels) and the observed and projected weekly incidence (lower panels) of confirmed and probable cases of Ebola virus disease (EVD), according to the date of symptom onset, from the week beginning June 30, 2014, until the week beginning January 12, 2015, on the basis of data reported through December 7 for Guinea and November 30 for Liberia and Sierra Leone. The projections shown in the lower panels were generated from R_t estimates derived from data on case incidence (daily situation reports) for the 7 weeks through December 7 for Guinea and November 30 for Liberia and Sierra Leone (the time period delineated by the vertical dotted lines).

The New England Journal of Medicine
Downloaded from nejm.org on February 6, 2015. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

Table 1. Characteristics Associated with Confirmed or Probable Ebola Virus Disease in Guinea, Liberia, and Sierra Leone.*

Characteristic	December 2013 to November 25, 2014	No. of Patients with Data	December 2013 to September 30, 2014	No. of Patients with Data	October 1 to November 25, 2014†	No. of Patients with Data	P Value‡
Incubation period — days							
Observed single-day exposures — median (IQR)§	9 (5–13)	1798	8 (5–13)	1285	10 (5–15)	513	
Fitted single-day exposures — mean (95% CI)¶	10.3 (9.9–10.7)	1798	9.7 (9.2–10.1)	1285	11.8 (11–12.7)	513	<0.001
Serial interval — days‖							
Observed data (IQR)	13 (8–18)	305	12.5 (8–17)	206	14 (8–20)	99	
Fitted data, gamma distribution (95% CI)	14.2 (13.1–15.3)	305	13.2 (12.1–14.5)	206	16.1 (14.1–18.4)	99	0.01
Interval from symptom onset, fitted data — mean days (95% CI)							
To hospitalization	5.0 (4.9–5.1)	4499	5.3 (5.1–5.5)	3038	4.3 (4.1–4.5)	1461	<0.001
To hospital discharge	15.1 (14.6–15.6)	1335	15.3 (14.7–15.8)	1085	14.4 (13.5–15.4)	250	0.06
To death	8.2 (7.9–8.4)	2741	8.8 (8.5–9.1)	2094	6.2 (5.8–6.6)	647	<0.001
Interval from hospitalization, fitted data — mean days (95% CI)							
To discharge	11.2 (10.8–11.7)	1004	11.4 (10.9–11.9)	813	10.6 (9.7–11.5)	191	0.07
To death	4.3 (4.1–4.5)	1167	4.4 (4.2–4.7)	930	3.8 (3.4–4.3)	237	0.01
Mean duration of hospital stay — days**	9.27		9.45		8.48		
Case fatality rate — rate (95% CI)††							
All patients	70.4 (69.2–71.6)		67.8 (66.4–69.2)		76.5 (74.2–78.7)		0.01
All hospitalized patients	60.7 (59.2–62.3)		60 (58.3–61.7)		63.7 (60.2–67.1)		0.39
According to sex							
Male	71.6 (69.9–73.2)		69.4 (67.4–71.4)		76.6 (73.2–79.7)		0.16
Female	68.9 (67.1–70.6)		66.0 (63.9–68.0)		75.7 (72.3–78.8)		0.05
According to age group							
<15 yr	68.7 (65.6–71.6)		64.5 (60.8–68.1)		75.9 (70.2–80.8)		0.18
15–44 yr	66.7 (65.0–68.3)		64.3 (62.4–66.2)		72.7 (69.3–75.9)		0.07
≥45 yr	79.4 (77.1–81.5)		77.5 (74.7–80.0)		83.2 (79.0–86.8)		0.47
According to occupation							
Health care worker	66.8 (61.9–71.3)		67.3 (62.1–72.1)		61.5 (48.0–73.5)		0.80
Non–health care worker	70.6 (69.4–71.9)		67.8 (66.3–69.3)		77.1 (74.7–79.3)		0.01

* CI denotes confidence interval, and IQR interquartile range.
† October 1, 2014, marked the initiation of the United Nations Mission for Ebola Emergency Response.
‡ The P values are for the comparisons between the period from December 2013 to September 30, 2014, and the period from October 1, 2014, to November 25, 2014.
§ Contacts on day 0 (the day of symptom onset) were excluded.
¶ Gamma distributions were fitted to confirmed and probable cases. Contacts on day 0 (the day of symptom onset) were excluded.
‖ Serial interval is defined as the interval between the onset of disease in an index case patient and the onset of disease in a person infected by that index case patient. The numbers here refer to the numbers of epidemiologically linked pairs in which the person infected by the index case patient reported only one direct contact.
** The duration reported here is the weighted average of the observed means of the distributions of durations from hospitalization to discharge and hospitalization to death.
†† The late-stage case fatality rate (October 1 to November 25, 2014) may be an overestimate, since there are likely to be more discharges than deaths yet to be recorded for patients with disease onset during this time period, because the mean time from hospitalization to death is shorter than the mean time from hospitalization to discharge (see the Supplementary Appendix).

The New England Journal of Medicine
Downloaded from nejm.org on February 6, 2015. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

still presents a huge challenge as we move into the second year of the epidemic in West Africa.

WHO Ebola Response Team

A list of authors (members of the WHO Ebola Response Team who contributed to this letter, in alphabetic order) is available with the full text of this letter at NEJM.org.

Supported by the Medical Research Council, the Bill and Melinda Gates Foundation, the Models of Infectious Disease Agent Study of the National Institute of General Medical Sciences (National Institutes of Health), the Health Protection Research Units of the National Institute for Health Research, European Union PREDEMICS consortium, Wellcome Trust, Fogarty International Center, and World Health Organization.

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

This letter was published on December 24, 2014, at NEJM.org.

1. WHO Ebola Response Team. Ebola virus disease in West Africa — the first 9 months of the epidemic and forward projections. N Engl J Med 2014;371:1481-95.
2. Ebola response roadmap — situation report. Geneva: World Health Organization (http://www.who.int/csr/disease/ebola/situation-reports/en/).
3. UN Mission for Ebola Emergency Response (UNMEER). External situation report (http://www.un.org/ebolaresponse/index.shtml#&panel1-1).

DOI: 10.1056/NEJMc1414992

Ebola in Freetown Area, Sierra Leone — A Case Study of 581 Patients

TO THE EDITOR: Schieffelin et al. (Nov. 27 issue)[1] reported on 106 patients with Ebola virus disease who were treated in Kenema, Sierra Leone, in May and June 2014. Here we report similar data on the 631 patients with Ebola virus disease, as confirmed by polymerase-chain-reaction assay, who were admitted to the Ebola treatment center at the Hastings Police Training School near Freetown, Sierra Leone, on or after September 20, 2014 (the date on which the first patients were admitted to that center). The 31% case fatality rate at Hastings is lower than the 74% rate reported by Schieffelin et al.

As of December 7, 2014, a total of 50 of the 631 patients with laboratory-confirmed Ebola virus disease were still inpatients at Hastings, and 581 had either died or been discharged after testing negative for the Ebola virus in follow-up laboratory tests. In total, 183 of the 581 patients for whom a final disposition is known died, representing a case fatality rate of 31.5%; among the patients who died, 38 were dead on arrival and the other 145 died after admission. We have observed a decreasing case fatality rate among inpatients at Hastings, from 47.7% among the first 151 patients (September 20 to October 13), to 31.7% among the next 126 patients with a final disposition (October 14 to November 4), to 23.4% among the next 304 patients (November 5 to December 7).

The most common symptoms reported at admission were fatigue, anorexia, fever, vomiting and nausea, diarrhea, muscle pain, joint pain, and headache. On average, patients were admitted 3 or 4 days after the onset of symptoms. The inpatients who died usually did so within 3 or 4 days after admission; survivors usually were hospitalized for about 2 weeks.

Our current treatment protocol is as follows (for additional details, see Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org): For 72 hours after admission, all patients receive 1 g of ceftriaxone intravenously every 12 hours and 500 mg of metronidazole intravenously every 8 hours, as well as 500 ml of Ringer's lactate every 8 or 12 hours and 500 ml of dextrose saline (5% and 0.9%, respectively) intravenously every 8 or 12 hours. All patients also receive 10 mg of vitamin K and 160 mg of artemether intramuscularly immediately on admission, as well as a 20-mg zinc sulfate tablet daily, a 400-mg ibuprofen tablet every 12 hours, and 10 mg of metoclopramide intravenously as needed for nausea or vomiting. After the first 3 days, continuing therapy includes a 400-mg metronidazole tablet every 8 hours for 7 days, a 500-mg cefuroxime tablet every 12 hours for 5 days, an artesunate–lumefantrine combination-therapy tablet daily for 3 days, a 400-mg ibuprofen tablet every 12 hours, and one capsule of Immuno-Boost nutrition supplement (Novopharm Formulations) daily. Oral rehydration solution and juice drinks are given freely. It is unclear why the case fatality rate is decreasing at Hastings. We are unable to assess any individual component of the treatments we used, since we applied a

The New England Journal of Medicine
Downloaded from nejm.org on February 6, 2015. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.