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REVIEW

The Population Dynamics and Control of Tuberculosis

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More than 36 million patients have been successfully treated via the World Health Organization's strategy for tuberculosis (TB) control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010. Here we review the changing relationship between the causative agent, *Mycobacterium tuberculosis*, and its human host and examine a range of factors that could explain the persistence of TB. Although there are ways to reduce susceptibility to infection and disease, and a high-efficacy vaccine would boost TB prevention, early diagnosis and drug treatment to interrupt transmission remain the top priorities for control. Whatever the technology used, success depends critically on the social, institutional, and epidemiological context in which it is applied.

A century or more of social and economic progress, reinforced by the postwar discovery of efficacious drugs, had driven tuberculosis (TB) to low levels in the rich world of the 1980s. With no systematic evaluation of data from developing countries, no forewarning of the impending spread of HIV/AIDS or of the demise of the Soviet Union, and no coherent approach to control, TB was invisible to international donors and taken to be a fact of life in the most-affected parts of the world.

Four events put TB firmly on the global health agenda. First, the 1990 Global Burden of Disease Study (GBD 1990) identified TB as one of the top 10 causes of morbidity and mortality worldwide. TB became prominent in health statistics because untreated disease, with a case fatality rate of around 50%, cost millions of young adults decades of healthy life. Second, GBD 1990 and subsequent analyses began to measure the impact of the spread of HIV/AIDS and the health consequences of social and economic crisis in eastern Europe. Third, clinical and economic studies showed that combination drug treatment for TB was among the most effective and cost-effective of all health interventions. Fourth, in response to all these observations, the World Health Organization (WHO) launched a new control strategy, based on Directly Observed Treatment and Short-course drug therapy (DOTS).

In 2006 the Stop TB Strategy added new elements to DOTS, articulating the importance of managing drug-resistant and HIV-associated TB and of engaging the many different participants in health care. Twenty years on, systematic monitoring and evaluation have revealed both successes and failures of DOTS and the Stop TB Strategy. Among the successes, 36 million patients were treated worldwide between 1995 and 2008, and up to 8 million deaths were averted (*1*). WHO's target cure rate of 85% was exceeded in the 2007–2008 global cohort of 2.7 million new sputum smear-positive patients, and case detection in 2008 reached an estimated 61%, close to the 70% target. A combination of surveys, surveillance, and mathematical modeling suggests that targets of halving 1990 levels of prevalence and mortality by 2015 could be reached in four of six WHO regions. The exceptions are Africa (sub-Sahara) and Europe (former Soviet countries).

Worldwide, TB incidence per capita is falling at an estimated 1% per year. Although this slow rate of decline satisfies the Millennium Development Goal (MDG) for TB, which is to ensure that the incidence rate is falling by 2015, the world's population is growing at about 2% per year, so the total number of new TB cases is still rising (*1*). There are expected to be 9.8 million new cases in 2010, more than in any previous year in history. Eighty percent of these cases will be found in the 20 to 25 highest-burden countries, and more than one-third in India and China. A review of cases reported by 134 countries between 1998 and 2007 found that only 35 had per capita rates of decline exceeding 5% per year (*2*). These were countries with either small populations (<20 million) or high incomes [gross domestic product (GDP) > US$10,000 per capita]. Incidence rates were increasing in 41 countries, 19 in sub-Saharan Africa.

With MDG target year 2015 now in sight, we examine here a range of factors that affect TB burden and trends, and which could explain why drug treatment programs have had such little impact on TB transmission and case load.

TB Epidemiology and Control: The Standard Model

The expected effects of control are derived from the standard model of TB natural history in which the pathogen, *Mycobacterium tuberculosis*, is considered a single entity and the response to lung infection is represented by two dichotomies: fast (primary progression) or slow transition (via latency) from infection to infectious or noninfectious disease (Fig. 1) (*3*). This compartmentalization simplifies the natural history, makes epidemiological calculations easier, and facilitates the management of patients who can be placed in a few distinct categories. DOTS and the Stop TB

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Strategy have given priority to patients that present at clinics with infectious, sputum smear-positive TB, as reflected in the WHO targets for case detection and cure.

The standard model has been formalized mathematically in various ways (*4*); one interpretation predicts that TB incidence per capita will fall at 5 to 10% per year when target values of case detection (70%) and cure (85%) have been exceeded (*5*). These results were derived mainly from the large-scale impact of drug treatment in Europe and North America after 1950. In England and Wales, as in the United States, the number of new TB cases per capita fell by 5 to 6% annually for 30 years and TB deaths at 9 to 10% annually (Fig. 2A). On a smaller scale, among Eskimo communities, intensive drug treatment supplemented by isoniazid preventive therapy has achieved even faster rates of decline in cases (13% per year) and deaths (30% per year) (*6*).

These early achievements in Europe and North America defined expectations for high-burden countries in the developing world, and there have been a few successes. To pick just one, Estonia has reversed the post-Soviet rise in TB, cutting the numbers of cases and deaths and case fatality, and pushing down multidrug-resistant TB (MDR-TB) at least as quickly as drug-sensitive TB (Fig. 2B) (*7*, *8*). Estonia has shown what can be done with a good control program, but their achievement remains exceptional. Nearly two decades after the formulation of DOTS, and more than half a century after the development of combination therapy, the potential of drugs to reduce transmission has been only partly realized (Fig. 2, C and D) (*1*). We now look for explanations, by examining characteristics of the pathogen and its transmission, of humans as hosts, and of the structure of pathogen and human populations.

Certain Strains of *M. tuberculosis* Are More Transmissible Than Others

Before phenotypic (e.g., sensitivity to drugs) and genotypic (e.g., DNA fingerprinting) variation among strains could be observed, there was some justification for treating *M. tuberculosis* as a single organism. But as the analysis of genetic variation has become faster and cheaper, using a greater range of discerning techniques, much information has emerged about *M. tuberculosis* as a family of strains and lineages. Some of this is old biology, newly uncovered; other findings show how TB epidemiology is changing in the world today. Recent investigations have revealed hypervariable regions of the genome (*9*), the evolutionary origins of the *M. tuberculosis* complex (*10*), how this pathogen has spread around the world from African origins (*11*), and which genes code for drug resistance (*12*, *13*). The data have demonstrated variation in the evolutionary fitness of drug-resistant Beijing and other strains, that different strains spread more or less
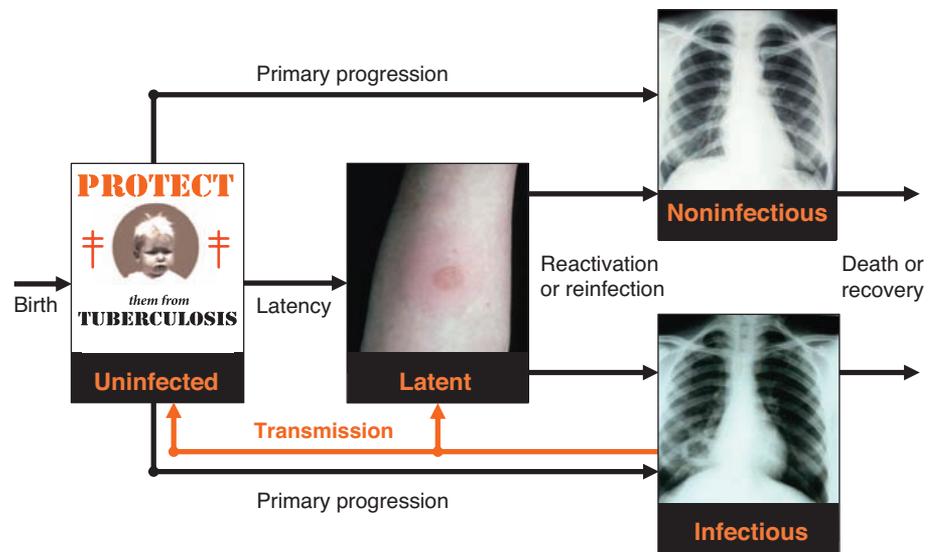

Fig. 1. Compartmental model of tuberculosis transmission, infection, reinfection, reactivation, and disease. Latent infection is commonly identified by a tuberculin skin test. Cavitary lung disease is most infectious (lower chest x-ray); noncavitary (upper chest x-ray) and extrapulmonary disease are less infectious or noninfectious. In the simplest mathematical models, TB is assumed to exist in a closed population, with no immigration or emigration and a constant number of people at each age (*3*). [Credits: "Protect" poster: American Lung Association/National Library of Medicine; "Latent": Bart's MedicalLibrary/Phototake; x-rays: Wellcome Images]

quickly through populations, and that there are strains more and less capable of causing active TB (*7*, *14–18*) (Fig. 3A). From all this work it is clear that parameters of the standard model, as they relate to the characteristics of *M. tuberculosis*, vary among strains and settings, and through time. The magnitude of this variation and its epidemiological consequences are largely unquantified, though the success of control programs may depend on it.

Numerous Human Genetic Polymorphisms Are Linked to TB

High death rates from TB in 17th- to 19th-century Europe (≈20 to 30% of all mortality) exerted relatively strong selection pressure for genes that protect against TB, as compared with other infections. Even so, it is unlikely that selection was strong enough to explain much of the decline in TB in 20th-century Europe (Fig. 2A) (*19*). Now, in the early 21st century, mortality rates are far lower than in 19th-century Europe, even in countries considered to be highly endemic for TB (e.g., ≈3% of deaths are due to TB in Southeast Asia). We can infer that natural selection has a negligible role in the decline of TB today.

More plausibly, geographically varying rates of selection in the past have influenced the present distribution of polymorphisms linked to TB. A variety of genetic variants are known to affect susceptibility to TB, including those of the major histocompatibility complex, the macrophage protein SLC11A1 (also known as NRAMP), the vitamin D receptor, and the interferon-γ and nitric oxide synthase pathways (*20*). Case control and genome-wide association studies will doubtless

reveal more genetic mechanisms of resistance, but effects of modest size (odds ratios, OR < 3) will probably be the norm. Even with weak effects, common genes can account for a large fraction of cases in some settings. For example, children carrying the NRAMP NO2 polymorphism at one site in the southern United States were three times as likely to have TB. Because of its high prevalence (76%) in that population, this variant accounted for most (85%) childhood TB (*21*). The main motive for studying human genetic determinants of TB has been to devise better tools for control, including vaccines and personalized drug regimens. Consequently, there have been few studies of how polymorphisms can explain contemporary epidemiological differences among populations—the background to control in any setting.

From an evolutionary perspective, we expect the outcome of infection to be influenced by gene-gene interactions within hosts and by interactions between pathogen and host genotypes. New evidence that *M. tuberculosis* lineages are adapted to specific host populations is therefore consistent with expectations (*20*, *22*) (Fig. 3B). Given multiple polymorphisms and gene interactions, whose expression depends on environmental context, we anticipate a greater variety of responses to infection than are captured by the dichotomies of the standard model (Fig. 1).

Some Infected People Are at High Risk of Developing Active TB

The tuberculin skin test and interferon-γ release assays are measures of cellular immunity and

putative markers of latent infection (*23*). These tests monitor a diversity of responses to infection, with varying rates of progression and recession including states with no persistent infection but primed T cells; low populations of nonreplicating bacteria; and replicating bacteria kept at subclinical levels by immunity (*24*). Individuals that have been exposed to *M. tuberculosis*, with various environmental and genetic backgrounds, might pass through any number of these states, and the variable (among individuals) and changing (through time) response to infection could be an attribute of pathogen or host, or of the interplay between combinations of hosts and pathogens (Fig. 3B) (*25*). This unfolding story of latency is another reminder that the fast-slow dichotomy in Fig. 1 is a coarse representation of a continuum. And the balance of different kinds of latent state might vary from one population to another depending on, for example, the ambient and recent history of infection.

Isoniazid preventive therapy (IPT) is cheap and highly efficacious (up to 90%) in stopping progression to active TB among people who are skin-test positive. IPT is recommended for HIV-positives in TB endemic areas, though few patients receive it (*26*). It is not widely used among HIV-negatives because hundreds of infected people have to be tuberculin tested and then treated to prevent one case, the course of treatment is long (6 to 9 months), and there are side effects, albeit at low frequency. The result is that, despite having an effective drug, progression from latent to active TB is largely unchecked.

Some Kinds of People and Patients Transmit More Infections Than Others

The standard TB model distinguishes sputum smear-positive cases from smear-negative cases (Fig. 1). This routine differential diagnosis is not ideal because smear microscopy fails to confirm the presence of *M. tuberculosis* in many true TB cases (culture is more sensitive). But it does offer an underexploited opportunity to search actively for the most infectious cases in a community. In Morocco, for example, half the smear-positive cases are found among men aged 15 to 44 years, who make up only a quarter of the population and who are a focus of transmission, especially in densely populated urban areas (*27*).

The number of infections transmitted by a TB case depends not only on the bacterial load in sputum, but also on the duration of infectiousness. An episode of TB can be prolonged by events that take place before, during, and after diagnosis. There may be delays before diagnosis when health services are inaccessible, service charges are unaffordable, and procedures in infection control are not observed. Private, out-of-pocket expenditure is a major barrier to seeking health care and accounts for a large fraction of spending on health in poor countries (Fig. 3C). While traditional diagnostic tests have limited sensitivity

(sputum smear microscopy) and specificity (chest x-ray), further needless errors arise through their improper use. Some failures of standard procedure for preventing infection have had dramatic consequences, such as the 2008 South African outbreak of extensively drug-resistant TB (XDR-TB) caused mainly by hospital transmission (*28*).

More subtly, there could be an interaction between the severity of illness and a patient's behavioral response to it. If patients with moderate disease tolerate it for longer, they might transmit more infections during extended episodes of illness. The ratio of TB prevalence to incidence is a measure of the duration of illness, which increases markedly with age in some settings. The prevalence/incidence ratio exceeded 10 years among elderly people in the Republic of (South) Korea, which suggests that they were persistent sources of infection (*29, 30*). To the extent that disease severity is a characteristic of bacterial genotype, this is potentially a mechanism for the selection of strains of lower virulence.

Infectiousness does not always end with diagnosis. Although combination drug therapy has the potential to cure almost all patients carrying drug-sensitive and drug-resistant strains of *M. tuberculosis*, cutting transmission and preventing most TB deaths, some patients fail treatment because they do not complete the full course, or because they are given inappropriate combinations of drugs. The consequences can be serious, clinically and epidemiologically; for example, treatment failure is the most obvious explanation for the persistently high fraction (≈10%) of patients with recurrent episodes of smear-positive TB in India (*1*).

Most HIV Epidemics Have Peaked, But Prevalence Is Falling Slowly

HIV coinfection is the most powerful known risk factor for susceptibility to *M. tuberculosis* infection and progression to active disease. The incidence rate ratio of TB among HIV-positives
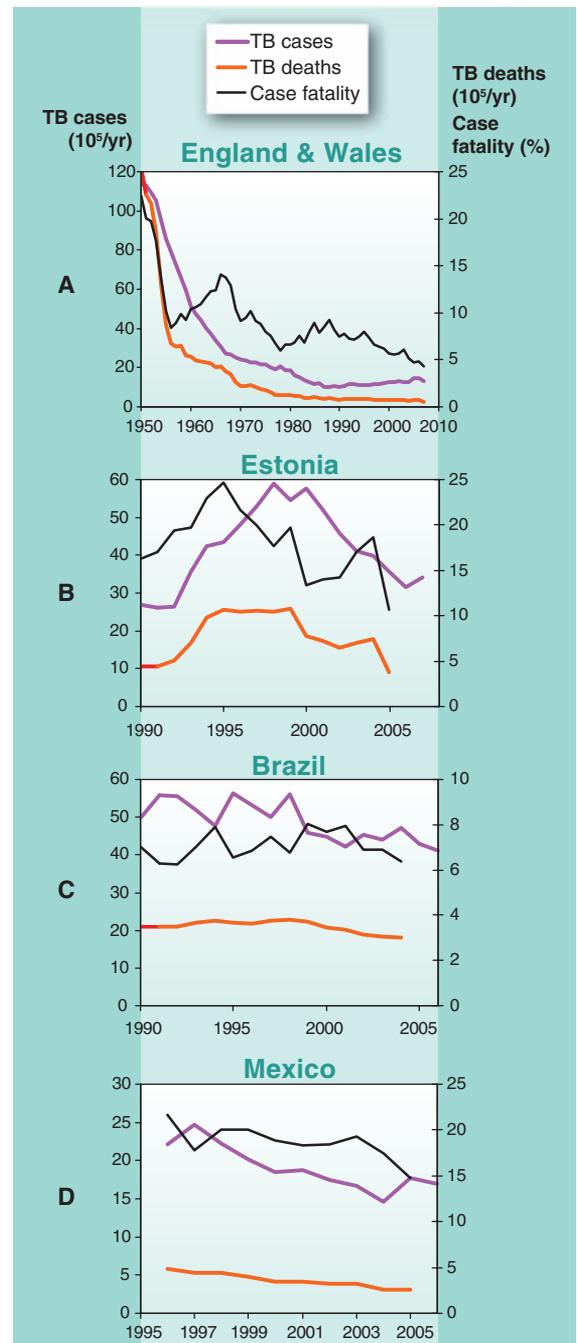

Fig. 2. Trends in TB cases and deaths per 100,000 population reported from (**A**) England and Wales (1913 to 2007), (**B**) Estonia (1990 to 2007), (**C**) Brazil (1990 to 2006), and (**D**) Mexico (1996 to 2006). The decline in European countries such as England and Wales (A) between 1950 and 1980 (cases 6%/year, deaths 10%/year) set expectations that have not been met in most developing countries. Estonia (B) is an unusual example of success in former Soviet Europe, showing how the rise of drug-sensitive and MDR-TB can be reversed by early diagnosis and treatment. Cases have fallen at 7%/year and deaths at 11%/year since the peak in 1998. TB decline has been sluggish in Brazil (C) (cases 2%/year, deaths 1%/year) and somewhat faster in Mexico (D) (cases 4%/year, deaths 7%/year), but still below potential. Data from the UK Health Protection Agency (www.hpa.org.uk) and (*1, 7, 8*).

as compared with HIV-negatives is on the order of 20 in countries with high HIV prevalence (*1*). The effect at population level has been to treble the number of TB cases reported annually from sub-Saharan Africa, and the increase has been greatest in eastern and southern parts of the continent. HIV epidemics have now peaked in the worst-affected African countries. In Tanzania, HIV seroprevalence data indicate that the HIV incidence rate was already falling by 1990, and prevalence by 1996. Consequently, the TB incidence rate has also been in slow decline since 2000 (Fig. 3D).

Although HIV epidemics have generated a large excess of TB cases, it is still not known whether coinfection has generated more or fewer *M. tuberculosis* infections than otherwise expected. Some studies have found that HIV-infected TB cases are less likely to be smear-positive than those cases uninfected with HIV, and that illness typically progresses more quickly, so that the infectious period before diagnosis is shorter. The "disease duration ratio" for HIV-positive TB cases as compared with HIV-negatives has been compared in two South African communities (*31*), but neither study calculated the total number of infections transmitted.

Epidemics of Some Chronic Diseases Exacerbate TB

Apart from HIV, other factors well known to increase susceptibility to infection and disease include alcohol abuse, diabetes, undernutrition, and tobacco smoking (*32*). The adverse effects of smoking are probably due to a combination of mechanical lung damage, oxidative stress, and the inhibition of T cell–mediated immune pathways that produce interferon-γ, interleukin-12, and tumor necrosis factor–α (*33*). Smokers typically have about twice the risk of pulmonary TB as compared with nonsmokers and, in India, up to half of all male TB deaths have been attributed to smoking (*34*). The prevalence of smoking in India, as in most other developing countries, is no longer increasing. But the number of smokers and smoking-related deaths is rising with population growth (*35*). Smoking is therefore expected to increase the number of TB cases and deaths too.

Like smoking, diabetes is associated with the suppression of cell-mediated immunity, though this might not fully explain the roughly threefold increase in TB risk among diabetics (*36*). Unlike smoking, both the prevalence of diabetes and the number of diabetes cases are rising worldwide. The increase is faster in developing than in high-income countries, with onset at younger ages in Asia (*37*, *38*). Approximately 20% of smear-positive TB cases were attributed to concurrent diabetes in India in 2000 (*39*). If the projected rise from 25 million diabetes cases in 2000 to 80 million in 2030 is accurate, and the risk ratio remains the same, then 42% of smear-positive TB cases in India will be attributable to diabetes in 2030. Each TB case caused by diabetes would

infect other people, adding to the TB burden. Paradoxically, diabetes is linked to obesity, but whereas the former is a risk factor for TB, the latter is evidently protective (*40*). This apparent contradiction is yet to be resolved.

During the 1990s in post-Soviet Russia, alcoholism was a major cause of premature death and may also have contributed to the resurgence of TB (*41*). The number of overweight or obese people is increasing worldwide, but so is the number who are underweight. The number of undernourished people has grown by an estimated 9% since 1990, exceeding a billion in 2009, with unknown impact on TB (*42*).

Most People Now Live in High-Density Urban Areas

As often observed, infectious diseases are a penalty for high-density urban living; TB reached a peak in 19th-century Europe as urbanization went hand in hand with industrialization. In India, the risk of TB infection is higher in urban than in rural areas (*43*), and the urban population of India is expected to double between 2010 and 2030, reaching nearly 600 million people. But city life has advantages that offset the relatively high contact rates: Compared with rural areas, a higher proportion of people are wealthy and have better access to health services. In line with this view, the percentage of people in Indian cities living in poverty (as judged by income and living conditions) halved from 49% in 1973–1974 to 26% in 2004–2005 (*44*). Whether this downward trend in urban poverty will forestall an increase in TB remains an open question, not least because urbanization is confounded with other factors such as the rising prevalence of diabetes (*38*).

In China, internal migration has played a bigger part in urban growth than in India (*45*), with important consequences for TB. The number of TB cases per 100,000 inhabitants of Beijing declined from 20 in 1980 to 7 in 1993, but has since remained more or less steady as the number of cases among migrants to the city has increased.

In the low-incidence, high-income countries of western Europe and north America, immigration from high-burden countries has become a dominant factor in TB epidemiology. Most TB cases in the Netherlands, Norway, the United Kingdom, and the United States are due to infections brought in by young, foreign-born adults. These immigrants typically live in inner-city areas, often with poor access to health care. Consequently, TB incidence is falling more slowly in countries that have a larger proportion of foreign-born cases (*2*).

Populations Are Aging

Most of the countries where TB remains highly endemic are in demographic and epidemiological transition. Longevity is increasing, birth rates are falling, and populations are becoming older on average. The average age of the Indian population was 28 years in 2010 but will be 39 years in 2050.

Greater longevity is swelling the age classes that now have the highest TB incidence rates, namely adults over 45 years.

But it is not yet clear whether we can expect more or less TB in aging populations. With longer life spans, more people survive to acquire infection. With falling fertility, a population acquires fewer susceptibles each year. Greater longevity and lower fertility both tend to increase the prevalence of infection. Individuals carrying latent infections are a source of TB arising by reactivation, but they are also partially immune to reinfection. A simple elaboration of the standard TB model suggests that, on balance, aging will cause a small reduction in TB incidence per capita, unless the risk of developing TB after exposure is relatively high in older people (*3*). A relatively high risk of TB among the elderly is a real possibility, and could explain the slowing decline of TB in Hong Kong (*46*). To resolve this question, the standard model needs to be extended to explore the interplay between survival, fertility, and the risk of TB with age. Whether TB incidence (per capita or total case load) rises or falls in aging populations, the proportion of cases among elderly people is almost certain to increase in most countries.

Young Adults Are Rejuvenating TB Epidemics

The standard TB model assumes that patterns of mixing among infectious cases and their contacts, and the risk of TB among those infected, are constant through time. Consequently, when transmission is reduced by drug treatment, the average age of new cases should increase. The reason is that a progressively higher proportion of these cases comes from older rather than recent infections. In some countries where TB is in slow decline, like China, there are clear deviations from the expected pattern. The average age of older Chinese women (>55 years) with smear-positive TB has been steadily increasing, but the reverse is true for younger women with TB (Fig. 3E). Mexico, Myanmar, Sri Lanka, and Vietnam show the same phenomenon, for men or women or both.

There are at least four possible explanations. First, HIV coinfection generates a disproportionate number of cases among young men and women. Second, infections are imported into cities by young, foreign-born adults. Third, there are higher contact and transmission rates among young adults migrating internally to high-density urban areas. Fourth, novel strains like Beijing are found predominantly among younger cases and could have higher rates of transmission than other strains. Whatever the cause in any setting, the overrepresentation of TB in young adults is a departure from the standard model, and another obstacle to TB control.

Economic Shocks Can Cause Detrimental and Lasting Epidemiological Changes

Financial crises can interrupt health services while augmenting the risk of TB associated with, for ex-
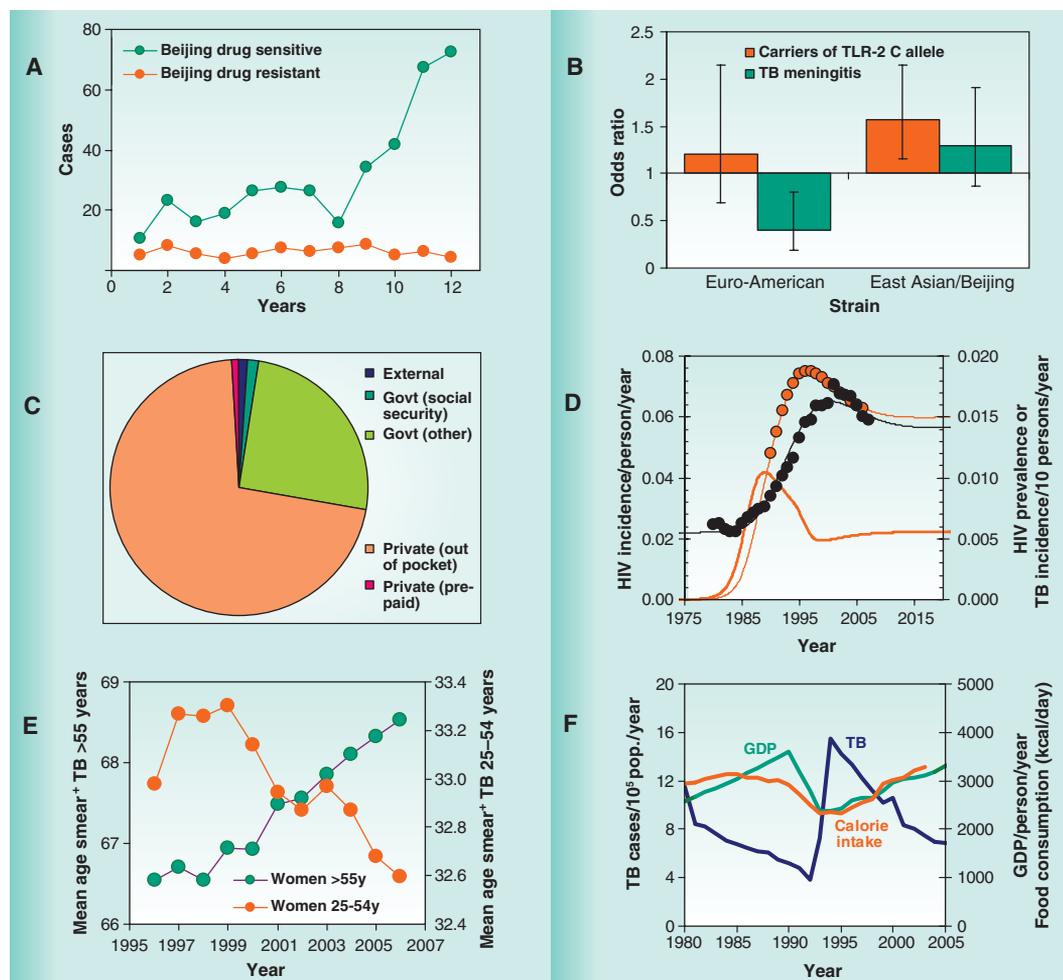
Fig. 3. Understanding the factors that affect TB trends will help to make control programs more successful. (**A**) Two strains of *M. tuberculosis* with different dynamics. Annual number of drug-sensitive (green) and drug-resistant (orange) cases of the Beijing clade. The number of cases caused by the drug-susceptible clade rose steeply after year 8. Data from (*17*). (**B**) Interactions between host and bacterial genotypes affect the risk of TB. In Vietnam, individuals carrying the C allele at the TLR-2 T597C locus appeared more likely to have TB caused by the East-Asian/Beijing genotype than by other genotypes (orange). Individuals infected with the Euro-American lineage of *M. tuberculosis* were less likely to have meningeal than pulmonary tuberculosis (green), suggesting that these strains are less capable of extrapulmonary dissemination within hosts. Data from (*22*). (**C**) Sources of health expenditure in India. Seventy-two percent of spending on health is private, out-of-pocket, a characteristic of many developing countries. For individuals on low incomes, an episode of TB can cost the equivalent of several months' salary. Source: WHO national health accounts (www.who.int/nha/en). (**D**) HIV prevalence has peaked in most countries, and TB epidemics are expected to turn downwards after a delay of 4 to 5 years. Here a mathematical model has been used to interpret and project trends in HIV incidence (orange line), HIV prevalence (orange line and points), and TB incidence (black line and points) in Tanzania. Source: authors' calculations. (**E**) Rejuvenation of the TB epidemic in China. As the risk of infection declines, the average age of smear-positive TB cases increases among elderly women (green), but falls among young women (orange). The disproportionately large number of cases among young adults is an obstacle to TB control. Data from (*1*). (**F**) Economic shock and tuberculosis in Cuba. After 1991, GDP (green) and food energy consumption (orange, kcal/day) dropped sharply, as TB incidence (blue) increased. TB cases started falling again slowly as GDP and calorie intake recovered (*1*, *47*).

ample, alcoholism, malnutrition, and the congregation of displaced people. The impact on TB dynamics is strongly asymmetric because brief periods of elevated transmission, or of rapid breakdown from infection to disease, generate an abundance of new infections, which typically have an incubation period of several years. Reductions in incidence that took decades to achieve can be reversed within months, requiring decades for recovery. After the dissolution of the Soviet Union in

1991, excess TB cases and deaths in the newly independent states were tightly linked to lost economic productivity, and countries with close Soviet ties were also vulnerable, notably Cuba (Fig. 3F) (*47*). During the early 1990s in Cuba, protein, fat, and calorie intake fell with GDP, and there was a rise in the proportion of children born underweight. Almost 20 years later, TB incidence in the former Soviet countries and Cuba has still not returned to the low levels reported in 1991.

These observations leave a series of questions unanswered. First, the relative contribution of failing health services and failing health to excess morbidity and mortality is not known. Second, the characteristics of countries and populations that are vulnerable to these extreme events—for example, the nature of their health care systems—have not been defined. Third, these extreme events might point to smaller but perhaps more widespread social, economic, and medical determinants of TB trends, including chronic diseases.

TB Persistence and the Outlook for Control

In the face of widespread drug treatment, there are two possible reasons why the number of TB cases is still growing. Either transmission has not been reduced, or lower transmission rates have been offset by increasing susceptibility to infection and disease, augmented by population growth (Fig. 1).

There is plenty of evidence that transmission persists, from many settings. Delays before diagnosis can explain the propagation of infection in households, public spaces, clinics, and other points of congregation. Some of these delays are inherent to a system of control that has relied on patients to present themselves at health centers. And after diagnosis, treatment failure is a cause of long-lasting or recurrent episodes of infectious TB.

Although the traditional problems of case detection and case management remain, it is becoming clearer how and when social, economic, and evolutionary factors also affect transmission. One is the growth of cities, driven partly by internal and international migration. Another is the emergence of novel strains of *M. tuberculosis*, some of which have higher reproductive fitness. To account for these factors will require better data, and structural and quantitative adjustments to the standard model in Fig. 1.

For 30 years, HIV coinfection has been the most prominent cause of increasing susceptibility to *M. tuberculosis* infection, and of rapid progression from infection to disease. Other aggravating factors are the rising numbers of alcoholics, diabetics, smokers, and elderly and undernourished

people. Large economic shocks, which affect both transmission and susceptibility, have shown how long-term gains in TB control can be swiftly and durably reversed. The gross effects of some economic and social crises have been evaluated retrospectively, but the timing and magnitude of such perturbations are practically impossible to anticipate.

Despite the uncertainties, we can draw some specific conclusions about the shorter- and longer-term prospects for TB control. The immediate priority is to pursue the goals of DOTS and the Stop TB Strategy because, in the face of a rising case load and persistent transmission, the greatest clinical and epidemiological benefits will come from prompt diagnosis and effective treatment. The present instruments for achieving this are not ideal, but there is clearly potential to deploy them more effectively: to accurately diagnose drug-sensitive and drug-resistant cases, select efficacious drug regimens, prevent transmission in clinics and hospitals, and actively seek TB cases in high-risk populations.

Improved technology will support these efforts, led by new diagnostics (e.g., those based on nucleic acid amplification and antigen detection). A broader portfolio of drugs is also needed to contain resistance, along with shorter regimens (<6 months) to make it easier for patients to complete treatment. There are currently fewer than 10 novel drugs in clinical trials, but the widening pipeline is certain to provide some options for changing and shortening regimens.

As HIV epidemics continue to generate a large but slowly falling number of TB cases, the challenge for TB and HIV/AIDS control programs is to aggressively implement the methods that are known to work, including antiretroviral therapy (ART) and isoniazid preventive therapy (IPT) to prevent TB among HIV-positives, and active TB case finding among HIV-positives followed by appropriate treatment for both infections (*26*, *48*). Widespread and frequent HIV testing, with immediate ART for those who test positive, has the potential to improve clinical outcomes and to reduce the number of both new HIV infections and TB cases (*49*). These are in addition to other methods for HIV prevention, including the use of condoms and male circumcision.

There are other options for reducing susceptibility to infection, and for slowing the progression to active disease, but they will be hard to implement quickly. If all smokers quit, there would be far fewer TB cases and deaths, especially in populous Asia (*50*). Given that the proportion of men who smoke has been falling at only 2% per year in the UK and the USA, more slowly in Japan, and hardly at all yet in China and India, the removal of smoking as a risk factor for TB is likely to take decades (*51*). The result is that, although there are major health benefits from tobacco control, diabetes prevention, and nutritional interventions, these can play only supporting roles in TB control.

New technology to remove or neutralize infection—a better vaccine than BCG (bacille Calmette-Guérin) or practical methods for treating latent infection—could radically alter the approach to TB control (*52*), shifting the emphasis from cure to prevention. But this change will not happen soon. A major objective of vaccine research in the next 5 years is to establish sites to carry out efficacy trials. Preventive therapy might be reinvigorated if it becomes possible to identify, with some immunological or genetic marker, a subset of people who have a high risk of progressing to active TB. The hard task is to design a test that can be used in frequent surveys; regular sampling is needed to detect individuals at high risk because they pass quickly through the latent state.

Whatever the social, economic, and epidemiological context, TB control programs rely on the health systems of which they are part. TB drugs, equipment, and specialists are essential, but so are the other features of health services: nursing staff, laboratory networks, policies on private and public health care, financial protection schemes, and methods to engage patients and civil society. The instruments of policy, as much as those of technology, provide ways to reverse the rise of TB.

In sum, we have given examples of persistent transmission and of enhanced susceptibility to infection and disease, but it is easier to find evidence of the former. We conclude that control programs have been less effective than expected in cutting transmission mainly because patients are not diagnosed and cured quickly enough. The priority now is not to abandon the basic principles of chemotherapy, but rather to implement them with greater vigor.

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