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OREGON PUBLIC HEALTH DIVISION • OREGON HEALTH AUTHORITY

ALL ABOUT EBOLA

Diseases desperate grown
by desperate appliance are relieved
or not at all.

Shakespeare, *Hamlet*

During December 2013, unnoticed by the wider world, a 2-year-old boy named Emile died in Meliandou, Guinea — the first case in what has become history's largest recorded outbreak of Ebola virus infection. This smoldering outbreak of fever, severe diarrhea, vomiting, and high fatality rate remained a mystery until March 2014, when sera from 20 patients with suspected hemorrhagic fever were tested for Ebola virus (EBOV); 15 were positive by PCR, and the virus was isolated in culture from 5.[1]

The World Health Organization (WHO) announced the outbreak March 23, 2014[2], and by the end of that month, 122 confirmed or suspected cases were identified, 80 (66%) of whom had died. Cases were increasingly identified through the spring and summer; transmission extended into Liberia and Sierra Leone. On August 8, with more than 1,700 cases and 900 deaths, WHO declared a "Public Health Emergency of International Concern." Case counts have since accelerated and have now been reported in Guinea, Liberia, Sierra Leone, Nigeria, Mali, and Senegal. Spain had one case, four fell ill while in the United States, and the U.K had one. As of December 31, a worldwide total of 20,206 confirmed, probable, or suspect cases have been reported to WHO as part of this outbreak; 7,905 (39%) have died. Several hundred cases are still being reported weekly (Figure).[3]

Figure. Reported cases of Ebola, Aug 29, 2014– Dec 19, 2014 (Source WHO)

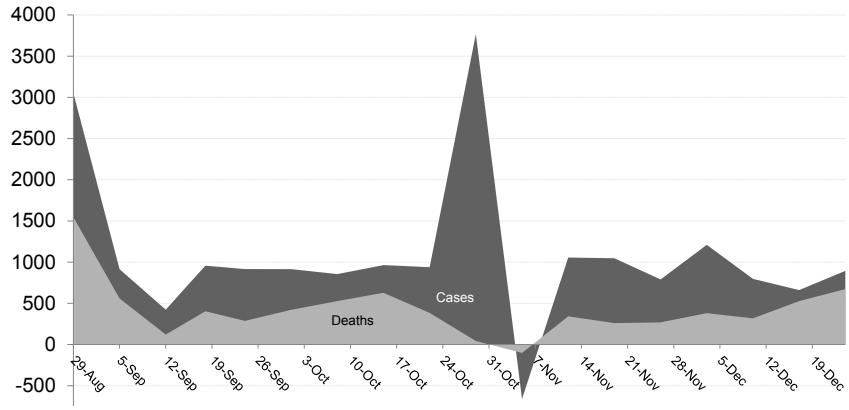


Figure. Cases are shown by week of report. The apparent increase in cases seen Oct 29 and dip in cases Nov 5 represent artifacts from data corrections.

HISTORY

Ebola was discovered in 1976 following outbreaks in northern Zaire (now the Democratic Republic of the Congo [DRC]) and southern Sudan. A specimen from a Zaire case was sent to CDC, where culture yielded a virus resembling the Marburg filovirus discovered in 1967. Human sera from the Zaire and Sudan outbreaks reacted with antigen from the new virus but not with Marburg antigen, demonstrating that the new virus was a distinct filovirus; it was named for the Ebola River, which flowed near the epicenter of the Zaire outbreak.[4] Since 1976, a couple of dozen outbreaks of 1–425 cases each have been reported from sub-Saharan Africa.[5] Five species of EBOV have been distinguished by viral RNA sequencing: Zaire, Sudan, Bundibugyo, Reston and Taï Forest. The strain causing the current outbreak in West Africa is closely related to Zaire EBOV, but distinguishable from previous variants thereof.[1] Hemorrhage has been reported uncommonly; instead, the illness has a distinctly gastrointestinal flavor, with some patients having cholera-like quantities (>5 liters/d) of watery diarrhea.[6]

TRANSMISSION

Person-to-person transmission and risk to healthcare workers was recognized in the 1976 Zaire outbreak. The initial spike in cases occurred among recipients of injections at the Yambuku Mission Hospital, where slim supplies of needles and syringes led to their reuse, often with only warm-water rinsing between. Within a month, illness among 13 of the 17 hospital staff (11 of whom died) forced closure of the hospital, but not before cases had spread to several other villages. Sixty-two (5.6%) of 1,103 household contacts of cases fell ill. Hospital closure, isolation of patients, contact precautions, and disinfection procedures ended the outbreak after 2 months and 318 cases, 280 (88%) of whom died.[7]

An outbreak centered in Kikwit in southwestern DRC involved 315 cases during January–July 1995; the case-fatality rate was 81%. Eighty (25%) of the cases were health-care workers. Of 170 patients for whom data were available, 159 (94%) reported contact with another suspect Ebola case.[8] A substudy of household transmission from 27 primary household cases found that 28 (29%) of the 95 household members who had touched the case subsequently contracted Ebola, while *none* of the 78 household members who *didn't* touch the case became ill. Among those 95 who had touched the case, risk was elevated among adults, those who reported contact with body fluids, and those who shared a hospital bed with the case.[9]

Data like these argue strongly that direct contact with patients or bodily fluids are required for Ebola transmis-

sion. Our domestic epidemiology seems to confirm this: among all contacts of the 10 cases known to have been in the United States to date (*vide infra*), only two acquired the virus here — both health-care professionals who cared for a patient in the terminal stages of his illness.[10]

WHERE'S THE RESERVOIR?

The virus hasn't been isolated in the wild other than from humans and non-human primates; but infected primates generally suffer brief and often fatal illness, making them improbable reservoirs. Early testing of thousands of other species including bats, rodents, dogs, pigs, bedbugs, mosquitoes, and even plants, came up blank.[7, 11]

Circumstantial evidence implicates bats as a reservoir. Anecdotally, some primary human cases had been in caves or buildings inhabited by bats. Investigators recovered virus from tadarid and *Epomophorus* bats for up to 21 days following inoculation, but not from similarly inoculated pigeons, frogs, toads, snakes, tortoises, a variety of insects, or plants from outbreak areas. The loci of outbreaks in Africa seem consistent with tadarid bat populations.[12] Several years ago, serologic and PCR evidence of Ebola virus infection in fruit bats was reported.[13]

An April 2014 investigation into the source of Emile's infection concluded that bush meat was an unlikely source. Primates are rare in that part of Guinea; and most large game consumed in the area arrived, smoked, from distant regions. On the other hand, insectivorous bats are commonly found there under the roofs of houses and are routinely hunted and grilled over small fires by children. Two-year-old Emile may have been infected by bats living in a hollow tree in which children played frequently.[14]

SUPPORTIVE CARE

Fatalities in the 1976 outbreak in Zaire were thought to have been the consequence of hypovolemic shock.[7] Physicians treating patients in the United States have been impressed by the loss of intravascular fluid — not only from bleeding but from diarrhea and increased vascular permeability; one patient treated at Emory had up to 4 liters of diarrhea per day.[15] Hypokalemia and hypocalcemia were striking; both Emory patients required significant volume and electrolyte replenishment.[15] Supportive medical care like this may be making a difference: the reported case-fatality rate has fallen from 66% (through March) to 39%, in association with the establishment of Ebola Treatment Units in affected West African countries.

INVESTIGATIONAL TREATMENTS

Some specific treatment possibilities have been floated, though none have yet been approved by FDA. Already in the 1976 Zaire outbreak, treatment with convalescent plasma was contemplated;* 201 units were collected from 26 patients who had recovered from their infections, but only one patient was treated with it.[7] During the 1995 outbreak in Kikwit, 8 "seriously ill Ebola patients with severe asthenia" were treated with 150–450 mL convalescent blood donated by earlier patients; 7 of the 8 survived in the midst of an outbreak in which 88% of cases died.[16] Convalescent whole blood or plasma has been given to several patients in the current outbreak, and WHO has produced guidance regarding appropriate donors and candidates for treatment, collection and screening of blood, preparation and storage, and administration of such products. Briefly, they suggest that they be given only to patients with confirmed Ebola; and plasma should be administered in two doses of 200–250 mL for adults or 10mL/kg for children. A clinical trial is under way employing Cerus's "INTERCEPT" system for inactivation of potential blood-borne pathogens from donor plasma; convalescent plasma donors and patients with acute Ebola are being recruited.†

ZMapp™ (Mapp Biopharmaceutical) is a cocktail of "humanized" monoclonal antibodies directed against 3 Ebola antigenic targets and produced in tobacco plants.‡ A recent study injected macaque monkeys with EBOV intramuscularly; 18 of 18 monkeys that received ZMapp 3–5 days later survived, while all 3 control monkeys died.[17] The drug has been given to some humans with Ebola, but no human efficacy trials have been undertaken. No clinical trials involving ZMapp are currently found on ClinicalTrials.gov.

Favipiravir is a nucleoside analogue polymerase inhibitor approved in Japan for treatment of influenza. It has shown promise in a mouse model of EBOV infection. Patients are being recruited in Guinea for an open-label phase 2 trial.§

Brincidofovir (CMX001, Chimerix) is an oral prodrug of the IV-only nucleoside analog cidofovir; the latter is approved by FDA only for treatment of CMV retinitis in AIDS patients, but it evidences activity *in vitro* against a variety of viruses including Ebola. Chimerix plans to recruit healthy volunteers for a phase 2 study of brincidofovir's safety and antiviral activity.¶ It is available to patients under an Investigational New Drug (IND) application.

Tekmira Pharmaceuticals has a cocktail of three small interfering RNA (siRNA) sequences formulated into "stable nucleic acid-lipid particles" (SNALPs) to get them into cells. Six of seven macaques treated with the SNALPs after Ebola challenge survived, while the two control macaques succumbed.[18] Phase 1 trials of related products** were suspended, however, and no new human trials are listed with ClinicalTrials.gov. But TKM-Ebola is available under an IND application and has been administered to at least one patient in the U.S.

BCX4430 (BioCryst Pharmaceuticals) is an adenine analog RNA chain terminator that has demonstrated efficacy in a mouse model of Ebola.[19] Healthy human subjects are being recruited for a phase 1 dose-ranging, safety and pharmacokinetic study.††

VACCINE PROSPECTS

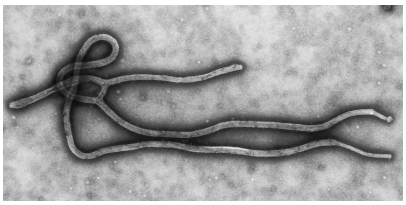
Adenoviruses can be programmed to elaborate proteins from other viruses, thereby serving as vaccine

* perhaps why Dustin Hoffman was so anxious to "find this monkey."
† NCT02295501
‡ *http://mappbio.com*
§ NCT02329054
¶ NCT02271347
** NCT01518881 and NCT02041715
†† NCT02319772

vectors; but underlying immunity to human adenoviruses can thwart the ability of the vector virus to replicate and express the proteins. The work-around is to use a chimpanzee adenovirus, to which humans are susceptible. A "cAd3" vector vaccine that expresses ebolavirus glycoprotein has shown efficacy in a macaque model and immunogenicity in healthy human adults.[20] Trials are ongoing.‡‡

Vesicular stomatitis virus is another promising vaccine vector. Intramuscular injection of VSV expressing Ebola glycoproteins completely protected 3 of 3 macaques against challenge with aerosolized EBOV 28 days later, whereas all 3 control macaques succumbed 6–8 days after challenge.[21] Several phase 1 dose-escalation, safety and immunogenicity trails are recruiting patients.§§ One trial was suspended to investigate reports of arthritis in vaccinees.¶¶

EBOLA IN THE U.S.A.



To date, the United States has seen 10 cases of Ebola. Six of these had fallen ill in West Africa and were airlifted hither for medical care. Four patients became ill while in the U.S. and are thus attributed in WHO's log;[22] these include the initial case who presented to Texas Health Presbyterian Hospital Dallas, two nurses who contracted illness after caring for him there, and a physician who returned from health-care work in Guinea apparently hale, only to fall ill in New York. Two of the 10 patients died; the other 8 have recovered.

OF PUMs AND PUIs

Before the outbreak ~150 persons had been arriving in the U.S. daily from Guinea, Sierra Leone and Liberia. Since October 11, all such passengers have been routed through 5 airports: New York JFK; Newark; Washington, D.C. Dulles; Atlanta Hartsfield; and Chicago's O'Hare. The passengers are screened in Africa for EBOV exposure, and high-risk travelers are prohibited from commercial travel until they complete a 21-day monitoring period. Lower-risk passengers are screened on arrival in the U.S.; those with signs or symptoms suggestive of Ebola are taken to an emergency department for evaluation, with testing and isolation if indicated.[23] Asymptomatic passengers may proceed to their final destinations by commercial aircraft. All receive a thermometer, and their names and contact information are forwarded to the relevant state health departments for monitoring.

For 21 days, these "Persons Under Monitoring" (PUMs) are asked to take their temperature twice daily and to report symptoms at least daily to the local public health department. PUMs who develop symptoms become "Persons Under Investigation" (PUIs). In Oregon, local health officials arrange for the prompt transport of such persons to a hospital for evaluation under strict contact isolation.

PUMs have arrived at PDX at a rate of ~2 per week. Of Oregon's 28 PUMs logged as of December 31, 16 have completed their 21-day monitoring periods, 3 traveled out of state (their monitoring passed to the destination state), and 9 remain under monitoring. None have come down with Ebola. One PUM spiked a fever October 31 and was observed for 3 days in a specially prepared isolation unit at Providence Milwaukie Medical Center; she was released when her symptoms resolved under treatment for an alternative diagnosis.

Any hospital in Oregon is expected to assess and stabilize a PUI safely for at least 24 hours. Patients who require further evaluation or treatment will be transferred to one of 9 hospital systems in Oregon that are prepared to draw labs and care for such patients until Ebola can be ruled in or out. Because patients with Ebola are not reliably viremic until day 3 of illness, and specimens must be shipped to an out-of-state reference lab for testing, "ruling out" Ebola may take 96 hours. Patients with confirmed Ebola will be transported to a CDC-certified Ebola treatment hospital. Currently, 35 U.S. hospitals have been so certified — the nearest to us being U.C. Davis, California.[24]

CDC summarized all Ebola clinical inquiry calls triaged since July at its Emergency Operations Center from state health departments and physicians.[25] Of 160 persons with ≥1 risk factor for Ebola, 138 (86%) reported travel to a country with ongoing EBOV transmission, and 22 (14%) reported contact (e.g., during health-care work) with a person with Ebola or their infectious fluids. Of these, 118 (74%) developed ≥1 sign or symptom consistent with Ebola; of these, 51 (43%) were tested for EBOV, plus another 10 persons without risk factors or symptoms. The remaining persons were not tested for EBOV, presumably because an alternative diagnosis arose or symptoms resolved spontaneously. Documented alternative diagnoses included malaria and viral illnesses (e.g., influenza). As noted above, 4 tested positive for EBOV; all reported contact or had cared for a person with fatal Ebola.

In toto, of the 2,263 travelers returning to the U.S. from Guinea, Sierra Leone, and Liberia during Oct 11–Nov 15, 2014, 1 developed Ebola after arrival.

CDC recommends avoiding nonessential travel to Guinea, Sierra Leone and Liberia.[26] Those who travel to assist with the medical and humanitarian crisis should, before departing, develop a "game plan" with their physician and local health department to protect themselves abroad and to complete the monitoring period upon return.

THE BOTTOM LINE

Until the outbreak in West Africa is quelled, we will probably see more Ebola cases in the U.S. among persons — especially health-care workers — returning from affected countries. The risk to the general public is near zero: persons are not contagious before they develop

‡‡ NCT02231866 and NCT02289027
§§ NCT02283099; NCT02280408; NCT02314923; NCT02296983; NCT02269423
¶¶ NCT02287480

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symptoms, and monitoring allows rapid recognition of symptoms and isolation of suspected cases before they can spread the illness. Healthcare professionals caring for patients with Ebola must be meticulous regarding their use of personal protective equipment: all skin and mucous membranes must be covered with impermeable barriers. Rigorous training to don and doff personal protective equipment safely under exacting supervision may mean the difference between life and death.[27]

FOR MORE INFORMATION

- WHO situation reports: *www.afro.who.int/en/clusters-a-programmes/dpc/epidemic-a-pandemic-alert-and-response/sitreps.html*
- CDC guidance and updates: *www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html*
- Oregon Health Authority info for health-care providers and public health partners: *https://public.health.oregon.gov/Preparedness/CurrentHazards/Events/EbolaResponse/Pages/EbolaPartners.aspx*
- Investigational Ebola treatments and vaccines: see review by Bryan M. Bishop, PharmD.[28]
- Email us at *ebola.oregon@state.or.us*.

REFERENCES

1. Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola virus disease in Guinea. NEJM 2014;371:1418–25.
2. WHO. Global Alert and Response (GAR): Ebola virus disease in Guinea. 2014. Available at *www.who.int/csr/don/2014_03_23_ebola/en/*, accessed 5 Dec 2014.
3. WHO. Ebola data and statistics: latest available situation summary. 2014. *http://apps.who.int/gho/data/view.ebola-sitrep.ebola-summary-latest?lang=en*, accessed 31 Dec 2014.
4. Johnson KM, Lange JV, Webb PA, Murphy FA. Isolation and partial characterisation of a new virus causing acute haemorrhagic fever in Zaire. Lancet 1977;1:569–71.
5. CDC. Outbreaks Chronology: Ebola Virus Disease. 2014. Available at *www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html*, accessed 5 Dec 2014.
6. Chertow DS, Kleine C, Edwards JK, Scaini R, Giuliani R, Sprecher A. Ebola virus disease in West Africa — clinical manifestations and management. NEJM 2014;371:2054–7.
7. Ebola haemorrhagic fever in Zaire, 1976. Bull WHO 1978;56:271–93.
8. Khan AS, Tshioko FK, Heymann DL, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179 Suppl 1:S76–86.
9. Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179 Suppl 1:S87–91.
10. CDC. CDC confirmed positive test by Texas Lab and patient has been notified. 2014. Available at *www.cdc.gov/media/releases/2014/s1015-texas-second-health-care-worker.html*, accessed 5 Dec 2014.
11. Breman JG, Johnson KM, van der Groen G, et al. A search for Ebola virus in animals in the Democratic Republic of the Congo and Cameroon: ecologic, virologic, and serologic surveys, 1979–1980. Ebola Virus Study Teams. J Infect Dis 1999;179 Suppl 1:S139–47.
12. Swanepoel R, Leman PA, Burt FJ, et al. Experimental inoculation of plants and animals with Ebola virus. Emerg Infect Dis 1996;2:321–5.
13. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. Nature 2005;438:575–6.
14. Saéz AM, Weiss S, Nowak K, et al. Investigating the zoonotic origin of the West African Ebola epidemic. EMBO Mol Med 2014. doi: 10.15252/emmm.201404792.
15. Lyon GM, Mehta AK, Varkey JB, et al. Clinical care of two patients with Ebola virus disease in the United States. NEJM 2014;371:2402–9.
16. Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis 1999;179 Suppl 1:S18–23.
17. Qiu X, Wong G, Audet J, et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature 2014;514:47–53.
18. Geisbert TW, Lee AC, Robbins M, et al. Postexposure protection of non-human primates against a lethal Ebola virus challenge with RNA interference: a proof-of-concept study. Lancet 2010;375:1896–905.
19. Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. Nature 2014;508:402–5.
20. Ledgerwood JE, DeZure AD, Stanley DA, et al. Chimpanzee Adenovirus Vector Ebola Vaccine - Preliminary Report. NEJM 2014. doi: 10.1056/NEJMoa1410863.
21. Geisbert TW, Daddario-Dicaprio KM, Geisbert JB, et al. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. Vaccine 2008;26:6894–900.
22. WHO. Global Alert and Response (GAR): Ebola response roadmap - Situation report. 2014. Available at *www.who.int/csr/disease/ebola/situation-reports/en/*, accessed 31 Dec 2014.
23. CDC. Information for ill travelers: Ebola; what you need to do. 2014. Available at *wwwnc.cdc.gov/travel/pdf/ebola-ill-traveler-symptoms-exposure.pdf*, accessed 5 Dec 2014.
24. CDC. Current Ebola Treatment Centers. 2014. Available at www.cdc.gov/vhf/ebola/hcp/current-treatment-centers.html, accessed 31 Dec 2014.
25. CDC. Clinical inquiries regarding Ebola virus disease received by CDC—United States, July 9–November 15, 2014. MMWR 2014;63:1175–9.
26. CDC. Travel Health Notices. 2014. *wwwnc.cdc.gov/travel/notices*, accessed 5 Dec 2014.
27. CDC. Guidance on personal protective equipment to be used by healthcare workers during management of patients with Ebola virus disease in U.S. hospitals, including procedures for putting on (donning) and removing (doffing). 2014. *www.cdc.gov/vhf/ebola/hcp/procedures-for-ppe.html*, accessed 8 Dec 2014.
28. Bishop BM. Potential and emerging treatment options for Ebola virus disease. Ann Pharmacother 2014. doi: 10.1177/1060028014561227.

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