

Chapter 1

Major Infectious Diseases: Key Messages from *Disease Control Priorities, Third Edition*

King K. Holmes, Stefano Bertozzi, Barry R. Bloom, Prabhat Jha, Hellen Gelband, Lisa M. DeMaria, and Susan Horton



INTRODUCTION

Infectious diseases were responsible for the largest global burden of premature death and disability until the end of the twentieth century, when that distinction passed to noncommunicable diseases. Over the previous centuries, global pandemics of infectious diseases, such as smallpox, cholera, and influenza, periodically threatened the survival of entire populations. At least as early as the late 1800s, improved living conditions (such as better sanitation and piped water supplies), particularly in high-income countries (HICs), began to drive down the infectious disease burden.

By the mid-twentieth century, safe, effective, and affordable vaccines and the increasing availability of antibiotics had further reduced the toll of infectious diseases in HICs. Not until the second half of the twentieth century did large-scale efforts begin to better control infectious diseases in low- and middle-income countries (LMICs), where the infectious disease burden was greatest and highly varied. These efforts included a global commitment to immunize the world's children against the major infections for which vaccines are available and global campaigns to control malaria and diarrheal disease. The International Health Regulations of the World Health Organization (WHO) represent a key agreement among 196 countries to implement metrics and measures to detect and control outbreaks of infectious diseases and to prevent pandemics (World Health Assembly 2005).

Global under-five mortality fell by almost two-thirds (from 14 percent to 5 percent) between 1970 and 2010 (Norheim and others 2015). In 1980, smallpox, responsible for 300 million–500 million deaths in the twentieth century, was declared to be the first disease eradicated from the planet following a global immunization campaign led by the WHO. Wild Poliovirus has been eliminated from all but three countries (Afghanistan, Nigeria, and Pakistan) and currently is the focus of a major eradication program.

The decline of the vaccine-preventable diseases has contributed to a recognition of the potential for using vaccines to prevent other infectious diseases, including human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), malaria, hepatitis C, and a variety of neglected tropical diseases (NTDs). Hepatitis B and C substantially increase the risk of death from cirrhosis and liver cancer. The effect of viral hepatitis is significant. Indeed, an important recent study (Stanaway and others 2015) found that viral hepatitis led to an estimated 0.9 million deaths in 1990 (including hepatitis-caused deaths from cirrhosis and liver cancer). Furthermore, this number has been increasing rapidly—to an estimated 1.5 million deaths in 2013—despite the fact that hepatitis B is a vaccine-preventable disease and that hepatitis B and C are both treatable.

Emerging pandemic viral infections remain a constant threat, many entering the human population from

contact with animals. The most recent such infections include SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), and Ebola and Zika viruses (Madhav and others 2018) as well as, perennially, influenza and chikungunya infections. Compared with antibiotics to treat bacterial infections, relatively few antiviral drugs have been developed to treat these emerging viral infections. Therefore, the most important intervention is to break the chain of transmission. A global increase in antibiotic-resistant bacteria includes a small but growing number that are resistant to most or essentially all of the available antimicrobials.

Spectacular progress has been made in reducing mortality from most infectious diseases (table 1.1). For example, in low-income countries (LICs) from 2000 to 2010, the number of deaths before age 70 years from HIV/AIDS, TB, and malaria fell by 46 percent, 35 percent, and 36 percent, respectively (Norheim and others 2015). Rapid progress was also reported in other country income groups. However, table 1.1 shows also that if the death rates of 2010 remain static, about 5.1 million people will still die in 2030 from these three conditions and from other communicable diseases, many of which are concentrated in LMICs. In contrast, mortality in HICs from these conditions (except for HIV/AIDS) will be relatively small, although major pandemics of other pathogens are not predictable. Hence, infectious diseases will remain a major threat to humankind, especially in LMICs, requiring vigilance, surveillance, and new interventions of all types.

APPROACHES TO INFECTIOUS DISEASE CONTROL IN THE TWENTY-FIRST CENTURY

Vaccines and curative treatments for some of the major infectious diseases have existed for decades. Many of them are relatively inexpensive and highly cost-effective, yet many are underused because of cost and lack of access attributed to poorly functioning health care systems. New drugs and vaccines will continue to be the mainstays in preventing and treating infections, but delivery of such interventions will be critical to driving down the burden of infection.

An ultimate goal for selected infections is eradication. To date, only two diseases—smallpox in humans and rinderpest in cattle and other ruminant animals—have been eradicated. Elimination of polio, yaws, and Guinea worm infections is being pursued. This is a more distant but still possible goal for malaria (Shretta and others 2017). A handful of other infections—such as measles, mumps, rubella, lymphatic filariasis, and cysticercosis—are candidates for elimination because of disease characteristics or the available means to control them (CDC 1993). Those infectious diseases that persist require continued effort to develop new drugs and vaccines for treatment and prevention as well as strategies that allow such treatments to be used most effectively across the globe. Despite the development of new drugs to combat infectious diseases, antimicrobial resistance is threatening to remove many of the tools in our current armamentarium.

Table 1.1 Projected 2030 Mortality and 10-Year Trends for Selected Infections, by Country Income Group

Cause	Deaths in 2030 (millions)	Change (% per decade) ^a	Deaths in 2030 (millions)	Change (% per decade) ^a	Deaths in 2030 (millions)	Change (% per decade) ^a	Deaths in 2030 (millions)	Change (% per decade) ^a	Deaths in 2030 (millions)
	Low income		Lower middle income		Upper middle income		High income		Global ^c
HIV/AIDS	0.92	-46	0.76	0	0.41	17	< 0.01	—	2.10
Tuberculosis	0.32	-35	0.65	-43	0.14	-52	< 0.01	—	1.12
Malaria	0.37	-36	0.33	-28	0.02	—	< 0.01	—	0.73
Other communicable diseases ^b	0.35	-23	0.59	-15	0.14	-30	0.05	—	1.13
All causes	8.62	-24	18.11	-16	11.60	-23	3.00	-16	41.33

Source: Norheim and others 2015.

Note: — = not available; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome. Table estimates the number of deaths before age 70 years (age 0–69 years) that would occur in 2030 if the rate of change (percentage per decade) during 2000–10 were to continue for standardized death rates of those under age 70 years in each country income group (as classified by the World Bank).

a. "Change (% per decade)" = percentage change during 2000–10.

b. "Other communicable diseases" mostly align with other infectious conditions covered in this volume (such as hepatitis, sexually transmitted infections, and neglected tropical diseases) but not completely for some diseases (for example, meningitis).

c. Global totals are by summation of each of the four regions.

Infection Control: Targeting and Integration of Specialized Services

One approach—targeting settings and populations with the highest transmission rates—is being used to improve HIV/AIDS control. The continued emergence of new pandemics, like Ebola, will be addressed with similarly targeted approaches. However, for the ongoing, highly prevalent infections in LMICs—TB, hepatitis, sexually transmitted infections (STIs), malaria, typhoid, and other febrile illnesses—the future lies in improving and integrating services at the primary care level and up the chain to the highest levels of hospital care.

The high incidence of comorbidities—such as TB and viral hepatitis in immunocompromised persons with HIV infection—calls for integration of HIV, TB, and viral hepatitis diagnosis and treatment. Patients who are seen in STI clinics and their sex partners have an elevated risk of having another STI, such as HIV infection. Therefore, integration of HIV testing, care, and evaluation of sex partners into all STI clinic settings offers opportunities for efficiently managing this set of infections. Selected populations for whom specialized services are already the norm (such as pregnant women) can receive additional attention. This may include screening for HIV and syphilis (see chapter 6 of this volume, John-Stewart and others 2017).

Health care service integration at this level requires strategic planning. For example, integration of HIV and TB diagnosis and management must be done in ways that are safe: crowded clinics with long waiting times create a perfect opportunity for TB transmission from someone with active TB to an immunosuppressed HIV patient. Integrated, population-level intervention packages can focus not only on interventions that are financed mainly by the health sector, such as increased immunization and treatment, but also on interventions related to the agriculture or infrastructure sector (and financed mainly by those ministries, not the health ministry), such as the following:

- Improve access to sanitation, clean water, and hygiene.
- Reduce population growth and crowding.
- Decrease day-to-day close contact with animals.
- Change the environments that sustain vectors of important pathogens.

A related cross-sectoral priority is preventing antimicrobial resistance through the development, availability, and use of affordable diagnostics to guide appropriate antimicrobial use in humans, while also enforcing policies to prevent nontherapeutic use of antimicrobials as growth promoters in livestock.

Importance of Rapid Differential Diagnosis in Infection Control

Even for infectious diseases requiring specialized services, many infections will initially be diagnosed or suspected at the primary care level or first-level hospital and then referred to a second- or third-level hospital. Many infectious illnesses are caused by pathogens that can be life threatening. This makes differential diagnosis—based in part on symptom assessment, clinical manifestations, physical exam, medical history, history of exposures, age and gender, laboratory testing where available, and availability of treatment—the key to population infection control (Burnett and others 2016).

The widespread adoption of rapid tests for malaria diagnosis is an example of an easy-to-use diagnostic that has vastly improved malaria treatment in many places. Rapid point-of-care tests are available for HIV, hepatitis C, influenza, and syphilis but are still in development for some other infections. In addition, conventional microbiology is being transformed by molecular testing, which could be available even in LICs within the decade. A series of publications illustrates the significant effect of integrated infectious disease training on diagnosis (in Uganda) and infectious disease management (Imani and others 2015; Weaver and others 2014)

This volume focuses on major infectious diseases that are common in LMICs, particularly among adults (see box 1.1). Unlike most of the serious infections that predominate among children, many of these are long-lived chronic infections (including some acquired as children). The perspective includes an emphasis on what has changed since the first edition of *Disease Control Priorities in Developing Countries* in 1993 (box 1.2). We first review the major interventions for priority infectious diseases, namely HIV/AIDS, other STIs, TB, malaria and other febrile illnesses, hepatitis, and NTDs. We then address the cross-cutting issues of antimicrobial resistance.

Box 1.1

Volume Focus: Infectious Disease Control

This volume focuses on *control* of the major infectious diseases. Infectious disease control involves not only prevention of transmission and spread of infectious disease at the population and individual levels, but also effective treatment and cure of infectious diseases in individuals.

Box 1.2

Comment by the Series Editors of *Disease Control Priorities, Third Edition*

Budgets constrain choices. Policy analysis helps decision makers achieve the greatest value from limited resources. In 1993, the World Bank published the first edition of *Disease Control Priorities in Developing Countries (DCP1)*, which sought to assess systematically the cost-effectiveness (value for money) of interventions that would address the major sources of disease burden in LMICs (Jamison and others 1993). The World Bank's 1993 *World Development Report* on health drew heavily on the findings in *DCP1* to conclude that specific interventions against noncommunicable diseases were cost-effective, even in environments where substantial burdens of infection and undernutrition persisted (World Bank 1993).

Disease Control Priorities in Developing Countries, second edition (*DCP2*), published in 2006, updated and extended *DCP1* in several respects, explicitly considering the implications for health care systems of expanded intervention coverage (Jamison and others 2006). One way that health care systems can expand coverage of health interventions is through selected delivery platforms for those interventions that require similar logistics but address heterogeneous health problems. Platforms often provide a more natural unit for investment than do individual interventions, but conventional health economics has offered little understanding of how to make choices across platforms. Analysis of the costs of packages and platforms—and of the health improvements they can generate in given epidemiological environments—can help guide health care system investments and development.

This third edition of *Disease Control Priorities (DCP3)* introduces the notion of packages of interventions (Jamison and others 2015–18). Whereas “platforms” refer to logistically related sets of interventions, “packages” comprise conceptually related ones. (The 21 packages of interventions developed in the nine volumes of *DCP3* include those targeting surgery and cardiovascular disease, for example.) In addition, *DCP3* explicitly considers the financial risk protection objective of health care systems. In populations lacking access to health insurance or prepaid

care, medical expenses that are high relative to income can be impoverishing. Where incomes are low, seemingly inexpensive medical procedures can have catastrophic financial effects. *DCP3* considers financial protection and the distribution across income groups of the outcomes from policies (for example, public financing of health care) to increase intervention uptake and to improve delivery quality (Verguet, Laxminarayan, and Jamison 2015). All of the volumes seek to combine the available science about interventions implemented in specific locales and conditions with informed judgment to reach reasonable conclusions about the effects of intervention mixes in diverse environments. *DCP3*'s broad aim is to delineate essential intervention packages—such as those, in this volume, for major infectious diseases—and their related delivery platforms. This information will assist decision makers in allocating often tightly constrained budgets and achieving health care system objectives.

Four of *DCP3*'s nine volumes were published in 2015 and 2016, and the remaining five will appear in 2017 and 2018. The volumes appear in an environment in which serious discussion continues about quantifying and achieving the Sustainable Development Goal (SDG) for health (UN 2015b). *DCP3*'s analyses are well placed to assist in choosing the means to attain the health SDG and assessing the related costs. These volumes, and the analytic efforts on which they are based, will enable researchers to explore SDG-related and other broad policy conclusions and generalizations. The final volume will report those conclusions. Each volume will provide specific policy analyses on the full range of interventions, packages, and policies relevant to its health topic.

Dean T. Jamison

Rachel Nugent

Hellen Gelband

Susan Horton

Prabhat Jha

Ramanan Laxminarayan

Charles N. Mock

We provide updated estimates of the cost-effectiveness of the major sets of interventions, recognizing that there are large knowledge gaps concerning the economics of many conditions in LMICs. We conclude by outlining future strategies that are relevant to continued progress against these major infectious diseases.

MAJOR INFECTIOUS DISEASES IN THIS VOLUME

HIV/AIDS and Other Sexually Transmitted Infections

HIV/AIDS, the worst human pandemic since the 1918 influenza epidemic, has accounted for more than 25 million deaths since it was first identified in 1981 and it has hit Sub-Saharan Africa the hardest. However, the tide is beginning to turn as life-extending antiretroviral treatment (ART) and preventive interventions are scaled up and as sexual behaviors may have become less risky in many settings.

Antiretroviral drugs are now widely available in most settings and are highly affordable at US\$315 per person per year (UNAIDS 2015). Worldwide, 17 million HIV-infected people are receiving these life-extending drugs—an impressive number given that only 2.2 million people were on ART in 2005. However, this number is still far short of the Joint United Nations Programme on HIV/AIDS (UNAIDS) target to treat the 37 million people currently living with HIV. The estimated

number of deaths annually from HIV/AIDS has declined from 2 million in 2005 to 1.1 million in 2015, the lowest number since 1998 (UNAIDS 2015, 2016). Yet AIDS still ranks sixth among the global causes of death—and first in Sub-Saharan Africa.

Building on the progress to date, UNAIDS has set two important goals: (a) a 75 percent reduction in new HIV infections (compared with 2010) by 2030 and (b) successful achievement of the UNAIDS 90-90-90 campaign, which seeks to have 90 percent of all people living with HIV knowing they have HIV, 90 percent of those diagnosed with HIV receiving treatment, and 90 percent of those on treatment having an undetectable viral load (virally suppressed). Furthermore, UNAIDS seeks to eliminate mother-to-child transmission of both HIV and syphilis. We now have the tools to attain these goals, even despite the remaining challenges of needing an HIV vaccine for prevention (as we have vaccines to prevent hepatitis B virus [HBV] and human papillomavirus [HPV] infection); an effective cure for HIV infection (as we have for the hepatitis C virus [HCV] infection); and an effective suppressive therapy for hepatitis B.

In addition to effective medical interventions (table 1.2), national legislative and policy frameworks are needed to enable effective deployment of these interventions. Mother-to-child transmission of HIV will not be eliminated by 2030, the current goalpost, without effective national policies to support prevention. Even more important, laws and policies to protect and reduce

Table 1.2 Essential HIV/AIDS Intervention Package, by Delivery Platform

Intervention type	Delivery platforms ^a				
	Nationwide policies and regulations	Community health post or pharmacy	Primary health center	First-level hospital	Second- and third-level hospitals
<i>Prevention</i>					
Legal and human rights	1. Laws and policies to protect and reduce stigma for key populations, with full decriminalization of LGBT population*	2. Gender-based violence counseling and rape-response referral (medical and justice)			
Structural interventions	3. Universal access to HIV testing, with immediate linkage to care and treatment and intensified outreach to populations at higher risk of infection				
	4. Universal access to drug substitution therapy for addiction				
	5. Brothels: Condoms required*				
	6. Needle exchange encouraged*				

table continues next page

Table 1.2 Essential HIV/AIDS Intervention Package, by Delivery Platform (continued)

Intervention type	Delivery platforms ^a			
	Nationwide policies and regulations	Community health post or pharmacy	Primary health center	First-level hospital Second- and third-level hospitals
Direct (biological) prevention			7. PrEP for discordant couples 8. Male circumcision service provision* 9. PMTCT (Option B+)	
Behavioral interventions: Prevention		10. HIV education and counseling for pregnant women, sex workers, IDUs, GBT males, and HIV+ persons and their partners* 11. Access to needle exchange for IDU* 12. Condom distribution* 13. Partner notification* 14. Adherence support for high-risk or failing patients		
Social marketing: Information, education, and communication	15. Promotion of condoms, VMMC, and testing at national and facility-based levels*			
Treatment				
Treatment	16. Policies and guidelines to support all steps of HIV care continuum, including expanded testing through diverse strategies; linkage to care; ART initiation with support for adherence and retention; and performance and efficiency optimization through data-driven management, task shifting, and decentralization, as appropriate for level of epidemic	17. Community-based HIV testing and counseling (for example, through mobile units or venue-based testing)* 18. Household HIV testing and counseling in high-prevalence settings 19. Referral and navigation of HIV+ individuals to HIV care sites to ensure linkage	20. Provider-initiated counseling and HIV testing (as well as TB and STI testing) for all in contact with health care system in high-prevalence settings, including prenatal care* 21. ART initiation 22. Support for adherence and retention 23. Laboratory viral load monitoring	
Behavioral and structural interventions: Care		24. Adherence support including adherence clubs, community-based ART groups, text reminders, and other means 25. Nutrition, transportation, and financial reimbursement	26. Case manager	

Note: Interventions shown in orange indicate areas that are relatively neglected by governments. ART = antiretroviral treatment; GBT = gay, bisexual, or transgender; HIV = human immunodeficiency virus; HIV+ = HIV-positive; IDU = injection drug users; LGBT = lesbian, gay, bisexual, and transgender; Option B+ = a three-drug ART regime in pregnancy and postpartum for HIV-positive mothers; PMTCT = prevention of mother-to-child transmission; PrEP = preexposure prophylaxis; STI = sexually transmitted infection; TB = tuberculosis; VMMC = voluntary male medical circumcision.

a. All interventions listed for lower-level platforms can be provided at higher levels. Similarly, each facility level represents a spectrum and diversity of capabilities. The column in which intervention is listed is the lowest level of the health care system in which it would usually be provided.

Interventions marked with an asterisk (*) should be closely integrated with STI prevention and treatment interventions.

stigma for key populations are urgently needed in many countries. Indeed, in recent years, lesbian, gay, bisexual, and transgender (LGBT) rights have regressed in some settings, and criminalization of these populations has increased. Two chapters in this volume provide useful detail for policy makers who are considering such issues: chapter 8 (Wilson and Taaffe 2017) outlines the factors to consider when tailoring a response to a local epidemic, and chapter 9 (Kahn and others 2017) presents various models that can help guide decisions regarding the cost-effectiveness of the different interventions.

Optimal HIV management requires managing people across the continuum of care, from testing to counseling and from ART to adherence support. Sociocultural barriers in gaining access to care include the following:

- Fear of diagnosis, complicated by a culture of stigma and discrimination in many countries
- Structural barriers such as distance to health clinics
- System-level barriers such as clinic hours, coordination among clinics, and shortages of health care workers

Biomedical interventions that have come to the forefront since the publication of *Disease Control Priorities in Developing Countries*, second edition (DCP2) by the World Bank (Jamison and others 2006) and that have proven highly effective at preventing HIV transmission include treatment as prevention (Gomez and others 2013); preexposure prophylaxis (PrEP); male circumcision; and new treatment regimens for prevention of mother-to-child transmission (PMTCT). Furthermore, these interventions can be successfully delivered at first-level care facilities, thereby increasing accessibility.

PrEP—using a once-a-day tablet, the current version of which includes two antiretroviral drugs—provides a method beyond condoms for at-risk people to prevent becoming infected with HIV (Baeten 2016; Jenness and others 2016). PrEP access is still limited in LMICs and does not prevent other STIs.

Voluntary male medical circumcision (VMMC) significantly reduces sexual acquisition of HIV by men and is most cost-effective in settings where HIV is highly prevalent. Recent studies have shown that demand is high for VMMC, which can be offered at some first-level health care facilities and at health centers. In some countries, VMMC has even been delivered effectively in mobile vans.

Advances have increased the effectiveness of PMTCT treatment as well. For an HIV-infected mother not yet receiving ART, the recommendations are to start ART at the first prenatal visit (regardless of the mother's CD4 cell count or WHO clinical stage)¹ and to continue lifelong ART. Use of this protocol could significantly

reduce the number of newborns infected during the birth process and the mother-to-child transmission of HIV. Substantial progress has been made in this regard: new pediatric HIV infections declined by 50 percent from 2010 to 2015 (UNAIDS 2016).

Interventions to offer household-based testing in high-prevalence settings will contribute to the first “90” of the UNAIDS 90-90-90 goals (90 percent of all people living with HIV know they have HIV). Interventions to effectively and promptly link newly diagnosed persons living with HIV to services and treatment contribute to the second “90” (90 percent of HIV-diagnosed people receive treatment) and are critical across all settings. Finally, multiple strategies for promoting adherence to treatment and retention in care—ranging from community support groups to mobile health interventions—are critical to ensuring that treatment is effective and continuous, thus achieving the third “90” (90 percent of those being treated have an undetectable viral load).

Burden of STIs other than HIV/AIDS

In addition to HIV, another 40 bacterial, viral, and parasitic pathogens have been identified as primarily sexually transmitted, or as potentially sexually transmissible (see annex 1A). The common curable bacterial STIs include trichomoniasis, chlamydia infection, gonorrhea, and syphilis. In 2012, the WHO estimated the global incidence of these four curable STIs among men and women ages 15–49 years: 131 million new cases of chlamydia infection, 78 million of gonorrhea, 143 million of trichomoniasis, and 6 million of syphilis (WHO 2016b). These estimates mean that approximately 1 million new infections could be cured with existing treatments each day (Newman and others 2015).

Other common sexually transmitted pathogens are herpes simplex virus (HSV-1 and HSV-2, both of which cause genital herpes) and HPV.² In 2012, the global prevalence of HSV-2 among men and women ages 15–49 years was 417 million, with higher prevalence in women than in men. An estimated 19.2 million individuals ages 15–34 years were newly infected with HSV-2 in 2012 (Looker and others 2015).

Extensive studies of the prevalence of oncogenic genital HPV infections included a global systematic review of age-specific prevalence of oncogenic types of HPV infection in males (Smith and others 2011) and in females (Winer and others 2012). In general, these studies show high prevalence of oncogenic HPV types among those with new sex partners or a high number of lifetime partners.

Common STIs may cause significant complications to women's reproductive health, including pelvic inflammatory disease, tubal pregnancy infertility, cervical cancer, perinatal and neonatal morbidity, mother-to-child

transmission of syphilis or HIV, and a host of other conditions (Chesson, Mayaud, and Aral 2017, chapter 10 in this volume). However, for morbidity and mortality, years of life lost, disability-adjusted life years (DALYs), and costs of medical care, the major STIs are as follows:

- HIV infection
- HBV and HCV infection
- HPV infection, with HPV-related genital, anal, and oropharyngeal cancers
- Syphilis, with its related perinatal and pediatric morbidity and mortality
- HSV-1 and HSV-2 infection, with related central nervous system and pediatric morbidity

In aggregate, these major pathogens cause extensive morbidity and mortality attributable to unsafe sex. Moreover, the consequences of STIs disproportionately affect women and children. STIs, including HIV/AIDS, are one of the leading causes of morbidity and mortality, as measured by DALYs, for reproductive-age women in LMICs (Owusu-Edusei and others 2014).

In addition to the mortality and morbidity attributable to the major STI pathogens listed earlier, other STI pathogens account for severe morbidity, including infertility, ectopic pregnancy, epididymitis, neonatal eye infection, and other common diseases. These other pathogens that can be transmitted sexually include the Zika and Ebola viruses and group C *Neisseria meningitidis*. Sexual transmissions of these pathogens have been documented but are not yet well studied (Hader 2017).

Unsafe Sex as a Global Risk Factor for Death and Disability in Adolescents and Young Adults

The Global Burden of Disease (GBD) study recently reported annual assessments of risk factors for death and DALYs in adolescents and young adults in 188 countries for 2013 (Mokdad and others 2016). Among adolescent males ages 15–19 years, unsafe sex was the second most common risk factor for death. Among adolescent females ages 15–19 years, unsafe sex was the number one risk factor. Among young adults ages 20–24 years (males and females combined), unsafe sex was the second most common risk factor.

As for the risk of disability (as measured by DALYs), unsafe sex was the second most common risk factor in 2013. Important to the global burden, the number and proportion of the worldwide population who are adolescents are also steadily growing (Hader 2017).

Key Populations for STI Control in LMICs

Although adolescents and young adults experience a large proportion of STIs, including HIV infection, the

role of key populations in the epidemiology and control of HIV and other STIs in LMICs has become increasingly clear (Baral and others 2007; Baral and others 2012). These key populations include, in particular, female sex workers; men who have sex with men (MSM), who are understudied and underserved in most LMICs; and injection drug users, who are at risk not only for HIV but also for other blood-borne STIs such as syphilis and hepatitis viruses. Patterns of sexual networks linking MSM with heterosexual populations warrant future research.

Until recently, HCV was repeatedly described as *not* sexually transmitted, and its transmission had been associated with injection drug use, blood transfusions, and iatrogenic exposures but not with heterosexual transmission. However, HCV recently has been found in the semen of men with HCV viremia, and rectal HCV shedding was found in 20 of 43 (47 percent) HIV-infected MSM who also had HCV infection. The presence of HCV in rectal fluid was associated with high blood levels of HCV (Foster and others 2017). Most important, co-infections with HCV and HIV have been commonly found in Australia, Europe, and North America. Thus, screening for HCV—a curable infection—is now being recommended for HIV-infected MSM in high-income countries (Harrison and others 2017; Kratz and others 2015; Nanduri and others 2016).

STI Interventions: Prevention, Treatment, and Education

Prevention and treatment are both important to STI control, and the HIV epidemic has influenced changes in the approach to STI prevention in general. During the 1980s and 1990s, behavioral prevention dominated the HIV world and gained prominence in the STI domain. However, since the turn of the century, recognition has grown that behavioral interventions (heavily weighted toward condom use) have not decreased STI incidence sufficiently and sustainably (Aral 2011; Kippax and Stephenson 2012).

STI Prevention

Concurrently, remarkable progress has been made in biomedical approaches to preventing HIV/AIDS, including male circumcision, PrEP, and ART (Baeten and others 2012; Dodd, Garnett, and Hallett 2010; Grant and others 2010; Katz and Wright 2008; Pretorius and others 2010). Given the success of these biomedical approaches, the field of STI prevention is increasingly drawing on them, reinforced by development of effective biomedical interventions for preventing STIs other than HIV. More specifically, these interventions include promotion and provision of the HPV and HBV vaccines to females and males, early detection and curative treatment of HCV infection, point-of-care

diagnostic tests for syphilis, dual tests for syphilis and HIV, and an understanding of the effects of male circumcision for preventing certain STIs other than HIV.

In addition, clinical platforms offering STI-related reproductive health services are playing a key role in screening patients for HIV and HCV. They also emphasize outreach to sex partners for HIV and other STI screening. Table 1.3 provides an assessment of the platforms and essential interventions for preventing and treating STIs.

Pharmacy Treatment of STIs and Clinician Online Education

Individual treatment of STIs in LMICs is largely based on syndromic management, which is often provided by pharmacies without clinical examination. Provision of guidelines and training to pharmacy workers can significantly improve STI management by pharmacy workers (García and others 2012).

However, this practice, linked to the increasing availability of new antimicrobials in LMICs, may be contributing to emerging antimicrobial resistance in LMICs (Miller-Petrie, Pant, and Laxminarayan 2017, chapter 18 of this volume). Although the common curable STIs can be managed effectively in LMICs with widely available antibiotics, global development of antibiotic resistance has eroded the success of treatment of some infections, including gonorrhoea.

Canchihuaman and others (2011) have also demonstrated the feasibility and effectiveness of using computer-based education to reach out to clinicians and midwives to vastly expand and improve the scope and effect of online continuing education of STI management. This approach is a critical and effective step to guide large groups of clinicians and communities, even in remote rural areas, to better health care in general but especially regarding infectious diseases.

Table 1.3 Essential STI Intervention Package, by Delivery Platform

		Platforms for intervention delivery				
Nationwide, regional, and local health systems, policies and regulations		Community health post ^a	Pharmacies ^b	Primary health and reproductive health clinics ^c	First-level hospitals	Second-, and third-level hospitals ^d
Structural	<ol style="list-style-type: none"> Organize, coordinate, and where possible, integrate programs for STI and HIV/AIDS into one national center and into regional centers, with essential funding and system support for local programs* National policies to enable prevention and treatment efforts for key populations* 	<ol style="list-style-type: none"> Linkages to clinical services for FSW, MSM, sex partners of persons with STI/HIV* Training for police to ensure access to services for key populations, especially needle exchange* Home-based services and Internet use for partner notification, HIV diagnosis, and initiating HIV treatment in patients with HIV infection* 	<ol style="list-style-type: none"> Training on syndromic treatment of STIs by pharmacists 			
Behavioral prevention	<ol style="list-style-type: none"> Social marketing linked to education on STI/HIV risks, and on sexual health, including condom and safe sex promotion*^e National curriculum and policy regarding sexual health education (including online education)* 	<ol style="list-style-type: none"> School-based sexual health education (STI/HIV risks, condom use, substance abuse, key vaccines, VMMC)* Condom promotion; Needle exchange for IDU*^f 				

table continues next page

Table 1.3 Essential STI Intervention Package, by Delivery Platform (continued)

		Platforms for intervention delivery				
Nationwide, regional, and local health systems, policies and regulations		Community health post ^a	Pharmacies ^b	Primary health and reproductive health clinics ^c	First-level hospitals	Second-, and third-level hospitals ^d
Biomedical prevention	11. Guidelines, funding, and social marketing for HPV and HBV vaccines; and for VMMC (adolescents, adults, infants)	12. School-based and health post provision of HPV and HBV vaccines, and linkage to or provision of VMMC services		16. Vaccine provision (HPV, HBV) (females and males)		
		13. Access to needle exchange for IDU*		17. VMMC*		
		14. Screening and treatment for major STIs among prison populations		18. Visual inspection with acetic acid for cervical dysplasia		
		15. Preexposure antimicrobial prophylaxis in high risk populations*				
Diagnosis and treatment	19. Guidelines for expedited partner therapy via pharmacies		20. Syndromic-based treatment of STIs		21. Diagnosis and treatment of suspected pelvic inflammatory disease; viral hepatitis; ART, plus detection and treatment or referral of comorbidities, and some HIV comorbidities	22. Diagnosis and treatment of anal, oropharyngeal, and liver cancers; and other HIV comorbidities.

Note: Interventions shown in orange indicate areas that are relatively neglected by governments. Interventions marked with an asterisk (*) should be closely integrated with HIV prevention and treatment interventions.

FSW = female sex workers; HBV = hepatitis B virus; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; HPV = human papillomavirus; IDU = injection drug users; MSM = men who have sex with men; PrEP = preexposure prophylaxis; STD = sexually transmitted disease; STI = sexually transmitted infection; VMMC = voluntary male medical circumcision.

a. This platform involves extension of health services beyond conventional clinical platforms to reach high-risk populations.

b. Pharmacies are very accessible (proximity, short wait times, low cost) and provide much of the treatment for STI syndromes. Yet, adherence to STD treatment guidelines in pharmacies has been dismal (Chalker and others 2000). However, training of physicians, midwives, and pharmacy workers can lead to greatly improved STD syndromic management (Garcia and others 2012). After training of pharmacy workers, pharmacy-based STD syndromic management was cost-effective, when only program costs are used, and cost saving from the societal perspective (Adams and others 2003).

c. For this volume, we are assuming that most clinical service delivery at the primary care and reproductive health clinics level is provided by nurses. Primary health clinics in LICs and MICs tend to lack diagnostic testing but also have lower costs and are more accessible than hospitals.

d. Service delivery by physicians, physician assistants, or nurses. Specialist expertise includes reproductive health, laboratory capacity, obstetrics and gynecology, and pediatrics.

e. Curricula should include information on condoms, safe-sex promotion and provision, warning signs, and accessing care.

f. Sanchez and others 1998.

Tuberculosis

TB is arguably the world's leading cause of death from an infectious agent.³ The WHO estimates that 10.4 million new cases and 1.5 million deaths occur from TB each year (WHO 2016a). One-third of TB cases remain unknown to the health care system. For those accessing treatment, however, prevalence and mortality have declined significantly, and millions of lives have been saved.

TB is caused by the bacterium *Mycobacterium tuberculosis*, which is transmitted between humans through

the respiratory route and most commonly affects the lungs but can damage any tissue. Only a minority (approximately 10 percent) of individuals infected with *M. tuberculosis* progress to active TB disease, while the remainder may maintain a latent infection that serves as a reservoir. TB has special challenges, including (a) a substantial number of patients with active disease are asymptomatic, capable of transmitting infection without knowing it; (b) patients must maintain compliance with treatment for six to nine months; and (c) the pathogen

persists in many infected individuals in a latent state for many years but can be reactivated over a lifetime to cause disease and become transmissible.

People at every rung of the socioeconomic ladder are at risk, although TB disproportionately affects the poor. Approximately 80 percent of patients reside in 22 high-burden countries. Treatment of TB disease requires multiple drugs for many months. These lengthy drug regimens are challenging for both patients and health care systems—especially in LMICs, where the disease burden often far outstrips local resources. For TB susceptible to first-line drugs (the least expensive), cure rates greater than 90 percent are expected at a cost of US\$200 to US\$500. The increasing incidence of multidrug-resistant TB (MDR-TB), which requires even longer treatment regimens with expensive and difficult-to-tolerate drugs, represents an emerging threat, not least to hospital and clinic personnel.

The United Nations' (UN) Sustainable Development Goal (SDG) 3 seeks to end the TB epidemic altogether by 2030, but the decline in incidence of TB has been slow, only about 1.5 percent per year.⁴ Without new tools, the UN targets are unlikely to be met even by 2050. The current policy of passive case finding (waiting for patients to be ill enough to seek treatment) is suboptimal in high-burden countries. Faster rates of progress on TB will require earlier, more accurate case detection; rapid commencement of and adherence to effective treatment; and, where possible, preventive treatment of latent TB (table 1.4).

Durable control will require new strategies and tools that are more effective than those now in use—for example, new, shorter drug regimens that are effective for both drug-sensitive and drug-resistant TB. These must be not only cost-effective but also affordable and capable of being effective on a large scale. In addition to new tools, effective TB control requires the strengthening of weak health care systems (including improvements in surveillance, information technology, logistics, and drug supply) and strengthening of community health care systems to be more responsive and effective.

Within the context of current knowledge, Bloom and others (2017) in chapter 11 in this volume advocate for optimizing the approaches known to be effective, including the following:

- Identify high-transmission countries and hot spots within countries where targeted efforts can be more effective and cost-effective.
- Increase early TB detection and diagnosis, particularly in selected high-burden countries, by introduction of new tools for active case finding.
- Rapidly provide appropriate and better maintenance for patients diagnosed with either drug-susceptible TB or MDR-TB, enabling higher levels of completion and care.

- Expand preventive therapy to reduce transmission from TB patients to contacts, especially to children and HIV-positive individuals.
- Emphasize community-based delivery of TB treatment and services wherever possible to improve treatment completion, reduce the dangers of hospital transmission, decrease costs, and improve patient quality of life.
- Improve hospital and clinic infection control.
- Enhance drug supply chains for access to TB treatments that have small markets.
- Expand information technology and electronic medical records to enable more effective disease control.

The need is urgent for new tools, including inexpensive and sensitive point-of-care diagnostic tests, rapid tests for drug resistance, new and shorter drug regimens for both drug-susceptible and drug-resistant TB, and a more effective vaccine to prevent the disease.

Malaria and Other Adult Febrile Illnesses

Febrile illnesses are major causes of morbidity and mortality in LMICs for children and adults, and most are largely indistinguishable on clinical presentation. Simple rapid diagnostic tests (RDTs) are lacking for the common, serious causes of fever except malaria, making appropriate treatment uncertain for most febrile patients, only a minority of whom have malaria.

Malaria

The massive investment in malaria control over the past decade has been successful in greatly reducing malaria prevalence, but eliminating malaria is a very distant goal in most of Sub-Saharan Africa and much of Asia. Continued progress depends on maintaining and increasing the use of effective preventive measures (such as insecticide-treated nets, indoor residual spraying, and intermittent preventive therapy for pregnant women and infants); widespread use of RDTs; and treatment with effective artemisinin-combination therapies (ACTs) to bring the countries with the highest endemic rates to preelimination levels (Shretta and others 2017, chapter 12 in this volume). Table 1.5 summarizes the essential interventions for prevention and treatment of malaria.

Continued surveillance and substantial expenditures over many years will be needed to eventually eradicate malaria, and whether it can be done globally without adding at least one more effective tool to the set of interventions in widespread use is unclear. The currently available vaccines may or may not be effective enough to boost results sufficiently. In April 2017, the WHO

Table 1.4 Essential Tuberculosis Intervention Package, by Delivery Platform

Intervention type	Delivery platform				Second- and third-level hospitals
	Nationwide policies and regulations	Community health post or pharmacy	Primary health center	First-level hospital	
Surveillance and disease detection	1. Passive case finding 2. Active case finding in high-burden countries	3. Symptomatic surveillance 4. Active contact tracing of TB-positive patients			
Data collection and patient tracking	5. Information systems				
Diagnosis and drug sensitivity testing	6. National guidelines promoting the provision of diagnostic labs; diagnostic technology including GeneXpert or culture for drug-susceptible TB; fixed/mobile X-ray; and training	7. Symptomatic diagnosis, local sputum smears	9. Sputum smears	12. GeneXpert/RIF ^a or culture for diagnosis of drug-susceptible TB	
Relapse and reinfection diagnosis		8. Referral for diagnosis and drug-susceptible TB tests	10. Testing of children and household members and HIV+ individuals for case finding in both drug-susceptible and MDR-TB cases 11. Availability of fixed/mobile X-ray for diagnosis		
Treatment of drug-susceptible TB	13. WHO guidelines: four-drug regimen for two months, then two drugs-regimen for four months	14. Provision and observation of treatment after one month at first-level hospital 15. Use of cell-phone SMS to support treatment adherence		16. Treatment of drug-susceptible TB until transmission is reduced (one month), then transfer of treatment to community level	
Treatment of drug-resistant TB	17. WHO guidelines: Multiple-drug regimen after drug-susceptible TB testing for nine months to two years		18. Provision of appropriate second-line drugs, monitoring 19. INH preventive therapy	20. Treatment until sputum is negative or GeneXpert is negative; treatment as outpatients after sputum is negative	21. Specialized treatment for treatment failures, MDR-TB, surgery
Coinfection with HIV		22. Provider incentives to improve quality of TB care	23. Referral or provision of HIV treatment as appropriate 24. Information systems to link diagnostic hospital care to outpatient and community care	25. Separate areas in health facilities for TB to avoid transmission to AIDS patients	

Note: Interventions shown in orange indicate areas that are relatively neglected by governments. HIV = human immunodeficiency virus; HIV+ = HIV-positive; INH = isoniazid; MDR-TB = multidrug-resistant tuberculosis; SMS = short message service (text messaging); TB = tuberculosis; WHO = World Health Organization.
a. GeneXpert/RIF refers to a new test that simultaneously detects *Mycobacterium* TB complex (MTBC) and resistance to rifampin (RIF).

announced that Ghana, Kenya, and Malawi will participate in a pilot malaria vaccine implementation program in select areas, beginning in 2018 (WHO 2017).

Despite global guidelines to the contrary, presumptive treatment of undifferentiated febrile illness as malaria is still appropriate in places where RDTs (or microscopy)

cannot be reliably applied and malaria prevalence is high (Babigumira, Gelband, and Garrison 2017, chapter 15 in this volume). When the test for malaria is negative, patients with severe disease should receive an antimicrobial regimen tailored to locally important nonmalarial pathogens (Crump and others 2017, chapter 14 in this volume).

Table 1.5 Essential Malaria Intervention Package, by Delivery Platform

Intervention type	Delivery platform ^a			
	Population-based health interventions	Community	Health center	Second- and third-level hospitals
<i>All malaria-endemic countries</i>				
Case management: Uncomplicated malaria (or fever)	1. Prophylaxis for travelers	2. Diagnosis with RDTs or microscopy, including parasite species 3. Treatment with ACTs (or current first-line combination) for malaria-positive individuals where diagnosis is available 4. Where both RDTs and microscopy are unavailable and malaria is common, presumptive treatment with ACTs for nonsevere suspected malaria; if severe, ACTs plus antibiotics 5. <i>Plasmodium vivax</i> : Chloroquine alone or chloroquine plus 14-day course of primaquine (for G6PD normal individuals) 6. Case investigation, reactive case detection, proactive case detection (including mass screening and treatment)		
Case management: Severe malaria		7. Single-dose rectal artesunate, then referral to first-level hospital		8. Parenteral artesunate, then full-course ACTs
Vector control: ITNs		9. ITNs available in health centers and antenatal clinics and via social marketing		
<i>Malaria elimination countries</i>				
		10. Mass drug administration to high-risk groups in geographic or demographic clusters 11. Single low-dose primaquine added to first-line treatment		
<i>Malaria control countries</i>				
Vector control: IRS		12. IRS in selected areas with high transmission and entomologic data on IRS susceptibility		
Vector control: Larviciding and water management		13. Larviciding and water management in specific circumstances where breeding sites can be identified and regularly targeted		
Mass drug administration		14. IPTp, IPTi, and SMC Sahel region		

Note: Interventions shown in orange indicate areas that are relatively neglected by governments. ACTs = artemisinin-combination therapies; G6PD = glucose-6-phosphate-dehydrogenase; IPTi = intermittent preventive treatment in infants; IPTp = intermittent preventive treatment of pregnant women; IRS = indoor residual spraying; ITN = insecticide-treated net; RDT = rapid diagnostic test; SMC = seasonal malaria chemoprevention.

a. All interventions listed for lower-level platforms can be provided at higher levels. Similarly, each facility level represents a spectrum and diversity of capabilities. The column in which an intervention is listed is the lowest level of the health care system in which it would usually be provided.

Where an understanding of locally important bloodstream infections and other pathogens is lacking, standardized fever etiology research is needed to inform management. The development of accurate point-of-care diagnostic or biomarker tests would improve targeting of antimicrobials.

Nonmalarial Fever

A diverse set of pathogens contributes to nonmalarial fever. Prevention efforts may target pathogen reservoirs (for example, by vaccinating livestock for brucellosis); target sources of infection (such as through vector control to reduce arbovirus infections); interrupt transmission (for example, by reducing occupational exposure to *Coxiella burnetii* among abattoir workers); and provide immunologic protection (such as through typhoid vaccines).⁵

A lack of knowledge and a lack of tools hamper progress in combating nonmalarial fevers. The predominant causes of fever in LMICs are largely unknown because research on fever etiology has not been done. National surveillance or sentinel site studies, preferably coordinated globally, are urgently needed to identify major causes of severe febrile illness, especially bloodstream infections and pathogens with specific treatments (for example, brucellosis, rickettsioses, and Q fever)

(Crump and others 2017, chapter 14 in this volume). Concomitantly, research to identify priorities for improvements in management, such as selection of empiric antimicrobial therapies, should be undertaken in the same countries.

The laboratory methods that can be used for research are impractical at the bedside in low-resource settings. For such settings, accurate RDTs are needed—first, to distinguish viral from bacterial (and potentially easily treatable) infections; and second, to provide pathogen-specific tests for major causes of treatable nonmalarial fevers, based on surveillance and other local research.

Finally, cost and outcome data are needed to develop credible estimates of the total burden of nonmalarial febrile illnesses and to enable accurate cost-effectiveness analyses related to fever in order to strengthen resource-stratified approaches to the adoption and integration of interventions (summarized in table 1.6). This information is particularly important because decisions on services to include in universal health coverage are being made.

Viral Hepatitis

Five mostly unrelated viruses—hepatitis A, B, C, D, and E—infect the liver, with varied routes of infection:

Table 1.6 Essential Intervention Package for Adult Febrile Illness, by Delivery Platform

Intervention type	Delivery platform ^a				
	Nationwide policies and regulations	Community health post or pharmacy	Primary health center	First-level hospital	Second- and third-level hospitals
Case management: All fevers	1. Standard practice guidelines 2. Essential medicines, including relevant antibacterials		3. Evaluation for malaria with RDT or microscopy (see malaria interventions) 4. If negative for malaria, referral if fever persists beyond seven days	5. Clinical history and examination to identify source of fever 6. Evaluation for malaria and HIV 7. Treatment for the apparent cause and reevaluation after one week	8. Reference diagnostics for major causes of nonmalarial fever
Case management: Severe febrile illness			9. Prereferral antimicrobial according to standard practice guidelines (for example, extended-spectrum cephalosporin)	10. Emergency management of septic shock with intravenous fluids, supplemental oxygen, and antimicrobial according to standard practice guidelines 11. Clinical history and physical examination to identify source of fever 12. Blood culture before antimicrobial; hemoglobin and glucose measurement 13. Treatment of apparent cause	14. Reference diagnostics for major causes of nonmalarial fever

table continues next page

Table 1.6 Essential Intervention Package for Adult Febrile Illness, by Delivery Platform (continued)

Intervention type	Delivery platform ^a				
	Nationwide policies and regulations	Community health post or pharmacy	Primary health center	First-level hospital	Second- and third-level hospitals
Prevention: Vaccines	15. National policy on typhoid vaccines 16. National policy on control of brucellosis and leptospirosis in livestock				
Prevention: Nonvaccine measures	17. National policies on control of sources of nationally important causes of nonmalarial fever (such as vector control for arbovirus infections) 18. National policies on interruption of transmission of nationally important causes of nonmalarial fever (for example, management of occupational exposure to <i>Coxiella burnetii</i> among abattoir workers)				
Surveillance	19. Nationwide or sentinel site surveillance to identify major causes of severe febrile illness, especially bloodstream infections 20. Assurance that national recommendations for antimicrobial management of severe febrile illness match etiologic findings				

Note: HIV = human immunodeficiency virus; RDT = rapid diagnostic test.

a. All interventions listed for lower-level platforms can be provided at higher levels. Similarly, each facility level represents a spectrum and diversity of capabilities. The column in which an intervention is listed is the lowest level of the health care system in which it would usually be provided.

- Hepatitis A and E are transmitted by the fecal-oral route through contaminated water and food; they can also be transmitted sexually.
 - Most hepatitis B (HBV) infections occur through mother-to-child and early-life horizontal transmission between family members, among adults through sexual intercourse, and through unsafe injection practices and transfusion of unscreened blood.
 - Most hepatitis C (HCV) infections occur through unsafe injections, either in medical settings (from reuse of medical equipment and substandard application of infection control measures) or through unsafe practices among people who inject drugs. Sexual transmission of hepatitis C is rare in heterosexual couples but more common among HIV/AIDS-infected MSM.
 - Hepatitis D is transmitted by blood and bodily fluids.
- Most hepatitis deaths (96 percent) are caused by HBV and HCV, which cause chronic, lifelong infection

resulting in progressive liver damage leading to cirrhosis and hepatocellular carcinoma. Mortality rates from hepatitis are highest in West Africa and parts of Asia; in absolute numbers, East Asia and South Asia account for just over half of hepatitis deaths, which totaled 1.45 million globally in 2013. An estimated 250 million people live with chronic HBV infection; 80 million have chronic HCV infection (Gower and others 2014; Schweitzer and others 2015).

In some West African countries, more than 8 percent of the population is infected with hepatitis. The regions with the highest prevalence of HCV infection are West and Central Africa, Eastern Europe, and Central Asia. Hepatitis C prevalence is extremely high in a few other countries as well, most notably the Arab Republic of Egypt and Pakistan, where high incidence persists largely because of weak preventive measures, such as reuse of syringes and needles in health care settings.

Hepatitis Prevention

Hepatitis A and E infections can be prevented through improved sanitation. Although no reliable estimates are available, the incidence of hepatitis A and E has declined likely as part of the overall reduction in the number of deaths owing to diarrhea. An effective hepatitis A vaccine exists, and 18 countries have introduced universal childhood hepatitis A vaccination.

The most notable achievement in hepatitis prevention is the reduction in incidence of acute and chronic HBV infection as a result of universal childhood hepatitis B vaccination. At the end of 2013, 183 of 194 countries had introduced universal childhood vaccination; global coverage with three doses of hepatitis B vaccine is estimated to be 81 percent effective (WHO 2015). Universal infant vaccination with high coverage levels has led to major reductions in the prevalence of chronic HBV infection among children. In China, the prevalence of chronic HBV infection declined from approximately 8 percent in 1992 to 1 percent in 2006 among children ages one to four years (Liang and others 2009).

However, challenges remain in achieving further reductions in incidence. Full protection for children requires that they receive the first vaccine dose within 24 hours of birth, which is a logistical challenge and a barrier to further progress.

Other proven interventions for hepatitis prevention that have not been fully implemented around the world (for various technical and political reasons) are universal safe injections, blood supply screening for HBV and HCV, and harm reduction for injection drug users (for example, provision of sterile needles and opioid substitutes).

Hepatitis Treatment

Chronic HBV and HCV infections can be treated effectively. The new direct-acting antiviral medicines for hepatitis C can cure more than 90 percent of individuals with chronic infection with a two- to three-month course of treatment, although the current costs of treatment are very high. Hepatitis C treatment could also reduce HCV transmission because people who have been cured do not transmit the infection. There is no cure for chronic hepatitis B, but effective antiviral treatments can suppress viral replication and prevent disease progression. Table 1.7 summarizes both the preventive and the treatment interventions for hepatitis.

Neglected Tropical Diseases

NTDs affect more than 1 billion of the poorest, most marginalized people of the world. These infections are a consequence of the environmental and socioeconomic conditions in which the poor live, and the ill health and disability they cause are a primary factor locking the poor into poverty. At least 18 diseases are recognized as NTDs by World Health Assembly resolutions.⁶ Although not covered further here, the WHO has recently added snakebite deaths to the NTD list. Snakebite causes about 50,000 deaths in India per year and an estimated 100,000 deaths globally (Mohapatra and others 2011).

The NTD concept was developed to draw attention to a disease control opportunity that had been overlooked by the Millennium Development Goals. The ending of NTD epidemics is now embedded within the SDGs for 2030, under target 3.3, reflecting the UN's High-Level Political Forum on Sustainable Development 2016 promise of "ensuring that no one is left behind."⁷ Chapter 17 of this volume (Fitzpatrick and others 2017) focuses on specific WHO targets for control, elimination, and eradication of a subset of these diseases.

Interventions to End NTDs

Three key interventions address a large share of the burden of disease caused by this set of diseases. In recognition of the increasingly integrated delivery of interventions to the poorest, most remote, and otherwise most marginalized communities of the world, we consider them by intervention rather than by disease, as follows:

- Preventive chemotherapy by mass drug administration
- Innovative and intensified disease management
- Vector ecology and management

Table 1.7 Essential Hepatitis Intervention Package, by Delivery Platform

Intervention type	Delivery platform ^a				
	Nationwide policies and regulations	Community health post or pharmacy	Primary health care	First-level hospital	Second- and third-level hospitals
Hepatitis B vaccination	1. Policy for universal newborn and childhood vaccination		2. Delivery of hepatitis B vaccination including birth dose		
Interventions to reduce hepatitis transmission in health care settings	3. Policy for hepatitis B vaccination of health care workers		4. Vaccination of health care workers		
Harm-reduction services for IDU	5. Policy for the provision of harm-reduction services (including injection equipment and opioid substitution therapy) to IDU; use of this wording for HIV or STI safe injection* 6. Community services: IDU-friendly harm reduction with sufficient coverage				
Hepatitis testing services	7. National testing policy identifying priority groups for testing and setting a testing strategy	8. Hepatitis testing of individuals as identified in the national testing policy	9. Referral of persons with hepatitis infection to care		
Hepatitis treatment	10. Treatment guidelines		11. Referral of persons with hepatitis infection to assessment for treatment eligibility 12. Assuming sufficient training, initiation of hepatitis treatment and follow-up	13. Treatment of hepatitis B and C for eligible persons 14. Mentoring of primary-care personnel involved in treatment initiation and follow-up	
				15. Screening blood transfusion for hepatitis B and C	

Note: Interventions shown in orange indicate areas that are relatively neglected by governments. HIV = human immunodeficiency virus; IDU = injection drug users; STI = sexually transmitted infection. Interventions marked with an asterisk (*) should be closely integrated with HIV/AIDS and STI prevention and treatment interventions.

a. All interventions listed for lower-level platforms can be provided at higher levels. Similarly, each facility level represents a spectrum and diversity of capabilities. The column in which an intervention is listed is the lowest level of the health care system in which it would usually be provided.

The interventions are discussed in detail in chapter 17 in this volume (Fitzpatrick and others 2017) but are summarized as follows:

Preventive chemotherapy by mass drug administration is effective against lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiases, and trachoma. The specific drugs and regimens vary by disease, and many populations are affected by more than one of these conditions. Mass campaigns can be combined to target several pathogens at once.

Innovative and intensified disease management refers to a shift from passive management to active surveillance, early diagnosis, and treatment, with the aim to eliminate or control, not just to manage. Treatment of Buruli ulcer, for example, has evolved from late-stage surgical removal of infected or dead tissue and correction of deformity to the early-stage use of antibiotics. The gains go beyond health benefits to include reductions in hospitalization costs to health care systems and to individuals.

The NTDs for which the primary intervention is disease management are Buruli ulcer, Chagas disease, human African trypanosomiasis (HAT), leishmaniasis, leprosy, and yaws.

Vector ecology and management aims to control the transmission of the causative pathogens of insect-borne NTDs with proven interventions that are applied in an ecologically friendly manner. The main NTDs for which this is an important strategy are Chagas disease, dengue, chikungunya, visceral leishmaniasis (kala azar), and Zika virus. Table 1.8 summarizes the essential interventions for preventing and treating NTDs.

Recent Progress against NTDs

Since the NTD concept took hold, substantial successes have been recorded, including a reduction in deaths caused by visceral leishmaniasis, rabies, schistosomiasis, HAT, Chagas disease, and soil-transmitted helminthiases (among which, for example, ascariasis is estimated to

Table 1.8 Essential Intervention Package for Neglected Tropical Diseases, by Delivery Platform

Intervention type	Delivery platform ^a				
	Nationwide policies or regulations	Community health post or pharmacy	Primary health care	First-level hospital	Second- and third-level hospitals
Preventive chemotherapy	1. Integrated guidelines and strategy on the coordinated use of preventive chemotherapy for NTDs	2. Mass drug administration for lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiases, trachoma, and food-borne trematodiasis as appropriate			
Innovative and intensified disease management	3. Integrated guidelines and strategy for skin-related NTDs including (in addition to those listed elsewhere in this table) Buruli ulcer and mycetoma	4. Lymphedema management 5. Early detection and treatment of Chagas disease, human African trypanosomiasis, leprosy, and leishmaniases 6. Total community treatment for yaws		7. Hydrocele and trichiasis surgery	
Vector ecology and management	8. Integrated vector management guidelines and strategy	9. Sustained vector management for Chagas disease, dengue, and visceral leishmaniasis			
Veterinary public health services	10. Not covered in <i>DCP3</i> chapter; for interventions for the control of echinococcosis and rabies, see World Bank (2012).				
Water, sanitation, and hygiene	11. See interventions in chapter 9 of <i>DCP3</i> volume 7 (Hutton and Chase 2017).				

Note: *DCP3* = *Disease Control Priorities*, third edition (Jamison and others 2015–18); NTDs = neglected tropical diseases.

a. All interventions listed for lower-level platforms can be provided at higher levels. Similarly, each facility level represents a spectrum and diversity of capabilities. The column in which an intervention is listed is the lowest level of the health care system in which it would usually be provided.

have caused 142,000 deaths in 2012, down from about 220,000 in 2000) (WHO 2014). In addition, the following results were recorded:

- New HAT cases have fallen by 80 percent between 2000 and 2014, to an estimated total of fewer than 4,000 cases per year.
- The number of cases of visceral leishmaniasis (kala azar) in Bangladesh, India, and Nepal fell by 75 percent between 2005 (when a regional program was launched) and 2014, to a reported 10,209 cases.
- In 2000, more than 130,000 cases of dracunculiasis (Guinea worm disease) were reported; in 2015, only 22 cases were reported, reflecting near eradication.

Much of the burden of NTDs occurs with morbidity rather than mortality—and here, too, the progress has been good, albeit somewhat less dramatic: the total number of DALYs decreased by 19 percent between 2000 and 2012, from 1.0 percent of the GBD to 0.8 percent (WHO 2014).

ANTIMICROBIAL RESISTANCE

Every use of an antibiotic, whether appropriate or inappropriate, exerts selection pressure, giving resistant bacteria an advantage and accelerating the development of resistance. Bacterial resistance to first-line, second-line, and last-resort antibiotics is growing wherever it has been monitored (CDDEP 2016). Increased travel, trade, and migration mean that resistant bacteria can spread faster than ever (Du and others 2016; Johnson and Woodford 2013).

The burden of antimicrobial resistance falls heavily on LMICs. They typically have high burdens and rapid spread of infectious disease, poor nutrition, and increasing rates of antibiotic consumption in humans and animals, in addition to weaker health care systems and sparse standards and regulations governing access, use, and quality of antibiotics (Okeke and others 2005).

Drivers of Increased Antibiotic Use

The increase in antibiotic use is driven by the burden of infectious disease as well as by economic, behavioral, environmental, and structural factors. For instance, expanded insurance coverage and increased physician density intensify the consumption of antibiotics (Klein and others 2015; Zhang, Lee, and Donohue 2010). Decision fatigue and patient demand also increase antibiotic prescribing.

Antibiotic consumption increased by an estimated 30 percent or more in 71 countries between 2000 and 2010, reaching approximately 70 billion standard units (single-dose units) in 2010 (Van Boeckel and others 2014). This increase was primarily in first-line classes of antibiotics, including penicillins and cephalosporins, which together make up more than half of global consumption. Use of last-resort antibiotic classes, especially carbapenems and polymyxins, also increased.

Despite the recent increases in antibiotic consumption worldwide, with few exceptions, per capita consumption in LMICs is much lower than in HICs. Alongside increasing consumption and rising rates of antibiotic resistance, lack of access to antibiotics is still a serious concern for most LMICs. Each year, pneumonia kills approximately 1 million children under age five years, and an estimated 445,000 could be saved with the universal provision of antibiotics for community-acquired pneumococcal infections (Miller-Petrie, Pant, and Laxminarayan 2017, chapter 18 in this volume). When they are available, first-line antibiotic treatments are still relatively affordable, but newer antibiotics needed to treat resistant infections may be out of reach for LMICs (Miller-Petrie, Pant, and Laxminarayan 2017, chapter 18 in this volume).⁸

Interventions to Ensure Appropriate Antibiotic Use

Certain interventions are effective at reducing antibiotic use or increasing appropriate use, but their effects on antibiotic resistance rates are difficult to determine because of the long timeline for effects to become apparent. Therefore, recommendations are based largely on success in changing patterns of use. Interventions aim to both reduce the *need* for antibiotics by preventing infections and reduce the *inappropriate or unnecessary use* of antibiotics (in both humans and animals). The broad categories of interventions are as follows (summarized from Miller-Petrie, Pant, and Laxminarayan 2017, chapter 18 of this volume):

- *Reduce and eventually phase out subtherapeutic antibiotic use in agriculture.* Improved sanitation and hygiene at the farm level would reduce the need for prophylactic antibiotics. Antibiotic use in animal agriculture should be reduced, focusing on the involvement of farmers and the agricultural industry in carefully phasing out the use of growth promoters and premixed animal feeds (Laxminarayan, Van Boeckel, and Teillant 2015).
- *Adopt incentives that encourage antibiotic stewardship and discourage overuse.* Ensuring that payments are not linked to prescribing and introducing rewards for compliance may improve prescribing patterns.

- *Improve hospital infection control and antibiotic stewardship.* Antibiotic stewardship programs, infection prevention and control, and especially handwashing with soap can reduce infections, antibiotic use, and resistance while also improving patient outcomes.
- *Educate health care professionals, policy makers, and the public about sustainable antibiotic use.* Although public awareness is growing that antibiotic resistance presents a threat, there is little awareness of individual actions to reduce antibiotic use. Patients, parents, health care providers, stakeholders, and hospital heads all need to be aware of what they can do to reduce unnecessary use.
- *Reduce the need for antibiotics through improved water, sanitation, and immunization.* Disease prevention achieves the dual purposes of keeping people healthy and saving antibiotic doses. Water, sanitation, hygiene, and vaccination should be core components of any response, with financing from infrastructure and health sectors.
- *Ensure political commitment to meet the threat of antibiotic resistance.* Without national commitment in the form of implemented action plans, the long-term sustainability of efforts to curb antibiotic resistance will be weakened. Although international efforts to curb antibiotic resistance have focused largely on national action, international support is also needed.

COST-EFFECTIVENESS OF INTERVENTIONS FOR ADULT INFECTIOUS DISEASE

The substantial mobilization of donor resources by organizations including The Global Fund to Fight AIDS, Tuberculosis, and Malaria; The President's Emergency Plan for AIDS Relief; and the President's Malaria Initiative has been accompanied by efforts to ensure value for money, which has led to a substantial literature on the costs and cost-effectiveness of interventions to combat some major infectious diseases (but little beyond these diseases).

Figure 1.1 summarizes various estimates of cost-effectiveness, measured per DALY prevented—the metric most commonly used in economic studies to compare cost-effectiveness across different health interventions. The estimates are summarized from expert searches of the literature undertaken for the chapters in this volume. For full details of the individual studies used, along with bibliographic references, see annex 1B. All cost-effectiveness results have been translated into 2012 U.S. dollars for comparability. A few studies (particularly publications from the WHO-CHOICE (CHOsing Interventions that are Cost-Effective)

project, which provides results in international dollars of a WHO region)⁹ could not be converted and were omitted.

Cost-effectiveness results depend on context. The cost-effectiveness of the same intervention in two different countries may vary depending on local costs; health interventions, on average, cost more in countries with higher income because of higher salaries. Vaccines generally cost more in countries not eligible for bulk purchasing discounts (such as prices of Gavi, the Vaccine Alliance).¹⁰ In addition, the cost-effectiveness of vaccination and screening programs (and some other interventions) vary according to prevalence of the condition; prevention programs are often more cost-effective where prevalence is higher. Cost-effectiveness may vary with comorbidities and with opportunities to deliver the intervention synergistically with other interventions (and therefore at lower cost). *Usual care* (the usual comparator of cost-effectiveness) may also vary.

In some cases, the interventions are subdivided by study location (for example, southern Africa or Southeast Asia) or by low-income or middle-income country designation. Where neither is specified, the results apply to low- and lower-middle-income countries, which are the main emphases of this third edition of *Disease Control Priorities* (Jamison and others 2015–18). Fewer results for upper-middle-income countries are included. HIV/AIDS interventions account for almost half of the interventions and studies, consistent with its share of funding relative to other health conditions.

Figure 1.1 represents a reductionist view of the large literature on cost-effectiveness of infectious disease interventions and should be interpreted with caution, especially when comparing results of two different studies that rely on inconsistent underlying assumptions. However, more than half of the interventions listed in figure 1.1 cost less than US\$100 per DALY prevented, suggesting that they could be cost-effective even in the poorest countries. These interventions include some that are preventive, such as providing female condoms to sex workers in South Africa (although in practice, widespread use has been difficult to achieve); undertaking voluntary male circumcision in high-incidence African countries; and supplying insecticide-treated nets in Africa to prevent malaria. Biomedical treatment interventions costing less than US\$100 per DALY prevented include treating severe malaria with artesunate; screening and treating pregnant women for syphilis; treating malaria (with ACTs); treating TB (with first-line drugs); and, for various NTDs, providing detection and treatment and preventive biomedical therapy for some conditions in endemic areas.

Figure 1.1 Estimated Costs of Selected Infectious Disease Interventions



Sources: Estimates based on sources listed by subject in annex 1B of this chapter.

Note: ACT = artemisinin-combination therapy; ART = antiretroviral treatment; ARV = antiretroviral; BCC = behavior change communications; DALY = disability-adjusted life year; HIV = human immunodeficiency virus; IRS = indoor residual spraying; ITNs = insecticide-treated nets; LAC = Latin America and the Caribbean; LICs = low-income countries; LMICs = low- and middle-income countries; MICs = middle-income countries; PrEP = preexposure prophylaxis (provision of ART to noninfected individuals at risk); PMTCT = prevention of mother-to-child transmission; S Af = southern Africa; SE Asia = Southeast Asia; STH = soil-transmitted helminthiasis; STI = sexually transmitted infection; TB = tuberculosis; UMICs = upper-middle-income countries.

a. "Option A" is a two-drug ART regimen in pregnancy and postpartum for HIV-positive mothers. "Option B" is a three-drug ART regime in pregnancy and postpartum for HIV-positive mothers.

Another group of interventions costs US\$100–US\$399 per DALY prevented and thus would be considered cost-effective (less than the per capita annual income) of all but the poorest four to five countries. This second group includes providing ART for people with HIV/AIDS, with pregnant women being a particularly high priority (to prevent transmission to their children while also treating HIV in the mother). This group of interventions also includes intermittent preventive treatment of malaria in infants and pregnant women as well as treatment of MDR-TB with second-line (more expensive) drugs.

Some interventions, such as those requiring behavioral change or those being implemented in Latin America, cost more than US\$400 per DALY prevented. These include programs aiming to change sexual behavior as well as vector control interventions for dengue. PrEP, which includes provision of ART to the uninfected partner in an HIV-serodiscordant couple, varies considerably in cost-effectiveness, ranging from being cost saving to costing more than US\$5,000 per DALY prevented, depending on the context.

Interventions can be cost-effective according to global norms but still too expensive for most LICs to provide to everyone in need, especially where prevalence of the condition is high. Examples include the provision of ART in low-income African countries (Alistar, Grant, and Bendavid 2014) and the treatment of drug-resistant TB (Fitzpatrick and Floyd 2012).

Certain other interventions are likely to be cost-effective, but no studies could be identified for the context. For example, needle exchange programs for injection drug users are expected to be cost-effective given that HIV prevalence among this group worldwide is 19 percent; such programs could also prevent hepatitis B and C (Wilson and others 2015). However, cost-effectiveness estimates for needle exchange programs were not identified for low- or lower-middle-income countries.

In yet other cases, studies evaluated interventions that have been superseded by more effective measures, or several studies of the same intervention had widely divergent results. These have not been included among studies used for the cost-effectiveness analysis of infectious disease interventions (for example, PMTCT Option A has now been supplanted by Option B/B+).

CONCLUSIONS

The variety and distribution of infectious diseases have evolved over time, and they will continue to challenge the global community—as the Zika and Ebola

virus outbreaks have reminded us over the past couple of years. Through basic and translational research, some of the most devastating diseases of humankind—polio, diphtheria, measles, and tetanus—have been dramatically reduced, and smallpox has been eradicated. Meanwhile, new pathogens emerge, and newly drug-resistant organisms represent continuing and unpredictable threats.

Four main challenges will need to be met to achieve meaningful progress in the fight against the diseases addressed in this volume.

1. Focusing and Targeting of Intervention Strategies

If we have relearned something in the decade since *DCP2*, it is that infectious diseases are not distributed uniformly—not across continents, not across countries, not even in communities. Strategies should be designed to understand and respond appropriately to disease hot spots and key populations, thus ensuring access to the most effective interventions for the right populations in the right places at the right time, especially in LMICs, where the disease burden is greatest. Given the prodigious heterogeneity in the distribution of diseases (both geographically and across population subgroups) and the scarcity of resources, efficiency is increased by matching those resources to the populations that would benefit the most. Globally, infectious diseases disproportionately affect people in LMICs, which, at current rates of progress, will bear the bulk of premature deaths from infectious disease in 2030. In LMICs, the poorer, more marginalized, and often stigmatized populations are most at risk and the hardest to reach. Whereas the need for *treatment* may become obvious as it is demanded by the sick, the need and demand for *prevention* are often poorly matched. Prevention efforts can track incidence only if we know where the incidence is highest, which requires purposeful, population-based surveillance. Reaching marginalized populations will require not only dedicating resources to them but also working to remove the stigma, discrimination, and taboos that hamper effective prevention and treatment.

2. Scale-Up of Interventions against Major Infectious Diseases

Although we have evidence of interventions that work to prevent and treat disease, in many cases, those services have not been implemented at the scale necessary to sufficiently reduce incidence and the resulting morbidity and mortality. Scaling up these interventions requires that they be tailored for distribution at the

lowest appropriate level of health care service delivery and that staff is adequately trained and supervised. Areas ripe for this approach include training of pharmacists in syndromic treatment of STIs and malaria RDTs at the lowest health care level. However, scale-up will not be possible unless we address the next challenge: integration.

3. Integration of Services More Effectively across Disease Areas

Reaching the world's poor with an entire arsenal of specialized clinics is impossible. People are frequently affected by more than one condition: those who are at risk for one NTD are also likely at risk for a number of others; sex workers are at risk for multiple STIs, and HIV patients are especially susceptible to TB infection. Moreover, treatment of infectious disease has grown increasingly complex (for example, ART and TB treatment) as well as costly (as evidenced by the new hepatitis C treatment). Consequently, efforts to combat certain major diseases that have similar modes of transmission (such as HIV, STIs, and hepatitis) would benefit from shared strategies for their prevention and diagnosis. Although specialized care is clearly needed for especially rare or difficult-to-treat conditions, standardizing prevention and treatment protocols and making information and communication technologies available enable care to be pushed out to integrated service points close to where patients live, study, and work. Proximity and integration of services help ensure continuity of care from prevention or diagnosis through treatment and follow-up care. Addressing each of these challenges requires strengthening of health care systems, including communication; information technology; logistics, drug and vaccine supplies; and training of health care providers, which includes community health workers in LMICs. Additionally, improving health care systems for infectious diseases, particularly those such as HIV, TB, and hepatitis that require extended medical treatment and monitoring, provides a basis and could serve as a model for improving care and treatment for noncommunicable diseases.

4. Development of New Technologies—Drugs, Vaccines, Diagnostics, Behavioral Interventions, and Delivery Methods—to Prevent and Treat These Diseases

Most urgent is the need for the global community to invest in developing new antimicrobials. This approach includes rethinking global development assistance to focus not only on providing services

and key inputs (drugs, diagnostics, and vaccines) but also on financing research and development and operational research to create new tools or to make far better use of existing tools (Hecht and others 2012). In particular, as antimicrobial resistance continues to increase, diseases once thought to be highly treatable could, without significant investment in development of new drugs, pose a much more serious threat to global health.

A generation ago, as antibiotics were cheating death and vaccines were clearing diseases from entire continents, the world's population believed that it was moving into the postinfectious disease era. HIV seemed to be the exception that proved the rule and, at any rate, would quickly be tamed with a vaccine. Instead, these genetically facile microorganisms, which have survival as their evolutionary goal, have taught us humility. We will still be struggling against infectious diseases in future generations, but the struggle will be far less costly in lives and resources if we invest today in their control.

ANNEXES

The following annexes to this chapter are available at <http://www.dcp-3.org/infectiousdiseases>:

- Annex 1A: Forty Sexually Transmitted and Sexually Transmissible Pathogens
- Annex 1B: Sources of Cost-Effectiveness Analysis for Selected Infectious Disease Interventions

ACKNOWLEDGMENTS

The editors of this volume wish to thank Desiree Bernard, Elisabeth Gunningham, Varsha Malhotra, and Alicair Peltonen for their valuable assistance on this effort. They especially thank Brianne Adderley for her hard work keeping this large endeavor well organized.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046 to US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

1. The U.S. Centers for Disease Control and Prevention (CDC) assesses the severity of HIV disease by cluster of differentiation 4 (CD4) cell counts and the presence of specific HIV-related conditions. The WHO Clinical Staging and Disease Classification System—which can be used readily in resource-constrained settings without access to CD4 cell count measurements or other diagnostic or laboratory testing methods—classifies HIV disease on the basis of clinical manifestations that clinicians can recognize and treat (U.S. Department of Health and Human Services 2014).
2. For a comprehensive list of sexually transmitted and sexually transmissible pathogens, see annex 1A at <http://www.dcp-3.org/infectiousdiseases>.
3. Whether TB or HIV causes more deaths depends on how one allocates the deaths in coinfecting individuals. There is no clear, correct answer.
4. SDG 3, titled “Good Health and Well-Being,” aims to “Ensure healthy lives and promote well-being for all at all ages.” It sets nine primary targets, including target 3.3: “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.”
5. See table 14.2. “Nonmalarial Febrile Diseases: Exposure, Diagnosis, Prevention, and Treatment” (Crump and others 2017, chapter 14 in this volume).
6. The 18th World Health Assembly—recognized NTDs are Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis (Guinea worm disease), echinococcosis, food-borne trematodiasis, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy (Hansen’s disease), lymphatic filariasis, mycetoma, onchocerciasis (river blindness), rabies, schistosomiasis, soil-transmitted helminthiasis, taeniasis/cysticercosis, trachoma, and yaws (endemic treponematosi) (“Neglected Tropical Diseases,” WHO website, http://www.who.int/neglected_diseases/diseases/en/).
7. The High-Level Political Forum on Sustainable Development is the UN’s central platform for the follow-up and review of the 2030 Agenda for Sustainable Development (UN 2015a), adopted at the United Nations Sustainable Development Summit on September 25, 2015 (“High-Level Political Forum on Sustainable Development 2016: Ensuring that No One Is Left Behind,” UN Sustainable Development Knowledge Platform, <https://sustainabledevelopment.un.org/hlpf/2016>).
8. As is represented by the photo on the cover of this volume, the high global burden of infectious diseases (both in humans and in animals), combined with the increasing availability, use, and dispensing of antimicrobials (often based upon syndromic diagnosis rather than on diagnostic tests), contribute to the global acceleration of antimicrobial resistance.
9. The CHOICE (CHOsing Interventions that are Cost-Effective) project is a WHO initiative developed in 1998 to provide policy makers with evidence for deciding on

interventions and programs that maximize health for the available resources (“Cost-Effectiveness and Strategic Planning (WHO-CHOICE),” WHO website, <http://www.who.int/choice/en/>). “An international dollar would buy in the cited country a comparable amount of goods and services a U.S. dollar would buy in the United States (“What Is an ‘International Dollar?’” World Bank Knowledge Base, <https://datahelpdesk.worldbank.org/knowledgebase/>).

10. Gavi, the Vaccine Alliance is an international organization established in 2000 to bring together the public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the poorest countries. For more information about Gavi’s vaccine pricing strategy, see Gavi, the Vaccine Alliance (2011).

REFERENCES

- Adams, E. J., P. J. García, G. P. Garnett, W. J. Edmunds, and K. K. Holmes. 2003. “The Cost-Effectiveness of Syndromic Management in Pharmacies in Lima, Peru.” *Sexually Transmitted Diseases* 30 (5): 379–87.
- Alistar, S. S., P. M. Grant, and E. Bendavid. 2014. “Comparative Effectiveness and Cost-Effectiveness of Antiretroviral Therapy and Pre-Exposure Prophylaxis for HIV Prevention in South Africa.” *BMC Medicine* 12 (1): 46.
- Aral, S. O. 2011. “Utility and Delivery of Behavioural Interventions to Prevent Sexually Transmitted Infections.” *Sexually Transmitted Infections* 87 (Suppl 2): ii31–33.
- Babigumira, J., H. Gelband, and L. P. Garrison Jr. 2017. “Cost-Effectiveness of Strategies for the Diagnosis and Treatment of Febrile Illness in Children.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Baeten, J. M. 2016. “Making an Impact with Preexposure Prophylaxis for Prevention of HIV Infection.” *Journal of Infectious Diseases* 214 (12): 1787–89.
- Baeten, J. M., D. Donnell, P. Ndase, N. R. Mugo, J. D. Campbell, and others. 2012. “Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women.” *New England Journal of Medicine* 367 (5): 399–410.
- Baral, S., C. Beyrer, K. Muessig, T. Poteat, A. L. Wirtz, and others. 2012. “Burden of HIV among Female Sex Workers in Low-Income and Middle-Income Countries: A Systematic Review and Meta-Analysis.” *The Lancet Infectious Diseases* 12 (7): 538–49.
- Baral, S., F. Sifakis, F. Cleghorn, and C. Beyrer. 2007. “Elevated Risk for HIV Infection among Men Who Have Sex with Men in Low- and Middle-Income Countries 2000–2006: A Systematic Review.” *PLoS Medicine* 4 (12): e339.
- Bloom, B. R., R. Atun, T. Cohen, C. Dye, H. Fraser, and others. 2017. “Tuberculosis.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.

- Burnett, S. M., M. K. Mbonye, R. Martin, A. Ronald, S. Zewadd-Muyania, and others. 2016. "Effect of On-Site Support on Laboratory Practice for Human Immunodeficiency Virus, Tuberculosis, and Malaria Testing." *American Journal of Clinical Pathology* 146 (4): 469–77.
- Canchihuaman, F. A., P. J. García, S. S. Gloyd, and K. K. Holmes. 2011. "An Interactive Internet-Based Continuing Education Course on Sexually Transmitted Diseases for Physicians and Midwives in Peru." *PLoS One* 6 (5): e19318.
- CDC (U.S. Centers for Disease Control and Prevention). 1993. "Recommendations of the International Task Force for Disease Eradication." *Morbidity and Mortality Weekly Report* 42 (RR-16): 8.
- CDDEP (Center for Disease Dynamics, Economics and Policy). 2016. "Resistance Map." CDDEP, Washington, DC. <http://www.cddep.org/projects/resistance-map>.
- Chalker, J., N. T. K. Chuc, T. Falkenberg, N. T. Do, and G. Tomson. 2000. "STD Management by Private Pharmacies in Hanoi: Practice and Knowledge of Drug Sellers." *Sexually Transmitted Infections* 76 (4): 299–302.
- Chesson, H. W., P. Mayaud, and S. O. Aral. 2017. "Sexually Transmitted Infections: Impact and Cost-Effectiveness of Prevention." In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Crump, J., P. N. Newton, S. J. Baird, and Y. Lubell. 2017. "Febrile Illness in Adolescents and Adults." In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Dodd, P. J., G. P. Garnett, and T. B. Hallett. 2010. "Examining the Promise of HIV Elimination by 'Test and Treat' in Hyper-Endemic Settings." *AIDS* 24 (5): 729–35.
- Du, L., J. You, K. M. Nicholas, and R. H. Cichewicz. 2016. "Chemoreactive Natural Products that Afford Resistance against Disparate Antibiotics and Toxins." *Angewandte Chemie International Edition* 18 (55): 4220–25.
- Fitzpatrick, C., U. Nwankwo, E. Lenk, S. de Vlas, and D. Bundy. 2017. "An Investment Case for Ending Neglected Tropical Diseases." In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Fitzpatrick, M. C., and K. Floyd. 2012. "A Systematic Review of the Cost and Cost-Effectiveness of Treatment for Multidrug-Resistant Tuberculosis." *Pharmacoeconomics* 30 (1): 63–80.
- Foster, A. L., M. M. Gaisa, R. M. Hijdra, S. S. Turner, T. J. Morey, and others. 2017. "Shedding of Hepatitis C Virus into the Rectum of HIV-Infected Men Who Have Sex with Men." *Clinical Infectious Diseases* 64 (3): 284–88.
- García, P. J., C. P. Carcamo, G. P. Garnett, P. E. Campos, and K. K. Holmes. 2012. "Improved STD Syndrome Management by a Network of Clinicians and Pharmacy Workers in Peru: The PREVEN Network." *PLoS One* 7 (10): e47750.
- Gavi, the Vaccine Alliance. 2011. "Market Shaping: Access to Low and Sustainable Vaccine Prices." Document 6a for the Gavi Pledging Conference, London, June 13. <http://www.gavialliance.org/library/publications/pledging-conference-for-immunisation/6a--market-shaping--access-to-low-and-sustainable-vaccine-prices/>.
- Gomez, G. B., A. Borquez, K. K. Case, A. Wheelock, A. Vassall, and C. Hankins. 2013. "The Cost and Impact of Scaling Up Pre-Exposure Prophylaxis for HIV Prevention: A Systematic Review of Cost-Effectiveness Modelling Studies." *PLoS Medicine* 10 (3): e1001401.
- Gower, E., C. Estes, S. Blach, K. Razavi-Shearer, and H. Razavi. 2014. "Global Epidemiology and Genotype Distribution of the Hepatitis C Virus Infection." *Journal of Hepatology* 61 (1): S45–57.
- Grant, R. M., J. R. Lama, P. L. Anderson, V. McMahan, A. Y. Liu, and others. 2010. "Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men." *New England Journal of Medicine* 363 (27): 2587–99.
- Hader, S. 2017. "(Preventing) the Coming Epidemic: HIV in Youth." Presentation to the annual Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, WA, February 15.
- Harrison, O. B., K. Cole, J. Peters, F. Cresswell, G. Dean, and others. 2017. "Genomic Analysis of Urogenital and Rectal *Neisseria Meningitidis* Isolates Reveals Encapsulated Hyperinvasive Meningococci and Coincident Multidrug-Resistant Gonococci." *Sexually Transmitted Infections* 2017 (January): 1–7. doi:10.1136/sextrans-2016-052781.
- Hecht, R., D. T. Jamison, J. Augenstein, G. Partridge, and K. Thorien. 2012. "Vaccine Research and Development." In *Rethink HIV: Smarter Ways to Invest in Ending HIV in Sub-Saharan Africa*, edited by B. Lomborg, 299–320. New York: Cambridge University Press.
- Hutton, G., and C. Chase. 2017. "Water Supply, Sanitation, and Hygiene." In *Disease Control Priorities* (third edition): Volume 7, *Injury Prevention and Environmental Health*, edited by C. N. Mock, O. Kobusingye, R. Nugent, and K. R. Smith. Washington, DC: World Bank.
- Imani, P. 2015. "Effect of Integrated Infectious Disease Training and On-Site Support on the Management of Childhood Illnesses in Uganda: A Cluster Randomized Trial." *BMC Pediatrics* 5 (13).
- Jamison, D. T., J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, and P. Musgrove, eds. 2006. *Disease Control Priorities in Developing Countries*, second edition. Washington, DC: World Bank and Oxford University Press.
- Jamison, D. T., W. H. Mosley, A. R. Measham, and J. L. Bobadilla, eds. 1993. *Disease Control Priorities in Developing Countries*. Washington, DC: World Bank and Oxford University Press.
- Jamison, D. T., R. Nugent, H. Gelband, S. Horton, P. Jha, R. Laxminarayan, and C. N. Mock, eds. 2015–18. *Disease Control Priorities*. Third edition. 9 volumes. Washington, DC: World Bank.
- Jenness, S. M., S. M. Goodreau, E. Rosenberg, E. N. Beylerian, K. W. Hoover, and others. 2016. "Impact of the Centers for Disease Control's HIV Preexposure Prophylaxis Guidelines

- for Men Who Have Sex with Men in the United States.” *The Journal of Infectious Diseases* 214 (12): 1800–07.
- Johnson, A. P., and N. Woodford. 2013. “Global Spread of Antibiotic Resistance: The Example of New Delhi Metallo- β -Lactamase (NDM)-Mediated Carbapenem Resistance.” *Journal of Medical Microbiology* 62 (Pt 4): 499–513.
- John-Stewart, G., R. W. Peeling, C. Levin, P. J. Garcia, D. Mabey, and J. Kinuthia. 2017. “Prevention of Mother-to-Child Transmission of HIV and Syphilis.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Kahn, J. G., L. Bollinger, J. Stover, and E. Marseille. 2017. “Improving the Efficiency of the HIV/AIDS Policy Response: A Guide to Resource Allocation Modeling.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Katz, I. T., and A. A. Wright. 2008. “Circumcision—A Surgical Strategy for HIV Prevention in Africa.” *New England Journal of Medicine* 359 (23): 2412–15.
- Kippax, S., and N. Stephenson. 2012. “Beyond the Distinction between Biomedical and Social Dimensions of HIV Prevention through the Lens of a Social Public Health.” *American Journal of Public Health* 102 (5): 789–99.
- Klein, E. Y., M. Makowsky, M. Orlando, E. Hatna, N. P. Braykov, and others. 2015. “Influence of Provider and Urgent Care Density across Different Socioeconomic Strata on Outpatient Antibiotic Prescribing in the USA.” *Journal of Antimicrobial Chemotherapy* 70 (5): 1580–87.
- Kratz, M. M., D. Weiss, A. Ridpath, J. R. Zucker, A. Geevarughese, and others. 2015. “Community-Based Outbreak of *Neisseria meningitidis* Serogroup C Infection in Men Who Have Sex with Men, New York City, New York, USA 2010–2013.” *Emerging Infectious Disease* 21 (8): 1379–86.
- Laxminarayan, R., T. Van Boeckel, and A. Teillant. 2015. “The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector.” Food, Agriculture, and Fisheries Papers 78, Organisation for Economic Co-operation and Development, Paris.
- Liang, X., S. Bi, W. Yang, L. Wang, G. Cui, and others 2009. “Evaluation of the Impact of Hepatitis B Vaccination among Children Born during 1992–2005 in China.” *Journal of Infectious Diseases* 200 (1): 39–47.
- Looker, K. J., A. S. Magaret, K. M. E. Turner, P. Vickerman, S. L. Gottlieb, and others. 2015. “Global Estimates of Prevalent and Incident Herpes Simplex Virus Type 2 Infections in 2012.” *PLoS One* 10 (10): e0140765.
- Madhav, N., B. Oppenheim, M. Galivan, P. Mulembakani, E. Rubin, and N. Wolfe. 2018. “Pandemics: Risks, Impacts, and Mitigation.” In *Disease Control Priorities* (third edition): Volume 9, *Disease Control Priorities: Improving Health and Reducing Poverty*, edited by D. T. Jamison, R. Nugent, H. Gelband, S. Horton, P. Jha, R. Laxminarayan, and C. N. Mock. Washington, DC: World Bank.
- Miller-Petrie, M., S. Pant, and R. Laxminarayan. 2017. “Drug-Resistant Infections.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Mohapatra, B., D. A. Warrell, W. Suraweera, P. Bhatia, N. Dhingra, and others. 2011. “Snakebite Mortality in India: A Nationally Representative Mortality Survey.” *PLoS Neglected Tropical Diseases* 5 (4): e1018.
- Mokdad, A. H., M. H. Forouzanfar, F. Daoud, A. A. Mokdad, C. El Bcheraoui, and others. 2016. “Global Burden of Diseases, Injury, and Risk Factors for Young People’s Health during 1990–2013: A Systematic Analysis for the Global Burden of Disease Study 2013.” *The Lancet* 387 (10036): 2383–401.
- Nanduri, S., C. Foo, V. Ngo, C. Jarashow, R. Civen, and others. 2016. “Outbreak of Serogroup C Meningococcal Disease Primarily Affecting Men Who Have Sex with Men—Southern California.” *Morbidity and Mortality Weekly Report* 65 (35): 939–40.
- Newman, L., J. Rowley, S. Vander Hoorn, N. S. Wijesooriya, M. Unemo, and others. 2015. “Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting.” *PLoS One* 10 (12): e0143304.
- Norheim, O., P. Jha, K. Admasu, T. Godal, R. Hum, and others. 2015. “Avoiding 40% of the Premature Deaths in Each Country, 2010–30: Review of National Mortality Trends to Help Quantify the UN Sustainable Development Goal for Health.” *The Lancet* 385 (9964): 239–52.
- Okeke, I. N., K. P. Klugman, Z. A. Bhutta, A. G. Duse, P. Jenkins, and others. 2005. “Antimicrobial Resistance in Developing Countries. Part II: Strategies for Containment.” *The Lancet Infectious Diseases* 5 (9): 568–80.
- Owusu-Eduesei, K., Jr., G. Tao, T. L. Gift, A. Wang, L. Wang, and others. 2014. “Cost-Effectiveness of Integrated Routine Offering of Prenatal HIV and Syphilis Screening in China.” *Sexually Transmitted Diseases* 41 (2): 103–10.
- Pretorius, C., J. Stover, L. Bollinger, N. Bacaer, and B. Williams. 2010. “Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa.” *PLOS ONE* 5(11).
- Sánchez, J., E. Gotuzzo, J. Escamilla, C. Carrillo, L. Moreyra, and others. 1998. “Sexually Transmitted Infections in Female Sex Workers: Reduced by Condom Use but Not by a Limited Periodic Examination Program.” *Sexually Transmitted Diseases* 25 (2): 82–89.
- Schweitzer, A., J. Horn, R. T. Mikolajczyk, G. Krause, and J. J. Ott. 2015. “Estimations of Worldwide Prevalence of Chronic Hepatitis B Virus Infection: A Systematic Review of Data Published Between 1965 and 2013.” *The Lancet* 386 (10003): 1546–55.
- Shretta, R., J. Liu, C. Cotter, J. Cohen, C. Dolenz, and others. 2017. “Malaria Elimination and Eradication.” In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.

- Smith J. S., P. A. Gilbert, A. Melendy, R. K. Rana, and J. M. Pimenta. 2011. "Age-Specific Prevalence of Human Papillomavirus Infection in Males: A Global Review." *Journal of Adolescent Health* 48 (6): 540–52.
- Stanaway, J. D., A. D. Flaxman, M. Naghavi, C. Fitzmaurice, T. Vos, and others. 2015. "The Global Burden of Viral Hepatitis from 1990 to 2013: Findings from the Global Burden of Disease Study 2013." *The Lancet* 388 (10049): 1081–88.
- UN (United Nations). 2015a. *Resolution Adopted by the General Assembly on 25 September 2015. Transforming Our World: The 2030 Agenda for Sustainable Development*. Resolution A/RES/70/1, United Nations General Assembly, New York.
- . 2015b. *The Millennium Development Goals Report 2015*. New York: UN.
- UNAIDS (Joint United Nations Programme on HIV/AIDS). 2015. *AIDS by the Numbers 2015*. Booklet, UNAIDS, Geneva.
- . 2016. "Global HIV Statistics." Fact sheet, November, UNAIDS, Geneva.
- U.S. Department of Health and Human Services. 2014. *Guide for HIV/AIDS Clinical Care*. Clinical reference guide, HIV/AIDS Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, MD.
- Van Boeckel, T. P., S. Gandra, A. Ashok, Q. Caudron, B. T. Grenfall, and others. 2014. "Global Antibiotic Consumption 2000 to 2010: An Analysis of National Pharmaceutical Sales Data." *The Lancet Infectious Diseases* 14 (8): 742–50.
- Verguet, S., R. Laxminarayan, and D. T. Jamison. 2015. "Universal Public Finance of Tuberculosis Treatment in India: An Extended Cost-Effectiveness Analysis." *Health Economics* 24 (3): 318–32.
- Weaver, M.R., S.M. Burnett, I. Crozier, S.N. Kinoti, I. Kirunda, and others. 2014. "Improving Facility Performance in Infectious Disease Care in Uganda: A Mixed Design Study with Pre/Post and Cluster Randomized Trial Components." *PLoS One*. 9(8).
- WHO (World Health Organization). 2014. "Global Health Estimates 2014 Summary Tables: DALY by Cause, Age, Sex by World Bank Income Category, 2000–2012." WHO, Geneva. http://www.who.int/healthinfo/global_burden_disease/en.
- . 2015. *Investing to Overcome the Global Impact of Neglected Tropical Diseases: Third WHO Report on Neglected Tropical Diseases*. Geneva: WHO.
- . 2016a. *Global Tuberculosis Report 2016*. Geneva: WHO.
- . 2016b. "Sexually Transmitted Infections (STIs)." Fact sheet, WHO, Geneva.
- . 2017. "Ghana, Kenya and Malawi to Take Part in WHO Malaria Vaccine Pilot Programme." News Release, WHO, Geneva, April 24.
- Wilson, D. P., B. Donald, A. J. Shattock, D. Wilson, and N. Fraser-Hurt. 2015. "The Cost-Effectiveness of Harm Reduction." *International Journal of Drug Policy* 26 (Suppl 1): S5–11.
- Wilson, D. P., and J. Taaffe. 2017. "Tailoring the Local HIV/AIDS Response to Local HIV/AIDS Epidemic." In *Disease Control Priorities* (third edition): Volume 6, *Major Infectious Diseases*, edited by K. K. Holmes, S. Bertozzi, B. R. Bloom, and P. Jha. Washington, DC: World Bank.
- Winer, R. L., J. P. Hughes, Q. Feng, L. F. Xi, S. K. Lee, and others. 2012. "Prevalence and Risk Factors for Oncogenic Human Papillomavirus Infections in High-Risk Mid-Adult Women." *Sexually Transmitted Diseases* 39 (11): 848–56.
- World Bank. 1993. *World Development Report 1993: Investing in Health*. Washington, DC: World Bank and Oxford University Press.
- . 2012. *People, Pathogens and Our Planet: Volume 2, The Economics of One Health*. Economic and Sector Work, Report 69145-GLB. Washington, DC: World Bank.
- World Health Assembly. 2005. *International Health Regulations (2005)*. Geneva: World Health Organization.
- Zhang, Y., B. Y. Lee, and J. M. Donohue. 2010. "Ambulatory Antibiotic Use and Prescription Drug Coverage in Older Adults." *Archives of Internal Medicine* 170 (15): 1308–14.

