Notes

INTRODUCTION

1. Nuland 1989.

2. I remain uncomfortable with current terminology for systems of medical knowledge. This work focuses on what is often referred to as "biomedicine" or "scientific medicine." Since this form of medicine is not practiced scientifically in much of Africa, however, neither term is appropriate. I have settled for "Western" medicine, even though this is a misnomer because the form of medicine that is said to have originated in Greco-Roman cultures drew from cultures across the East, and even from African cultures. "Modern" medicine is also a misnomer, since other systems continue to be practiced. However, since this form of medicine was brought to Africa from Europe and imposed upon the continent by colonialists, the term "Western" is particularly applicable. Present-day medical systems that derive from African culture are frequently referred to as "traditional," and I use this term on occasion. Many of these systems, however, have evolved considerably, and what passes for "tradition" is never static. Terms such as "alternative" or "complementary" medicine suggest that they are cheerfully practiced alongside Western medicine, which is not the case, and they suggest that African medicine is secondary, which is certainly not true for many patients. Because African medical systems have been suppressed, we have insufficient knowledge to determine whether they are complementary with biomedical protocols. I favor the term "indigenous" medicine, although not all nonwestern medicine is indigenous to a single culture. I refer to practitioners who are licensed by the state as "sanctioned" practitioners, borrowing the terminology from Djimde et al. 1998; these include doctors, nurses, pharmacists, and other health personnel trained in Western-type programs, as well as less professional and skilled primary health care workers, village health care workers, and public health officials recognized and trained by the state. Indigenous practitioners are also sanctioned providers. Unsanctioned providers, sometimes disparaged as "quacks," include those who practice any form of medicine—often, Western medicine—without any formal training or state registration. Most African states lack the resources or the will to proscribe and prosecute these illegitimate practitioners.

3. If the time available for the physical examination is short, precision declines sharply. Guyon et al. 1994 recorded a mean of fifty-four seconds consulting time per patient in Bangladesh.

4. See Wootton 2006. Despite the inability of routine diagnostic protocols to provide the correct diagnosis for all conditions, overinvestigation, sometimes referred to as "medical vampirism," is also potentially detrimental (Le Fanu 2000). In some instances, the quantity of blood taken for tests is so great as to cause anemia (Abrams 1979; Burnum 1986). The burden placed on health systems for expensive but useless tests is of concern in some places. So is the performance of tests to stroke the physician's ego or protect from liability, when the results would be obvious ("Reducing Tests" 1981; Showstack, Schroeder, and Matsumoto 1982; Griner and Glaser 1982). There is definitely a balance to be struck between diagnostic sufficiency and diagnostic abuse. A justifiable diagnostic is not an end in itself.

5. The terminology was coined by Chambers 1989. For more on the poverty-disease cycle, see Jeffrey Sachs 2005.

6. Foege 2002.
7. Brock 1999, 1.

CHAPTER 1

1. The University College Hospital is the premier institution for nursing education in Nigeria ("British Contributions to Medical Research and Education in Africa after the Second World War" 1999).

2. Pyrimethamine, a malaria preventative, was marketed as Daraprim and called "Sunday-Sunday medicine" because it was taken once a week.

3. Atta 2005.

4. Although malaria is a serious, even life-threatening, disease, attacks are so frequent and widespread that most West Africans consider malaria a relatively mild illness in adults.

5. Until recently, when its effectiveness was compromised by the emergence of drug resistance, chloramphenicol was the drug of choice for typhoid fever.

6. Porter 1998; Wootton 2006.

7. Such as Andreas Vesalis (1514–64), William Harvey (1578–1657), Giovanni Morgagni (1682–1771), and John Hunter (1728–93), who are chronicled by Nuland (1989) and Porter (1998).

8. Good historical overviews are provided by Nuland 1989 and Porter 1998. Leeuwenhoek is often erroneously given credit for building the first microscope; it was probably Zacharias Janssen (1590) who first peered through a tube in which he had mounted two lenses. Leeuwenhoek pioneered microscopy for biological observation. He was a prolific observer and contributor to the *Philosophical Transactions of the Royal Society* (of Great Britain), authoring 190 letters on microscopy between 1673 and 1723, and was elected a fellow of the Royal Society in 1680. Leeuwenhoek did not, and indeed could not, presuppose that microbes caused disease. He found that "animacules" were ubiquitous. He did not have the discriminatory power that later microbiologists used to delineate different subtypes; he did not even examine the specimens from infections. Koch's tuberculosis paper was published in 1882.

9. Cunningham 1992.

10. At the time, plant biologists were preoccupied with fungi, which were larger and more easily observed than bacteria. In the late 1850s, Anton deBary performed a controlled study to determine the role of the fungus *Phytophthora infestans* in the etiology of potato blight; he succeeded in demonstrating causation earlier than Koch. Other plant biologists questioned this explanation for deBary's data. We now know that the real causative organism was probably a virus carried on the fungal spores, so the skeptics may deserve some credit. The disconnect between the study of the biology of plants and humans as well as between studies on fungi and bacteria did not permit the debate to enter human medicine at that time.

11. Santer 2009; Wootton 2006.

12. The technology needed to move an individual bacterium, to the exclusion of other organisms that may be present, from an infected individual to a healthy one became available only in the last decade. In most cases, more than one bacterium is needed to seed an infection. Nineteenth-century microbiologists needed to be able to produce large numbers of identical bacteria from a mixture in order to inoculate healthy hosts. The production of pure cultures required the scientists to be able to isolate the candidate bacterium and to permit it to reproduce in a bacteria-free environment.

13. For example, Edwin Klebs (1834–1912) used fractional culture methods in his work with anthrax (Koch 1876). Although his results were consistent with later work, the

reproducibility of his experiments was a problem (Brock 1999). In 1878, Joseph Lister, who coined the term "germ theory," probably produced a pure culture by subculturing *Lactobacilli* in very dilute milk samples until he obtained samples that contained one organism. The qualifier "probably" is significant. Current methods of liquid fractionation used in water and milk assessment produce only a "most probable number" of bacteria, an estimate rather than an accurate count of individual bacteria. Lister's methodology was not precise, absolute, reproducible, or practicable.

14. Lister 1878; Schroeter 1875.

15. Koch, the son of an engineer, was born in 1843 in Clausthal, Germany. He studied natural sciences and medicine and was a student of Jacob Henle at Göttingen. After graduation, he practiced medicine and experimented in a private laboratory attached to his office. Koch's postulates were published after his seminal paper on the etiology of tuberculosis, which was the first of his papers to fulfill them rigorously (Koch 1882). Stated in their simplest form by Koch himself, the postulates are designed "to obtain a perfect proof to satisfy oneself that the parasite and the disease are not only correlated, but actually causally related, and that the parasite is the direct cause of the disease. This can only be done by completely separating the parasite from the diseased organism…and then introducing the isolated parasite into healthy organisms and induce the disease anew with all its characteristic symptoms and properties" (Koch 1884, translated by Brock 1999, 116). In order to separate the parasite from the host and all other materials associated with the disease, in vitro pure cultures must be prepared, which makes the study of causation dependent on techniques of microbial culture.

16. Anthrax (Koch 1876), wound fever (Koch 1880), tuberculosis (Koch 1882), and cholera in 1883.

17. In *Wives and Daughters,* a novel published in 1866 by the English novelist and social observer Elizabeth Gaskell, a mother says about her deceased husband and healthy daughter: "Poor dear Mr. Kirkpatrick was consumptive, and Cynthia may have inherited it, and a great sorrow might bring out the latent seeds. At times I am so fearful" (Gaskell 1866, 55).

18. Koch 1884. Daniel Salmon, who was working on causation at the same time as Koch, proposed even more stringent criteria for causation (Salmon 1881). In addition to criteria similar to Koch's postulates, he maintained that in order to establish causation, it must be possible to interrupt the pathogen's transmission cycle and obliterate the disease. Salmon spent years studying hog's cholera. He was able to fulfill Koch's postulates for *Salmonella cholerasius* in pigs, and others accepted this organism as the etiologic agent of the disease. Salmon himself was dissatisfied because he was unable to create a vaccine and thereby fulfill his more stringent criteria. In the final analysis, Salmon's reservations were justified in this case. In 1903, it was shown that a filterable RNA virus causes hog's cholera, and the confounding of *Salmonella cholerasius* was produced by the inability to eliminate the unseen virus from bacterial cultures. Instances similar to hog's cholera are unusual, however, and Koch's postulates have proved sufficient and reliable enough to attribute causation of numerous infectious diseases to specific microbial agents. Were Salmon's more stringent criteria applied, it is unlikely that causation would have been established for so many diseases in the short time after Koch began his work. However, a theory of causation that included a therapeutic intervention might have assisted in linking discovery and control more tightly. The science of virology developed after bacteriology because viruses are hundreds of times smaller than bacteria, so they remain invisible to the light microscope, and, without a cell structure of their own, they cannot be cultured outside of living beings. In the early twentieth century, the invention of tissue culture and electron microscopy allowed for many viruses to be rapidly described and cultured. For reviews, see Oldstone 1998 and Creager and Landecker 2009.

19. Koch 1881, 1882. Thomas Brock writes of Koch's 1881 paper, "Methods for the Study of Pathogenic Organisms": "If I had to choose one paper as most significant for the rise of microbiology, this would be it" (Brock 1999, 108).

20. This invaluable bit of laboratory ware is named for its inventor, Richard J. Petri 1887.

21. Nuland 1989, xvii.

22. See Twumasi 1975.

23. Sofowora 1982.

24. Needham 2000, 130–31; Hughes et al. 1993.

25. Groopman 2007.

26. Nuland 1989.

27. Thomas 1978, 85.

28. Addae 1997, 232.

29. Twumasi 1975; Ogungbamila and Ogundaini 1993.

CHAPTER 2

1. Ogonim's story is told in chapter 4 (Nwapa 1966).

2. Although the Aro confederation resisted British military domination, the Aros conquered many local groups and captured individuals across Ibo-land. They sold their captives into slavery from the eighteenth through the late nineteenth centuries See Acholonu 1999 and Orji 1982.

3. Onyeka Onwenu was educated at Wellesley College and the New School for Social Research in the United States. She returned to Nigeria and worked as a reporter for the Nigerian Television Authority for several years. The *ONOK* incident occurred just after she left journalism for a more lucrative and very successful musical career.

4. Based on data from the Malaria Foundation International, available at www.malaria.org and from Phillips 2001. According to the U.K.'s Department for International Development, Nigeria, like some other African countries, will not meet the Millennium Development Goal to decrease under-five mortality to two-thirds of 1990 levels by 2019. http://www.dfid.gov.uk/Documents/publications/PSA/E_Nigeria.pdf .

5. In his introduction to *Infection and Inequalities,* physician-anthropologist Paul Farmer writes: "I was accustomed to ferreting out accusations of sorcery and had previously spent some years trying to make sense of them. And that, paradoxically, is the primary function of such accusations: to make sense of suffering" (Farmer 1999, 3).

6. Spiritualist churches in modern Nigeria often double as faith healing houses. They do not use, and may even frown on, pharmaceuticals as well as indigenous medicines, sometimes to the detriment of patients (Etuk, Itam, and Asuquo 1999). Faith healers and prayer houses are one of several options used by ill patients in eastern Nigeria and elsewhere on the continent, and are often the venue of choice when a nonbiophysical etiology is suspected (Izugbara and Afangideh 2005).

7. The chance of child's caregiver spotting a fever is quite high and errs on the false-positive side. Therefore, determining the cause of this fever and prescription of effective medicines is the most important intervention (Schapira 1994; WHO 2006c; Wammanda and Onazi 2009). "Fever equals malaria" is a popular twentieth-century adage that advocates for diagnostic testing have begun to work hard to unteach (Hopkins, Asiimwe, and Bell 2009).

8. Needham et al. 2001 found that among the factors contributing to diagnostic delay among tuberculosis patients in Zambia were lower education and visiting a private doctor or traditional healer instead of a government clinic or hospital; women also were less likely to secure a timely diagnosis.

9. WHO 1996; Hopkins, Asiimwe, and Bell 2009.

10. According to Murphy and Breman 2001, approximately 2% of children who recover from cerebral malaria suffer brain damage that results in detectable learning disabilities.

11. Sachs 2005, 115.

12. Ross reputedly compared the significance of his discovery to that of Columbus's discovery of the American hemisphere. See the Nobel Prize citation at http://nobelprize.org/nobel_prizes/medicine/laureates/1902/, © The Nobel Foundation 1902.

13. In 2008, malaria infections and deaths in Africa respectively accounted for 85% and 89% of those worldwide (WHO 2009b).

14. Reviewed by Arrow, Panosian, and Gelband 2004.

15. *Plasmodium ovale* and *P. vivax,* two other species, also have a dormant hypnozoite stage. Hypnozoites can persist in an infected person for years, convert to the merozoitic form in the liver at an unexpected time, and resume an infectious cycle. However, *P. ovale* and *P. vivax* are relatively uncommon in Africa. Most infections in Africa are caused by *P. falciparum,* the most efficiently transmitted and deadliest species; the infection can be completely eliminated if treated with the right medicine, at the right time.

16. The predilection and, indeed, the imperative to self-medicate assumes that patients and their caregivers are competent to assess when they are ill. Whereas severely ill patients are easily identified, in mild illnesses the reliability of even this most basic premise is open to question. A history of fever is likely to bias a patient toward believing that their temperature is elevated, so that if clinical measurements are used to the exclusion of patient complaints, intermittent fevers would be missed. The problem with basing diagnosis on clinical signs and symptoms alone is that, in all but textbook cases, these criteria are unavoidably subjective. There are some important exceptions; for example, many conditions produce a characteristic rash. As more of these vaccine-preventable conditions, such as measles, become controlled, the ease with which infections can be delineated without diagnostic tests will continue to fall.

17. WHO 2006c, 8.

18. Ibid.

19. Reyburn et al. 2004; Gwer, Newton, and Berkley 2007.

20. Farmer 1999.

21. According to Millennium Development Goal evaluation estimates, African countries typically record between 40 and 260 deaths per 1,000 live births in children under five; in almost all African countries, infant mortality estimates remained the same or rose between 1990 and 2004. The Millennium Development Goal is to halve these deaths by 2015. http://millenniumindicators.un.org/unsd/mdg/SeriesDetail.aspx?srid=561&crid=.

22. It is easier to identify parasites in thin blood smears, but at low parasitemia, parasites are more likely to be visible in thick smears, so both thick and thin smears are advocated for diagnosis. A qualified laboratory practitioner can determine which *Plasmodium* species is present to delineate malignant tertian malaria from the more benign form of the disease. When properly conducted, the probability of false positives is small. The chief barriers to the routine use of this method are the high level of test-specific technical expertise required and the labor-intensity of the process. A skilled technician can typically read sixty slides a day (Durrhelm et al. 1997; Cheesebrough 1984; Barker et al. 1986; Zurovac, Midia, et al. 2006; Wongsrichanalai et al. 2007).

23. Assuming eight thousand white blood cells per milliliter of blood, the number of parasites per two hundred white blood cells multiplied by forty will yield the number of parasites per milliliter (Makler, Palmer, and Ager 1998). This method is best used when a white cell count is taken, as patients' white blood counts vary.

24. Durrhelm et al. 1997; Cheesebrough 1984.

25. Microscopists with very little basic education have successfully been employed for malaria diagnosis but high-quality on-the-job training and quality assurance are needed to ensure that smears are prepared and read correctly. In Ethiopia, where malaria is not hyperendemic but epidemics carry a potential for high mortality, diagnostic strength is a major asset. One assessment of the northern Gondar region of Ethiopia found that when a certified reference reader was asked to review slides processed by an operational diagnostic lab technician, the results concurred only 75% of the time, and up to 63% of diagnoses could represent false positives (Mitiku, Mengistu, and Gelaw 2003).

26. Okeke 2006.

27. Zurovac, Larson, et al. 2006.

28. For reviews of recently developed tests, see Makler, Palmer, and Ager 1998 and Bell, Wongsrichanalai, and Barnwell 2006. The sensitivity and specificity of today's rapid diagnostic tests for malaria approach that of microscopy, and in health centers where skilled technicians are not available to prepare and read stained slide smears, rapid diagnostic tests offer superior reliability (de Oliveira et al. 2009).

29. Unlike bacteria, malaria parasites cannot be routinely cultured. When detecting a pathogen is complex or expensive, detecting an immune response in the infected patient can serve as a useful surrogate. The presence of detectable antibody against a specific pathogen is usually indicative that the pathogen is, or was, in the body of the patient. In malaria-endemic areas, most people are exposed to *Plasmodia* several times a month and almost everyone has antibodies, regardless of whether they are currently ill. Some harbor low numbers of parasites that can be detected by molecular tests, some of which are actually too sensitive to employ for clinical diagnosis. Molecular tests may also require reagents that are presently difficult to source in developing countries, such as radioactive probes (Barker et al. 1986).

30. Makler, Palmer, and Ager 1998; Mitiku, Mengistu, and Gelaw 2003; Wongsrichanalai et al. 2007; WHO (2009a).

31. WHO 2008.

32. Costs of antimalarial drugs at the time of the 2003 Africa Malaria Report (WHO and UNICEF 2003) were (in US$) .13 for chloroquine, .14 for sulfadoxine-pyrimethamine (Fansidar), .20 for amodiaquine, and 1.00–3.00 for artemisinin-based combinations. More recent pricing comes from parameters used in cost-effectiveness assessment five years later by the WHO (Shillcutt et al. 2008).

33. WHO 2009a

34. Lubell et al. 2007. Bell and Perkins 2008 point out factors contributing to this problem and how it might be addressed.

35. Nabarro and Tayler 1998. See also http://www.rollbackmalaria.org/. Halting and reversing the incidence of malaria by 2015 is also Millennium Development Goal 6c http://www.undp.org/mdg/basics.shtml.

36. For example, a manufacturer donation program supplies the antifungal drug to many African countries, but fungal diagnostics are almost universally unavailable.

37. The Zambian Ministry of Health's policy (CBoH 2003) followed the international "Roll Back Malaria" proposal (WHO, RBM, 2001). In 2003, malaria was the greatest contributor to the disease burden in Zambia, with fifty thousand deaths from malaria each year and four million people, roughly a third of the population, sickened annually (Masiye and Rehnberg 2005). Zambia's program is consistent with the global plan to roll back malaria and has been proposed as a model for other African countries (Singer 2005). It advocates the use of insecticide-treated bed nets and access to treatment. Both interventions have been proven to be effective. The proposal to boost effectiveness with diagnostics only

came in 2006 (CBoH 2006). Challenges associated with artemether-lumefantrine rollout in Kenya are described by Amin et al. (2007). The study that evaluated testing in Kenyan health institutions and also provides an overview of malaria policy in that country is by Zurovac et al. 2008.

38. Phillips, Kumate-Rodriguez, and Mota-Hernández 1989.

39. de Vries, Kager, and Borgdorff 2004, 1161.

40. AMFm 2007.

41. Snow et al. 2003 present rough estimates of antimalarial use, and the cost estimate for antimalarials dispensed to patients with other infection is provided by Hopkins, Asiimwe, and Bell 2009. Thwing et al. 2009 reported that although approximately half of patients attending primary health care centers typically receive antimalarials, less than 5% of 864 laboratory-evaluated patients tested positive.

42. Chandler et al. 2008; Drakeley, Gosling, and Reyburn 2005; Lubell et al. 2007, 2008; Reyburn et al. 2004, 2006, 2007, 2008; Shillcutt et al. 2008; de Oliveira et al. 2009; Uzochukwu et al. 2009; Hamer et al. 2007; Msellem et al. 2009.

43. Reviewed by Perkins and Bell 2008 and Hopkins, Asiimwe, and Bell 2009. Following recent technical consultation, WHO recommended parasite-based diagnosis for all patients in highly endemic areas except young children, for whom a false-negative test could be fatal (WHO 2006d). The 2009 recommendation was for parasitological diagnosis in all patients (WHO 2009b). See D'Acremont et al. 2009 and English et al. 2009 for perspectives on the ongoing debate on the use of diagnostics for the very young.

44. Only 12 African countries has a policy recommending testing at the community level in 2008 (WHO 2009b). Initial evaluations of rapid diagnostic tests for malaria have proved unreliable when used by patients (Jelinek, Grobusch, and Harms 2001; Jelinek et al. 1999). Further development will be needed before a home-based test, or even one that can be used by every village health worker, becomes available. Present-day tests have almost overcome the challenge of making tests technically accessible, but sample collection remains a major roadblock. Collecting blood comes with some risks for patient and health worker and safely collecting the right amount of blood without contaminating it can be tricky (Luchavez et al. 2007).

45. The subhead title is from Grabowsky 2008, 1052). Barker et al. 1986; de Vries, Kager, and Borgdorff 2004; Zurovac, Larson, et al. 2006; WHO 2006d.

46. Editors, PLoS Medicine 2006.

47. Zambia's progress was recently reviewed by Steketee et al. 2008; WHO 2008 and 2009b summarize continent-wide progress in the Roll Back Malaria campaign.

48. Bohannon 2006, 599.

49. Carson 2002; Towner et al. 1980. See also chapter 6.

50. Nabarro 1999; Balter 2000; Nabarro and Tayler 1998. For information about the more recently proposed campaign to eradicate malaria, see chapter 7 and the Gates Foundation's website: http://www.gatesfoundation.org/GlobalHealth/Pri_Diseases/Malaria/default.htm.

51. See "the Abuja Declaration and the Plan of Action" 2000. Support for the initiative is largely disbursed through the Global Fund (Campbell 2008).

52. Snow et al. 2005, 214.

53. Nahlen et al. 2005, e3; Bell et al. 2005.

54. Mwanziva et al. 2008.

55. Snow et al. 2005, 216.

56. Mboera, Makundi, and Kitua 2007; Makundi et al. 2007; Okiro et al. 2007; Steketee et al. 2008.

57. Breman and Holloway 2007.

58. van Riet et al. 2007. Based on their research on malaria epidemiology in Angola, Thwing et al. 2009 recommend that resources for preventing, diagnosing, and treating malaria be focused on areas that are fifteen kilometers or more away from the city of Luanda.

59. Goodman et al. 2007.

CHAPTER 3

1. (1844, 25), quoted in Carter 2003.

2. Snow et al. 2003; Snow et al. 2005; Snow, Korenromp, and Gouws 2004.

3. Untreated severe malaria is invariably fatal. Mortality rates for treated severe malaria are from WHO 2006c. Patients with severe malaria can present with severe malarial anemia or cerebral malaria. Severe malarial anemia is defined as having less than five grams of hemoglobin per deciliter of blood with *Plasmodium falciparum* levels of over 10,000 per ml (McElroy et al. 1999). The signs of severe malaria described here commonly manifest in children; in adults, pulmonary and renal failure are more common (Planche and Krishna 2005; Arrow, Panosian, and Gelband 2004).

4. Evans et al. 2004 reported the Ghanaian study, the 2000 Tanzania study was published by Reyburn et al. 2004, and the other Kenya, Malawi, and Tanzania studies were respectively authored by Berkley et al. 2005, Peters et al. 2004, and Blomberg et al. 2007.

5. Mtove et al. 2010.

6. In a recent study, most Gabonese children evaluated had high prevaccination titers of antibody specific for one or more influenza viruses, suggesting that they had been exposed to these viruses before the study. The researchers hypothesize that influenza occurred routinely in Gabon but was probably misdiagnosed as malaria (van Riet et al. 2007, 7035). Relapsing fever or Lyme disease was recently reported as being misdiagnosed as malaria in Togo (Nordstrand et al. 2007).

7. This is one of many examples that demonstrates that testing is more useful as a first rather than as a last resort. Cheesebrough 1984 describes existing diagnostic tests for typhoid.

8. Olopoenia and King 2000; Mirza 1995; Baker, Favorov, and Dougan 2010.

9. Ibadin and Ogbimi 2004.

10. Osler 1892; Cox 1996.

11. Nsutebu, Martins, and Adiogo 2003; Nsutebu, Ndumbe, and Adiogo 2002; Nsutebu, Ndumbe, and Koulla 2002.

12. Mensah et al. 2000, 69.

13. Personal communication. Baker, Favorov, and Dougan 2010 have coauthored an informative review on the limitations of current tests and the challenges associated with developing diagnostics for typhoid. Two more recently developed typhoid tests are Tubex and Typhidot. Both have been employed in parts of Asia where typhoid is highly endemic but, like the Widal test, the sensitivity, specificity, and positive predictivity of these tests is too low. Efforts to develop typhoid tests that could be used at the point of care are few, and in very early stages of development. Preliminary efforts demonstrate that, although they would be challenging to develop, such tests are feasible (Fadeel et al. 2004; Hatta and Smits 2007; Naheed et al. 2008; Thompson et al. 2009; Baker, Favorov, and Dougan 2010; Helen Lee, personal communication).

14. Neil et al. 2009; O-tipo et al. 2009.

15. Chanteau et al. 2003; Bertherat et al. 2007.

16. Lin et al. 2005; Basnyat et al. 2005; Basnyat 2005; Tankhiwale, Agrawal, and Jalgaonkar 2003.

17. Baker, Favorov, and Dougan 2010.

18. Leavitt 1996.

19. Feglo, Frimpong, and Essel-Ahun 2004 published the Ghana study. The Gambian situation was learned from a personal communication with staff at the Royal Victoria Teaching Hospital, Banjul, in 2006.

20. Kariuki et al. 2006; Berkley et al. 2005; Mtove et al. 2010. There are convincing, if few, studies that focus on this problem, largely from Kenya, Tanzania, The Gambia, and Malawi. Almost nothing is known about the epidemiology of this important pathogen in much of central Africa and West Africa where there are few published reports on bacteremia etiology.

CHAPTER 4

1. Korenromp et al. 2003; Levine 2004.
2. Roper et al. 2004; Wongsrichanalai et al. 2002.
3. Trape 2001; Arrow, Panosian, and Gelband 2004; WHO and UNICEF 2003.
4. "Antimicrobials" include antibacterials, antivirals, antifungals, and antiprotozoals, including antimalarials. Antimicrobials may be synthetic or obtained from natural sources. Quinine, from cinchona bark, and artemisinin, from the Chinese medicinal plant Qinghaosu (*Artemisia annua*), are antimalarials from natural sources. Chloroquine and sulfadoxine-pyrimethamine (Fansidar) are synthetic antimalarials. "Antibiotic" refers to antimicrobials derived from microorganisms, which likely represent defense systems for the source organism. Like penicillin, the first antibiotic discovered and developed for therapeutic use, most (but not all) antibiotics are antibacterials and obtained from fungi or bacteria.
5. For a more comprehensive explanation of the biological basis and clinical consequences of resistance that is accessible to nonscientists, see Levy 2002. A more detailed and technical focus on the problem in developing countries is documented in Sosa et al. 2009.
6. Sokoloff 1954.
7. Paul Ehrlich, the acknowledged pioneer of chemotherapy, first used the term "magic bullet" to refer to the body's own immune system, not to antimicrobial drugs. Antibodies, agglutinating proteins produced by the immune system, have specific targets: "The protective materials which are present in the antiserums whether they be of the ambiceptor or opsonin type, find in infected organisms their point of attach only and exclusively in the bacteria not in the tissues. These antibodies are exclusively 'parasitotrophic' and not 'organotrophic' and so it is not surprising that they seek out their targets like magic bullets" (Ehrlich 1908, translated by Brock 1999, 177). Ehrlich is clearly describing a guided missile, not a targetless weapon. Later uses of the term have lacked this precision.
8. Ehrlich 1909.
9. Domagk 1935; Fleming 1929; and Chain et al. 1940.
10. "Flesh-eating bacteria" are usually Group A hemolytic streptococci. These reports are reviewed by Miller and Bohnhoff 1950.
11. Norrby 2005; Norrby, Nord, and Finch 2005; Talbot et al. 2006; Payne et al. 2007.
12. Talbot et al. 2006; Payne et al. 2007.
13. WHO published the statement, as well as a synthesis of expert recommendations and recommendations for resistance containment in developing countries (WHO 2001b; APUA 2001).
14. Leach et al. 1999; Mulholland et al. 1999; Palmer et al. 1999; Adegbola et al. 2005.
15. Enwere et al. 2006; Hill et al. 2007.
16. Lawn, Cousens, and Zupan 2005.
17. Ishengoma et al. 2009; Tegbaru et al. 2004.

18. Blomberg et al. 2007, 3. There are WHO guidelines for empiric treatment but these should be fine-tuned in response to local susceptibility patterns, something that rarely happens in resource-limited health systems (Graham and English 2009).

19. Bryce et al. 2005.

20. Ypres papyrus, 1600 BCE, quoted by Minot and Murphy 1983.

21. Brown 1996, 952.

22. Mabey et al. 2004, 235.

23. "The Right Tools Can Save Lives" 2006.

24. Palumbi 2001; Lundqvist et al. 2007.

25. Sofowora 1982.

26. Opintan and Newman 2007; Vila et al. 1994.

27. Fleming 1929; Poupard, Rittenhouse, and Walsh 1994; NCCLS 2003. George F. Reddish modified Fleming's diffusion method by cutting circular wells so that many different agents could be evaluated against a single organism seeded throughout the plate. This approach was increasingly used as more antibiotics were discovered and resistance became more commonplace. The Reddish "cup-plate" or "hole-in-the-plate" method is still used today in the preliminarily assessment of natural products. Antibiotic-containing cylinders and tablets also have been used, to reduce variability associated with uneven boring. Subsequently, paper discs impregnated with test agent became the standard and represent the method of choice of most laboratories worldwide. Although there were earlier experiments employing antimicrobial agents in broth, Fleming should also be given credit for originating the broth-dilution method in 1929, which later provided a means for directly measuring the minimum inhibitory concentration (MIC).

28. NCCLS 2003.

29. NCCLS 1990.

30. As more agents were introduced, S. D. Garrett proposed testing only critical concentrations (so-called "breakpoint" concentrations) so that more agents could be evaluated in a single dilution experiment (Ericsson and Sherris 1971). Multipoint inoculators permit several isolates to be printed in spots on a single agar plate. Tests can be automated or accelerated to yield results from some isolates after as little as six hours' incubation, as compared to overnight incubation for traditional methods. Because disc testing uses manufacturer-assured antimicrobial discs and media, the on-site requirements for quality assurance are fewer than for dilution tests. The E-test allows MICs to be determined with a method no more complicated or labor intensive than a disc test, but it remains very expensive. Although many of the additional quality assurance requirements for dilution tests can be avoided, the E-test requires quality assurance that is equivalent to disc testing, and insufficient attention to this matter has led to inaccuracies in their use in parts of Africa (Daly et al. 1997).

31. Tegbaru et al. 2004.

32. Polage et al. 2006.

33. Ukwuoma 2004.

34. Ukwuoma 2006. Additionally, a survey of seven regional hospitals in Ghana revealed that, while culture and identification data for test isolates agreed with results obtained at the University of Ghana Teaching Hospital's Central Laboratory in Accra, discrepancies in susceptibility data were seen in between 53% and 75% of isolates that were tested separately at both locations. In the private laboratories that perform most of the continent's susceptibility testing, external quality regulation is difficult or impossible (Newman et al. 2004).

35. Brown 1996; Newman et al. 2004; Ishengoma et al. 2009.

36. WHO 1973, 1996.

37. Plowe and Wellems 1995; Wilson et al. 2005; Magnaval et al. 2006.

38. Farcas et al. 2006.
39. Attaran et al. 2004.
40. D'Alessandro, Talisuna, and Boelaert 2005.
41. Researchers and hospital laboratories can often obtain free antimicrobial discs for susceptibility testing of new antimicrobials from the manufacturing pharmaceutical company. Often, the only discs donated in this manner to public hospital labs are for antimicrobials that are not in stock at the pharmacy because they are too expensive (Okeke et al. 2007).
42. Hardin 1968; Baquero and Campos 2003; Foster and Grundmann 2005; Okeke 2009.
43. Okeke and Lamikanra 1995, 2001.
44. Alubo 2001.
45. Peeling 2007, 83; Chappuis et al. 2007.
46. "Two Accused over 'Fake' HIV Tests" 2006.

CHAPTER 5

1. Doctors accept the responsibility of providing a cure; many urban physicians simply lack the resources to deliver it. Early in the history of medicine in Nigeria, some physicians worked in communities where they could follow their patients very closely (Colonial Office 1948). In 1888, the "Adeola scandal," in which an incompletely treated woman was discharged from a colonial hospital in Lagos, Nigeria, resulted in the dismissal of three doctors at a time when there were less than fifty allopathic doctors in the entire country (Schram 1971).
2. The WHO constitution defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1948).
3. Bank-Anthony, a businessman and investor, was born in 1907 in Kinshasa and educated at the prestigious Methodist Boys' high and Christian Missionary Service grammar schools in Lagos. The "Black Englishman," who was as well known for his charm as for his wealth, was awarded the Order of the British Empire (OBE) in 1958 and knighted by Queen Elizabeth II in 1962 for services to Nigeria. He was spotlighted by *Time Magazine* in 1965 (http://www.time.com/time/magazine/article/0,9171,842145,00.html). Bank-Anthony died in 1991 and was buried in a tomb at Ayinke House. The maternity center was named for his mother.
4. After I left Ikeja General Hospital in 1991, it was upgraded to a teaching hospital for Lagos State University, so practice there is no longer representative of a secondary care center. The hospital has not achieved the capabilities of a tertiary care center such as the Lagos University Teaching Hospital, however.
5. This facility has since been closed and replaced by a new facility with amenities that approach those at Ayinke House.
6. Patients may view the hospital as a place where sick people go to die as well as to be cured. This experience is poignantly illustrated in chapter 6 of Flora Nwapa's 1966 novel, *Efuru.* Ralph Schram (1971) also describes people's mistrust of hospitals during their development in Nigeria.
7. http://www.msf.org/msfinternational/invoke.cfm?component=article&method=full_html&objectid=2E1DE387-E018-0C72-09DC38F9F6E3DBA7.
8. For more on the Angola Marburg outbreak, see "Marburg Hemorrhagic Fever—Angola (46)" (2005). The 2007 Ebola outbreak in Uganda is described by Mason 2008 and Alsop 2007.
9. Other well-known hemorrhagic viruses are Lassa fever (discussed later in this chapter) and Rift Valley fever. Crimean-Congo hemorrhagic fever virus, hantavirus, and dengue virus produce hemorrhagic fevers, although their endemic foci are largely outside of sub-Saharan Africa.

10. Max Theiler was awarded the 1951 Nobel Prize in medicine for his work on the yellow fever virus and its control. A concise review of the path to the discovery of yellow fever virus, the vectors, and an effective vaccine is provided by Oldstone 1998, 45–72.

11. Mosquitoes are traditionally controlled by destruction of their habitats, by preventing contact with humans, or by chemical killing with insecticides. Because resistance inevitably emerges, chemical control is the least viable means for containing insect vectors in the long term, but it is the means that has been most widely applied. There is increasing interest in enhancing the other two methods, applying newer technologies such as biological control, and using multipronged strategies, such as insecticide-impregnated bed nets, which add a chemical to a barrier mechanism.

12. Schram 1971; Addae 1997.

13. For example, Close 1995; Fuller 1974; Preston 1995.

14. Oldstone 1998, 199.

15. For more on the hypothesis that Ebola has an ancient origin hypothesis, see Monath 1999 and Peterson et al. 2004. The alternative hypothesis, that Ebola is a new virus, is supported by data from Walsh, Biek, and Real 2005 and Suzuki and Gojobori 1997.

16. Most documented outbreaks have affected humans, but these viruses are also deadly for nonhuman primates. Ebola virus presently represents one of the greatest threats to primate populations. The lethality of the virus for chimpanzees and other primates suggests that they are not the viral reservoir, but are incidental hosts just as humans are (Leroy, Rouquet, et al. 2004; Walsh et al. 2003).

17. It is likely that the case-free periods are shorter than is commonly thought. A small human Ebola outbreak in a remote area can easily be missed due to population isolation or diagnostic insufficiency. Exposure to the Ebola virus (detected via antibodies) has been documented among populations in which an outbreak has never been reported (Teepe et al. 1983). It is even more likely that an ape outbreak will be overlooked.

18. Preston 1995.

19. The first documented human Marburg virus infection affected a German laboratory technician who was infected by an African green monkey (*Cercopithecus aethiops*) in 1967. This lab-focused outbreak was traced to monkeys imported from Uganda. Almost a decade later, the first of many Ebola hemorrhagic fever epidemics broke out in southern Sudan and northern Zaire.

20. The course and investigation of these outbreaks is reviewed by Garrett (1994, 100–152). See also Breman et al. 1977.

21. "Ebola Haemorrhagic Fever in Zaire, 1976" (1978, 273).

22. Lapses in infection control, including needle sharing, have been seen with fully trained medical practitioners and those they supervise (Fisher-Hoch et al. 1995). Needle reuse and other unsafe practices arising from shortages of essential supplies have declined but have not been entirely eliminated. The contributions of needle reuse to the dissemination of blood-borne diseases, including HIV, in Africa remain largely open to question (Priddy et al. 2005; Gisselquist et al. 2002; Schmid et al. 2004; Kernéis et al. 2009).

23. Among the many Medline-indexed scientific papers describing the outbreak, the most detailed account is that coauthored by Idris himself, which was published in the *Sudanese Journal of Public Health* (Idris and Idris 2006).

24. Maridi fared better than Yambuku, but Sudanese epidemiologists who investigated and contained the epidemic have listed five factors that constrained its control: inadequacies of transport, communications, and health personnel; fleeing contacts; and the absence of routine or scientific testing facilities (Idris and Idris 2006).

25. The other transmission route with similarly poor prognosis is through indigenous surgical burial rites, which include cleansing of the bodies and surgical evacuation of the internal organs of the deceased, typically performed by female relatives.

26. Khan et al. 1999.

27. For the Zairian dilemma, see Guimard et al. 1999 and *Ebola—The Plague Fighters* (1996). The use of plasma therapy in Yambuku is reported in "Ebola Haemorrhagic Fever in Zaire, 1976" (1978).

28. All cases of Ebola in the outbreak were confirmed retrospectively at the CDC in Atlanta.

29. Khan, Sanchez, and Pflieger 1998.

30. "Ebola Haemorrhagic Fever in Zaire, 1976" (1978);

Garrett 1994, 127–28; Johnson, Webb, and Heymann 1978; *Ebola—the Plague Fighters* (1996).

31. In polymerase chain reaction (PCR) tests, the principle involves the use of short but specific primers to amplify a known sequence in the presence of contaminating DNA from other living organisms, including the infected human host. In a reverse-transcriptase-PCR test, nucleic acid from the virus in the form of RNA is first converted to DNA and then subjected to virus-specific PCR amplification. Sequences specific to the target virus are amplified to a level that can be stained and detected with the naked eye. The degree of amplification is proportional to the initial amount of viral RNA so that the number of viruses, or viral load, can be estimated. Because RNA can be isolated from dead viruses, samples can be shipped and test specimens can be inactivated to protect laboratory technologists. This test is sensitive and rapid enough to identify infected patients early and inform treatment.

32. Towner et al. 2004. Other RT-PCR methods have similar promise (Drosten et al. 2002; Leroy et al. 2000).

33. Muyembe-Tamfum et al. 1999.

34. Holmes 1998, 535. Other accounts suggest that a diagnosis of Ebola virus was actually confirmed within twenty-four hours (Muyembe-Tamfum et al. 1999).

35. Holmes 1998, 534. The diagnostic timeline of the hospital-amplified Ebola outbreak in Kikwit, Zaire (now Democratic Republic of the Congo) and the consequences of delay in new cases were constructed from data documented by Muyembe-Tamfum et al. 1999 and Roels et al. 1999. There were 317 documented cases of Ebola virus infection in Kikwit in 1995; 245 of these died. The epidemic peaked during the week beginning April 30 and began to decline as soon as the disease was named (Roels et al. 1999).

36. See http://www.pbs.org/wgbh/nova/teachers/programs/2304_ebola.html. Press coverage of the epidemic was unprecedented; the virus and the previously unknown town of Kikwit became known across the globe (Garrett 2001).

37. The time between documentation of the first case reporting to an allopathic health center and processing of the first blood specimens was four and a half weeks for the 1995 Ebola outbreak in Kikwit. A satellite outbreak at Mosango General Hospital was only identified retrospectively (Bonnet, Akamituna, and Mazaya 1998).

38. Antibodies against Ebola have been found in humans and other primates as far away from the central African focus of disease as Cameroon (Leroy, Telfer, et al. 2004). Data from eastern Uganda have been available since 1983 (Teepe et al. 1983). Most countries in and around central Africa should have a strategy in place for dealing with outbreaks of Ebola and other hemorrhagic viruses, since there is a reasonable chance that they could occur in the future.

39. El Tahir 1977.

40. WHO and CDC 1998, http://www.cdc.gov/ncidod/dvrd/spb/mnpages/vhfmanual/entire.pdf.

41. Cohen 2004.

42. Ibid, e59.

43. SARS, then a new virus, was essentially identified by exclusion, but ruling out known diseases with similar symptoms was only possible with laboratory and radiological testing (Zhong and Zeng 2003). See also http://www.who.int/csr/sars/casedefinition/en/.

44. Groopman 2007.

45. "Outbreak News: Ebola Haemorrhagic Fever, Uganda—End of the Outbreak" (2008); Mason 2008.

46. Diamond 2002; Woolhouse 2002; Woolhouse and Gowtage-Sequeria 2005.

47. Mason 2008; Towner et al. 2008.

48. Mason 2008.

49. Holmes et al. 1990; Paweska 2007.

50. Arthur 2002.

51. Addae 1997; Mengara 2005; Twumasi 1975.

52. Garrett 1994, 123.

53. Obadare 2005; Leader and Snyder 2006.

54. In 2005, WHO expanded the repertoire of internationally notifiable diseases from cholera, the plague, and yellow fever to include all disease epidemics that could be classified as major public health events (WHO 2005). The longer list includes potentially pandemic influenza, Ebola, and Marburg disease, even though most African caregivers lack the access to local laboratories that could confirm any of these diagnoses.

55. A focus on infection control was justified here. The Gulu outbreak was noteworthy in that health-worker infections continued after the introduction of barrier nursing (Arthur 2002), suggesting that investments in training and facilities were needed in this area. The point is not that these changes were unnecessary but that they should have been accompanied by diagnostic development.

56. Lamunu et al. 2002, 9–10.

57. Khan et al. 1999, S76.

58. Arthur 2002.

59. Mason 2008.

60. Paweska 2007.

61. Frame et al. 1970; Fuller 1974; Fisher-Hoch et al. 1995; Wright 2004; Mellor 2004; Richmond and Baglole 2003; Bausch, Sesay, and Oshin 2004.

62. In Latin, *filo* means thread, and *arena* means sand. The only other arenavirus that infects humans is the recently described Lujo virus from southern Africa (Briese et al. 2009).

63. Troup et al. 1970.

64. There have been several chronicles of the first few outbreaks of Lassa fever and early investigations surrounding them; see, for example, Garrett 1994 and Fuller 1974.

65. Frame et al. 1970.

66. Richmond and Baglole 2003; Khan et al. 2008; Fichet-Calvet and Rogers 2009.

67. Monath 1975.

68. Guerrant et al. 2005.

69. In one case, in the Nigerian city of Jos, although there was some diagnostic delay, no patients or health workers were infected (Cooper et al. 1982).

70. Fisher-Hoch et al. 1995, 859.

71. See Bausch et al. 2001; Richmond and Baglole 2003. Khan et al. 2008 listed twenty-seven potential confounders, including systemic bacterial infections and parasitemias such as malaria. According to Carlos "Kent" Campbell, a malaria and Lassa researcher and Lassa fever survivor, "If you weren't paying close attention, you wouldn't be able to distinguish Lassa from malaria. They look exactly the same until the tail end of Lassa when the hemorrhaging starts" (Garrett 1994, 93).

72. Mortality rates from Khan et al. 2008. State of diagnostic facilities in Nigeria quoted in "Lassa Fever—Nigeria (05)" (2009). According to Inegbenebor, Okosun, and Inegbenebor 2010, "Irrua Specialist Teaching Hospital [in midwestern Nigeria] . . . was designated a special center for the treatment of Lassa fever. . . . Because of late presentation, a number of people still die even when treatment is offered."

73. Sierra Leone: quote from Richmond and Baglole 2003, 1273; Nigeria: Inegbenebor, Okosun, and Inegbenebor 2010.

74. Khan et al. 2008. Per capita expenditure on health from the WHO statistical information system at http://www.who.int/whosis/en/index.html.

75. Garrett 1994; Alibek and Handelman 1999.

76. According to Laurie Garrett (1994), "For years separate and often isolated research was conducted, and both superpowers [the United States and the Soviet Union] would eventually shut down their West African Lassa laboratories, leaving the Africans the ultimate losers" (1994, 194). A considerable body of U.S. data is published, and there is continuing evidence in the scientific literature of American efforts to understand the disease. Less is known about the USSR's research program. Neither of these initiatives resulted in a lasting diagnostic service for Kenema.

77. Positive predictive value of 0.81/1.00 based on fever, pharyngitis, retrosternal pain, and proteinuria (McCormick et al. 1987).

78. Ibid.

79. Mellor 2004.

80. Paweska 2007.

81. Bausch et al. 2000.

82. Mellor 2004; Bausch, Sesay, and Oshin 2004; Wright 2004.

83. Khan et al. 2008.

84. Richmond and Baglole 2003.

85. In 1957, there were international yellow fever vaccine laboratories in Yaba, Lagos, Nigeria; Dakar, Senegal; and Johannesburg, South Africa (Schram 1971). Yellow fever research was also conducted in Ghana.

86. Kirkland 2003, 6.

87. Harrison, Simonsen, and Waldman 2008.

88. Guimard et al. 1999.

89. Rouquet et al. 2005.

90. Leroy et al. 2005; Towner et al. 2007.

91. "Outbreak of Ebola Haemorrhagic Fever in Yambio, South Sudan, April–June 2004" (2005, 374).

92. Khan et al. 2008; "Lassa Fever—Nigeria (05)" (2009); Beatty et al. 2008.

CHAPTER 6

1. *Guardian* (Nigeria), 19 February 2005; Ojo 2004.

2. Ojo 2004.

3. Syphilis diagnosis in pregnant women (Terris-Prestholt et al. 2003; Watson-Jones et al. 2005); other publications detailing the need for and challenges facing diagnosis of diseases caused by sexually transmitted bacteria (Aledort et al. 2006; Peeling et al. 2006); bacterial sexually transmitted diseases and HIV susceptibility (White et al. 2008).

4. According to Chigwedere et al. 2008, who measured lives saved in nearby Botswana and Namibia, over three hundred thousand South African deaths can be attributed to denialism by the Mbeki government.

5. The phrase "lies, damned lies and statistics" was attributed to the British politician Benjamin Disraeli by the American writer Mark Twain (Samuel Clemens) in 1907. In that context, Twain/Disraeli listed three kinds of lies, among which statistics was the worst because it was the most deceptive. Other sources for the phrase are documented: in 1894, a physician named Pierce gave a paper to the Philadelphia Medical Society in which he characterized this triad of lies as a "proverbial" phrase.

6. Vaughan 1991; Hunt 1999.

7. See Vaughan 1991.

8. Davies 1956.

9. See Vaughan 1991, 132–44. Vaughan also describes the career of Albert Cook, a government-appointed crusader against "diseases of immorality" in the 1920s (1991, 137). Cook's retraction of his earlier conclusions only appeared in "grey" literature that is not listed in the principal medical indexes, such as Medline, and therefore unlikely to be read. A detailed reanalysis of the "epidemic" was presented by J. N. Davies (1956), years after most of the major players and their readers had died. Yaws is a skin disease caused by *Treponema pallidum* subspecies *pertenue. T. pallidum* subspecies *pallidum* is the causative organism of syphilis, the sexually transmitted disease. The two organisms are remarkably similar and challenging to delineate, even with present-day technology. It is possible that the Buganda epidemic was yaws, rather than syphilis. Another prevailing hypothesis is that, because yaws was well understood at the turn of the century, the Buganda epidemic must have been a treponemal disease that is different from syphilis and yaws but not sexually transmitted. Either way, it is clear that sexual intercourse was not the transmission mechanism, as the original chroniclers assumed. In a possible attempt to exonerate them, it has been claimed that "the pioneers of medicine in Uganda…worked under difficult and often disheartening conditions with courage and enthusiasm" (Davies 1956). The entire episode is unfortunate on many counts. Had the physicians been willing to acknowledge that the sick Baganda were possibly infected with a less virulent form of *T. palladium,* years later biological scientists might have used the causative organisms as a means to understand the pathogenesis of syphilis or even as the basis for a syphilis vaccine.

10. Murru 2004.

11. Ogunbodede 2005.

12. Nonspecificity of early tests has been studied by Lantin, Peitrequin, and Frei 1987 and Biggar et al. 1985. Newer tests have been developed as a result but second-, third-, and even fourth-generation antibody-based tests have been shown to underperform in Africa, making confirmatory testing essential. Cross-reacting antigens come from infective agents that are common in Africa, such as malaria and schistosomiasis (Biggar et al. 1985; Behets et al. 1991; Everett et al. 2010).

13. Alikor and Erhabor 2006.

14. Different African countries appear to have sustained very different AIDS epidemics, as summarized by Iliffe 2006. Extrapolation from the worst single-country data to the entire continent has exacerbated the myths surrounding AIDS.

15. Meda et al. 1999.

16. Chigwedere and Essex 2010.

17. Granich et al. 2009.

18. Pincock 2006; Olukoya and Ferguson 2003.

19. Schoofs 1999.

20. Oshisada 2006.

21. Adio 2004.

22. "Progress toward Strengthening Blood Transfusion Services—14 Countries, 2003–2007" (2008).

23. Iliffe 2006; Miles 2003; Gisselquist et al. 2004; Schmid et al. 2004.

24. Spurious treatments were also widely touted and eagerly patronized by AIDS patients in California in the 1980s. Then, as in West Africa today, diagnostic insufficiency and the absence of effective treatments allowed many to prey on the terminally ill (Shilts 1988).

25. Sources of information for traditional medical practitioners who treat patients with sexually transmitted diseases (adapted from Elujoba, Fadairo, and Irinoye 2002): the practitioners generally had local names for sexually transmitted syndromes and twenty-eight (54%) had a Yoruba term for AIDS. These terms included *Atosi egbe* (sexually transmitted disease with weight loss), *Arun igbalode* (disease of the times), and *Eedi* (the curse).

26. Elujoba, Fadairo, and Irinoye 2002.

27. Dodd 1996; Kwena 2004; Bateman 2006.

28. Ebenezer Obadare and Iruka Okeke have studied Abalaka's claim and its sociopolitical and biomedical significance. This analysis will be published in the scholarly literature.

29. Abalaka 2004. What appears to be a duplicate publication appeared in a Chinese journal, *Zhonghua Nan Ke Xue* (Abalaka 2005), three months later, again accompanied by an editorial (Huang and Lu 2005).

30. Abalaka 2004, 3820.

31. "Progress toward Strengthening Blood Transfusion Services—14 Countries, 2003–2007" (2008).

32. Kim and Gilks 2005.

33. Bizuwork et al. 2007; Cohen 2007; Mugyenyi et al. 2010. For more on the causes and consequences of slow antiretroviral roll-out across Africa, see Ford, Mills, and Calmy 2009.

34. WHO 1988; Amirali, Moshiro, and Ramaiya 2004. Patients with less common AIDS-related syndromes such as HIV-associated dementia are very likely to be missed, particularly when nonspecialists perform the diagnosis (Kvalsund et al. 2009).

35. Rapatski, Suppe, and Yorke 2005.

36. Araya et al. 2004.

CHAPTER 7

1. Berhane 2004.

2. For example, eleven West African countries have halted the transmission of river blindness, preventing six hundred thousand cases of blindness and reclaiming twenty-five million hectares of previously infested and now arable land (Levine 2004).

3. Unfortunately, in many parts of Africa, vaccines and chemicals have been used instead of broad-based prevention strategies, rather than in coordination with them.

4. Aylward et al. 2000; Aylward and Birmingham 2005.

5. Stetten 1978; even within the fiber matrix of human scabs, the virus cannot survive longer than two or three years.

6. Oldstone 1998.

7. Quoted in Robottom 1991, 8.

8. Adebayo Lamikanra, personal communication; Vaughan 1991; Oldstone 1998; Schram 1971, 159.

9. Jenner 1798. Jenner was not the first to make this observation. At least two prior examples of people who administered vaccinia to people because they hypothesized that it was protective are known in the United Kingdom: Benjamin Jetsy (1774), a British farmer, and Peter Plett, a schoolmaster from Holstein (1792) (Stetten 1978). Jenner was the first to investigate this idea experimentally and generate supporting data. For this reason, he is given credit for the discovery. Jenner also made his vaccine available for widespread evaluation.

10. Stetten 1978; Oldstone 1998.

11. Commentators called 1965 the "international cooperation year" (Levine 2004).

12. See Stetten 1978 for a smallpox eradication timeline.

13. A laboratory infection occurred in Birmingham, United Kingdom, in 1978.

14. Barrett 2004.

15. Stetten 1978.

16. Malian epithet for guinea worm (Levine 2004).

17. In 1991, the World Health Assembly passed a resolution supporting eradication: "Encouraged by the considerable progress achieved in many countries towards elimination of the disease; Aware that country-by-country elimination of dracunculiasis is considered to be the last step before global eradication can be declared…URGES the

director general [of WHO]…to support global efforts to eradicate dracunculiasis during the 1990s" (Forty-fourth World Health Assembly, Agenda item 17.2: Eradication of Dracunculiasis, Resolution WHA44.5, 13 May 1991, http://www.who.int/dracunculiasis/eradication/WHA44.5.pdf).

18. Sam-Abbenyi et al. 1999.

19. Iriemenam, Oyibo, and Fagbenro-Beyioku 2008; CDC 2010.

20. For historical overviews, see Oldstone 1998 and Oshinsky 2005.

21. Marx, Glass, and Sutter 2000; Minor 2004.

22. "Laboratory Support for Poliomyelitis Eradication: Memorandum from a WHO Meeting" (1989). The network has strengthened surveillance for other viruses and will need to continue to track polio viruses after polio vaccination is discontinued because immunocompromised patients can shed vaccine strains, that can on rare occasions mutate to disease-causing forms (Hull and Aylward 1999; Nsubuga et al. 2002).

23. http://www.cdc.gov/mmwR/preview/mmwrhtml/mm4908a3.htm. Appropriately designed eradication campaigns can build diagnostic infrastructure that has significant impact on the control and treatment of other diseases (Levine 2004).

24. Roberts 2009a, 2009b.

25. Oldstone 1998.

26. Scott et al. 2007; Helfand et al. 2005. Some studies suggest that other subpopulations may need to be vaccinated before nine months, although data are few (Tapia et al. 2005).

27. "Progress in Reducing Global Measles Deaths, 1999–2004" (2006); "Effects of Measles Control Activities, African Region, 1999–2005, "*MMWR* weekly 55 (37): 1017–21; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5537a3.htm?s_cid=mm5537a3_e.

28. These did not include a few high population countries such as the Democratic Republic of Congo and Nigeria. See data at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5537a3.htm?s_cid=mm5537a3_e#fig.

29. Hopkins 1976; Zahra 1956.

30. Agadzi et al. 1983, 1985.

31. McLean 1998; Aylward et al. 2000; Aylward 2006; "Update: International Task Force for Disease Eradication, 1990 and 1991" (1992).

32. Molyneux, Hopkins, and Zagaria 2004, 347.

33. Adegbola et al. 2005; Howie et al. 2007.

34. Sow et al. 2005.

35. Shearer et al. 2010 identified proximity to a country that has introduced the vaccine as a principal determinant of Hib adoption. I made the link to surveillance by comparing data on one year olds vaccinated against Hib between 1999 and 2007 (from the WHO statistical database at www.who.int/whosis), with published studies on Hib surveillance indexed by Medline.

36. Tan 2003; Musher 2006.

37. Gordon et al. 2003; Antonio et al. 2008; Adegbola et al. 2006.

38. Musher 2006; Pelton, Loughlin, and Marchant 2004; Moore et al. 2008.

39. The list of artists who fell victim to tuberculosis includes Frederic Chopin at age thirty-nine in 1810; John Keats at thirty-six in 1831; Emily Bronte at twenty-two in 1840 and Anne Bronte at twenty-nine in 1849; Heinrich Heine at fifty-nine in 1856; D. H. Lawrence at forty-five in 1930; and George Orwell at forty-seven in 1950.

40. Wainwright 1991; Feldman 2000.

41. WHO 2004.

42. Xu, Jin, and Zhang 2000.

43. WHO 2003. Some low-grade infections can be missed by sputum smear microscopy, which only detects bacterial concentrations above one-thousand bacteria per milliliter. More sensitive tests, including culture, enzyme-linked immunosorbent assays

(ELISA), and PCR, have been advocated, but implementation is difficult in rudimentary laboratories. Culture traditionally requires at least eight weeks and a Biosafety Level 3 laboratory. PCR has been successfully used at a research institute in Ghana but, like ELISA, it is presently too expensive for routine use (Wilson et al. 2003).

44. Yimer, Bjune, and Alene 2005.

45. Lawn, Afful, and Acheampong 1998; Steen and Mazonde 1998; Needham et al. 2001; Lienhardt et al. 2001.

46. Nicholls 2005.

47. WHO 2006b; Singh, Upshur, and Padayatchi 2007.

48. Basu et al. 2009; Dowdy et al. 2008; Basu et al. 2007. The inception of the epidemic is reviewed by Singh, Upshur, and Padayatchi 2007.

49. Smolinski et al. 2003.

50. Cox et al. 2006.

51. Gandhi et al. 2006; Basu et al. 2007; Singh, Upshur, and Padayatchi 2007; Jones, Hesketh, and Yudkin 2008.

52. STOP-TB 2006.

53. Johnson et al. 2008; Pai, Ramsay, and O'Brien 2008.

54. Pai et al. 2009; Pai and O'Brien 2008; Perkins, Roscigno, and Zumla 2006.

55. Paramasivan et al. 2010.

56. Institute of Medicine (U.S.) Committee for the Study on Malaria Prevention and Control: Status Review and Alternative Strategies and Oaks 1991; Carson 2002; Needham and Canning 2003.

57. The intense endemicity in Africa, the hypervirulence of the parasite *P. falciparum,* and the resilience of its vector *Anopheles gambiae* were important roadblocks to eradication and still present serious challenges to malaria control on the continent: "British Contributions to Medical Research and Education in Africa after the Second World War" (1999); Gallup and Sachs 2001; Arrow, Panosian, and Gelband 2004.

58. Bill and Melinda Gates Foundation 2007; Roberts and Enserink 2007.

59. Roberts and Enserink 2007, 1544.

60. Hoffman 2000, 1509.

61. Aylward et al. 2000.

CHAPTER 8

1. Nuland 1989, 420.

2. Tornheim et al. 2007, 541. The Yambuku investigation is documented in "Ebola Haemorrhagic Fever in Zaire, 1976" (1978).

3. Garrett 1994, 197.

4. For example, see Blair 1956, 258. Meredith Turshen (1984) acknowledges that diagnostic precision and medical record-keeping showed gradual improvement late in the colonial period, but they never reached optimal standards and have declined considerably in many African countries from the 1970s.

5. Mandomando et al. 2007.

6. Lamikanra, Okeke, et al., unpublished data in preparation for scholarly publication; Mandomando et al. 2007.

7. Feierman, Janzen, and Joint Committee on African Studies 1992, 18.

8. Curtin 1990; Addae 1997.

9. Curtin 1990.

10. Mortality rates for European civilians in Cameroon declined from 69 per 1,000 in the period 1893–1901 to 31 per 1,000 in 1903–12 (Curtin 1990).

11. Addae 1997; Packard 2000; Vaughan 1991.

12. Curtin 1990; Addae 1997.

13. Addae 1997, 185.

14. Ibid., 189.

15. Cited in ibid., 87–88. In 2004, most countries in sub-Saharan Africa had between <1 and 2 laboratory health workers per 10,000 population while in the Middle East and North Africa, the range was 2–7 (in 2001/2002, New Zealand, Finland and the United States respectively had 10, 20, and 23). Data from the WHO statistics database www.who.int/whosis.

16. Through their explorations, and by linking isolated areas by road and rail, colonialists facilitated the rapid spread of previously localized infectious conditions among previously nonimmune populations. Europeans imported tuberculosis and may have brought other diseases to Africa (Kiple 1993). Colonialists contributed less directly to the infectious disease burden by lowering nutritional status, first by substituting cash crops for food crops and later by introducing infant formula.

17. Vaughan 1991; Worboys 2000.

18. Dispensaries mostly served Africans. Europeans were discouraged from residing too far from towns with European quarters that were equipped with hospitals (Addae 1997, 30–31).

19. Schram 1971, 349. In contrast, both Western and indigenous doctors receive at least eighteen years of formal education and apprenticeship.

20. Colonial Office 1948; Brieger et al. 2004.

21. Ferguson 2007.

22. Packard 2000; Prins 1989.

23. "British Contributions to Medical Research and Education in Africa after the Second World War" (1999).

24. Zahra 1956, 931.

25. Oshinsky 2005, 71; emphasis added.

26. Suit No NIC/8/2006 (2008).

27. Twumasi 1975. See also Turshen 1984 for a critique of the emphasis on curative medicine in Tanzania.

28. Twumasi 1975, plate 20.

29. Ibid., 85.

30. Ibid.

31. Twumasi 1975; Turshen 1984; Addae 1997.

32. Quoted in Porter 1998, 679.

33. Nkrumah 1963, 163. The section title is an adaptation of a more popular Nkrumah quote made in response to a question about his allegiance to the United States or the Soviet Union: "We face neither East nor West; we face Forward."

34. Verhoef and Fluit 2006.

35. Barker et al. 1986; Gicquelais et al. 1990.

36. Barker et al. 1986, 231; Pettersson, Wigzell, and Perlman 1987.

37. Although almost a third of these people are mortuary staff, this includes pathologists and a large number of technicians, scientists, and consultants who work at the bench.

38. Kim 2005, 545.

39. PATH 2008; UNICEF and WHO 2009.

40. Kebede and Polderman 2004.

41. Vaughan 1991, 155.

42. Dineva et al. 2005; Panhotra et al. 2005; Prati 2006.

43. This system already operates for vaccines and drugs. For example, ivermectin, a potent, broad-spectrum antiparasitic and antihelminthic (deworming) drug, has a considerable veterinary market. Ivermectin has earned so much income from veterinary use

in the West—an estimated US$1 billion annually—that its innovator company, Merck Sharp and Dome, has been able to donate the drug to control programs in Africa and South America (Omura and Crump 2004; Geary 2005).

44. Malaria (Usdin, Guillerm, and Chirac 2006); meningococcal meningitis (Djibo et al. 2006; Chanteau et al. 2006); leishmaniasis (Diane et al. 2006); and plague (Chanteau et al. 2003).

45. Bosompem et al. 1997.

46. Usdin, Guillerm, and Chirac 2006.

CONCLUSION

1. Ishengoma et al. 2009.

2. Newman et al. 2004.

3. Polage et al. 2006.

4. Guyon et al. 1994; Reyburn et al. 2008.

5. Reyburn et al. 2008.

6. Megan Vaughan (1991) describes the layout of a yaws eradication clinic to illustrate what I call the conveyor belt mode. The author of the paper describing this system, which was built for mass health care delivery, stated that "the system has been aptly described as a 'sausage machine'" (Zahra 1956, 932). The description could not have originated in Nsukka, Nigeria, where the clinic was located, since sausages were unknown there. Vaughan concludes: "Though colonial biomedicine, and colonial states more generally, 'unitized' their subjects, they did not 'individualize' them for…there was a strong strand of thinking which held that Africans were, by definition, hardly capable of being individuals at all" (Vaughan 1991, 202–3).

7. See Turshen 1984; Twumasi 1975; and Obadare 2005.

8. Phillips, Van Bebber, and Issa 2006.

9. Shillcutt et al. 2008 modeled the cost-effectiveness of malaria diagnostics. They find that at low to medium prevalence, diagnostics are cost effective and cost-saving. At very high prevalences, using diagnostics does incur marginal additional costs in their model. However, they acknowledge that the model assumes that diagnostics are *only* used for malaria and that costing parameters used are conservative. Additionally, they do not include the cost of selective pressure, which promotes costly resistance in their analysis. Other studies illustrating the cost-effectiveness of malaria testing are detailed in chapter 2.

10. Garrett 1994, 198. Procuring anything in Africa today can be difficult, and diagnostic reagents present a particularly formidable challenge, since many are heat labile and need a cold chain for shipment. If routine diagnostic laboratories were dotted around the countries in which they exist, the most basic and bulky materials could be obtained from local suppliers and distributors. Interventions that focus on eradicating delays mediated by local customs officials could also be implemented specifically for diagnostics, analogous to expedited clearance for vaccine shipments.

11. The chairman of the Medical Laboratory Science Council of Nigeria, Professor Dennis Agbonlahor, remarked: "In University College Hospital (UCH), Ibadan, grouping antisera were produced in large quantities in the 1970s and 1980s by Medical Laboratory Scientists. Similarly, in the National Veterinary Research Institute, VOM, various culture media for the multiplication and maintenance of bacterial organisms were produced by Medical Laboratory Scientists. All these have been abandoned today in preference for imported ones, which are not necessarily better than locally produced ones" (quoted by Ukwuoma 2006).

12. Farmer 2004; Farmer et al. 1999; Scrimshaw 1974.

13. See Wolman et al.'s (2000) review of diagnostic test development. In 2008, the Quidel Corporation of San Diego manufactured rapid point-of-care diagnostics for influenza, respiratory syncytial virus, *Helicobacter pylori,* and Group A streptococci. See http://www/quidel.com/products/product_list.php?cat=1&by+state_disease&group=1. Following the 2002 anthrax spore attacks, scientists designed a rapid test to allow U.S. postal workers, who are not scientists, to screen mail for *Bacillus anthracis.* Similar methodology was subsequently used to rapidly identify Marburg-infected patients in Angola and patients with Rift Valley fever in Kenya (Ulrich et al. 2006; Duse 2008).

14. Maryke Henton, personal communication. See also http://en.bvt.fr/p-bvtfrpuben/display.aspx?srv=p-bvtfr&typ=pub&lang=en&cmd=view&style=styles/specie.xsl&select=PRODUCT[@IDeqPRODUCT_108].

15. Nwaka 2005; Commission for Africa 2005.

16. WHO 2006a.

17. For example, see the molecular lab-in-a-case marketed by Smith diagnostics, http://www.smithsdetection.com/eng/veterinary_diagnostics.php. For reviews that outline how new technologies can advance the development of appropriate diagnostics, see Perkins and Bell 2008 and Mabey et al. 2004.

18. Mtove et al. 2010. The test employed at the rural Tanzanian hospital is described at the manufacturer's website, http://www.hemocue.com/index.php?page=3002.

19. Michel et al. 2006; Boehme et al. 2007.

20. Peeling et al. 2006.

21. Okeke and Wain 2008.

22. Masum et al. 2007; Singer et al. 2008; Bosompem et al. 1997; Koukounari et al. 2009; Mathebula et al. 2009.

23. In addition to facilities, African scientists require funding to procure and maintain consumables, equipment, and services necessary for their research as well as networking, grant writing, and publication assistance (Okeke and Wain 2008; Mboya-Okeyo, Ridley, and Nwaka 2009; Kwabena Bosompem, personal communication).

24. Kennedy 2003.

25. Schram 1971; Addae 1997; Ojo 2004; Muula and Maseko 2006.

26. Breslauer et al. 2009; Bellina and Missoni 2009; Zimic et al. 2009.

27. Ihekweazu, Anya, and Anosike 2005; Berhan 2008; Larsen 2008.

28. Packard 2000, 106.

29. van den Brandhof et al. 2006.

30. Hampton et al. 1975.

31. Wolman et al. 2000.

32. van den Brandhof et al. 2006.

33. IID 2000; Hennessy et al. 2004.

34. van den Brandhof et al. 2006.

35. Bello et al. 2004; Andre et al. 2005; and personal communication from staff at Obafemi Awolowo University Teaching Hospital, Ile-Ife.

36. Million 2006.

37. Acute respiratory infections, AIDS, diarrhea, malaria, sexually transmitted infections, and tuberculosis ("The Right Tools Can Aave Lives" 2006).

38. Okeke et al. 2007.

39. Gillis 2005. Schistosomiasis (Kwabena Bosompem, personal communication); typhoid (Baker, Favorov, and Dougan 2010); *Haemophilus influenzae* type B (Shearer et al. 2010).

40. Jones et al. 2008.

41. Paramasivan et al. 2010.

42. Severe acute pneumonitis among deployed U.S. military personnel—Southwest Asia, 2003. This outbreak turned out to be noninfectious; however, justification for a

diagnostic facility was maintained because diagnostic support was needed for treatment and there was a potential threat of biological attack.

43. Craft and Riddell 2005. The labs were set up at locations as diverse as a makeshift building at the hospital that had served the Iraqi elite prior to the overthrow of Saddam Hussein. Before the establishment of these facilities, available diagnostic capabilities at the best sites were limited to blood smears for malaria, other slide parasitology, and Gram stain to visualize some bacteria. These facilities were inadequate but were equivalent to or better than those available in most sub-Saharan African countries. The U.S. military deemed it essential to provide on-site facilities for the culture and susceptibility testing of bacteria commonly implicated in community- and hospital-acquired infections and for serological tests for common viruses. A diagnostic laboratory entirely dependent on continuous supply and support from abroad is efficient over a short period of time, with assured procurement of supplies. Over the long term, this setup is expensive, impracticable, and typically unsustainable.

44. Barrett 2006, 181.

45. Jones et al. 2008.

46. Articulated by Michael Kazatchkine (2007) of the Global Fund in an interview published in the Bulletin of the World Health Organization.

47. In 1998, a £1 million grant from the British Department for International Development to the Malawi health services to support development of medical laboratory services was equivalent to 40% of the country's health budget for 2005–06. This sum was very useful, but still too small to alleviate diagnostic insufficiency at the grassroots (Muula and Maseko 2006).

48. WHO Regional Office for Africa 2008, 1.

49. Attaran 2005.

50. Mabey et al. 2004.

51. Data presented by Ishengoma et al. 2009, citing documents from the Tanzanian Ministry of Health.

52. Declaration of Alma-Ata 1978.

53. Ohrt et al. 2007.

54. Larsen 2008; Cohen 2007; Paramasivan et al. 2010.

55. The declaration states that "in order to improve and sustain access to laboratory services, there must be an integration of laboratory support for tuberculosis, malaria and HIV disease programs" (WHO Regional Office for Africa 2008, 2). It does, however, go on to define this as "part of the greater health system."

56. A century ago, medical research institutions provided clinical diagnostic services and produced biomedical reagents and vaccines. The Accra research laboratory was renowned for its work on plague following a 1908 epidemic, but also produced smallpox vaccine and provided clinical diagnostic services (Addae 1997, 183). Two decades later, laboratory services in Ghana were restructured so that diagnostic services were separated from research centers (Addae 1997, 188). Although the research institution continued to provide expertise and support for diagnostic services, diagnostic laboratory staffing was always poor, and patient-centered labs were gradually eroded. Today, the Noguchi Medical Research Institute is an international center of excellence for tropical disease research, while the Korle Bu teaching hospital laboratory struggles to maintain its uncharacteristically broad offerings of diagnostic services for its patients. The vast majority of patients who do not access tertiary care have few options for diagnostic support.

57. Feary et al. 2005.

58. Newman et al. 2004; Mutanda, Omari, and Wamola 1989; Ukwuoma 2004.

59. Hopkins, Asiimwe, and Bell 2009.

60. Laboratory safety must also be stepped up to assure the well-being of workers, patients, and the wider community.

61. Polage et al. 2006, 529.

62. Rather than the pain from the needle, patients are reluctant to undergo blood tests because of the loss of blood, which has spiritual as well as physiological significance in many cultures. The motives for drawing blood are often considered sinister, and include international blood trafficking conspiracy theories (Geissler et al. 2008; Masiye et al. 2008; Mfutso-Bengo et al. 2008).

63. Masiye et al. 2008; Mfutso-Bengo et al. 2008.

64. Many successful African biomedical science programs are initiated and sustained from the outside. However, Africa-led programs have great potential for sustainability, growth, and translational impact ("Science and Africa: A Message to the G8 Summit" 2005; Okeke and Wain 2008; Zumla et al. 2010).

65. African Network for Drugs and Diagnostic Innovation (Mboya-Okeyo, Ridley, and Nwaka 2009). Wellcome Trust African Institutions Initiative website, http://www.wellcome.ac.uk/Funding/Biomedical-science/International-funding/Global-health-research/WTX055734.htm.