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, 20142, and by the end of
that month, 122 confirmed or suspected
cases were identified, 80 (66%) of
whom had died. Cases were increas-
ingly 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 Inter-
national Concern.” Case counts have
since accelerated and have now been
reported in Guinea, Liberia, Sierra Le-
one, 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

**HISTORY**

Ebola was discovered in 1976 fol-
lowing 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, demonstrat-
ing 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, Bundi-
bugyo, Reston and Tai Forest. The
strain causing the current outbreak in
West Africa is closely related to Zaire
EBOV, but distinguishable from previ-
ous variants thereof.6 Hemorrhage has
been reported uncommonly; instead,
the illness has a distinctly gastrointes-
tinal 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 recog-
nized 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, ill-
ness 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, isola-
tion 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 hospi-
tal bed with the case.9

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

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**ALL ABOUT EBOLA**

**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.
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;20 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 Biopharmaceuticals) is a cocktail of “humanized” monoclonal antibodies directed against 3 Ebola antigenic targets and produced in tobacco plants.† perhaps why Dustin Hoffman was so anxious to “find this monkey.” NCT02295501.

http://mappbio.com

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

† NCT02295501
‡ NCT02319772
§ NCT02239054
¶ NCT02271347
** NCT01518861 and NCT02041715
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.\textsuperscript{20} Trials are ongoing.\textsuperscript{‡‡}

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.\textsuperscript{21} Several phase 1 dose-escalation, safety and immunogenicity trails are recruiting patients.\textsuperscript{§§} 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;\textsuperscript{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.\textsuperscript{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.\textsuperscript{24}

CDC summarized all Ebola clinical inquiry calls triaged since July at its Emergency Operations Center from state health departments and physicians.\textsuperscript{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.\textsuperscript{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...
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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. For more information, visit the following websites:


Oregon Health Authority info for health-care providers and public health partners: [https://public.health.oregon.gov/Preparedness/CurrentHazards/Events/EbolaResponse/Pages/EbolaPartners.aspx](https://public.health.oregon.gov/Preparedness/CurrentHazards/Events/EbolaResponse/Pages/EbolaPartners.aspx)

Investigational Ebola treatments and vaccines: see review by Bryan M. Bishop, PharmD.  

Email us at [ebola.oregon@state.or.us](mailto:ebola.oregon@state.or.us).

REFERENCES


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